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CJOG CLINICAL JOURNAL OF OBSTETRICS AND GYNECOLOGY
ISSN 2640-2890

Research Article

Neonatal Mortality Rate among Twin and Singleton Births with the Gestational Age of 34-37 Weeks: A Population-Based Study

Sedigheh Hantoushzadeh[1], Kayvan Mirnia[2], Hananeh Sadat Sadeghi[3], Parvaneh Sadeghimoghadam[4]*, Mohammad Aghaali[5], Mohammad Heidarzadeh[6], Abbas Habibelahi[7], Shima Rafiee[8], Mohammad Haddadi[1] and Amir Naddaf[9]

[1]Vali-E-Asr Reproductive Health Research Center, Family Health Research Institute, Tehran University of Medical Sciences, Tehran, Iran

[2]Children Medical Center, Pediatric Center of Excellence. Tehran University of Medical Sciences, Tehran, Iran

[3]Department of Demography, Tehran University, Tehran, Iran

[4]Department of Pediatrics, Vali-E-Asr Reproductive Health Research Center, Family Health Research Institute, Tehran University of Medical Sciences, Tehran, Iran

[5]Department of Family and Community Medicine, Qom, Iran

[6]Department of Pediatrics, Zahedan University of Medical Sciences, Zahedan, Iran

[7]Neonatal Health Office. MOME.IR IRAN, Tehran, Iran

[8]School of Medicine, Tehran University of Medical Sciences, Tehran, Iran

[9]Department of Pediatrics, School of Medicine, Maternal, Fetal, and Neonatal Research Center, Family Health Institute, Vali-E-Asr Hospital, Imam Khomeini Hospital Complex, Tehran University of Medical Sciences, Tehran, Iran

More Information

***Address for correspondence:**
Parvaneh Sadeghimoghadam, Department of Pediatrics, Vali-E-Asr Reproductive Health Research Center, Family Health Research Institute, Tehran University of Medical Sciences, Tehran, Iran,
Email: md_sadeghimoghadam@yahoo.com

Submitted: May 26, 2023
Approved: June 27, 2023
Published: June 28, 2023

How to cite this article: Hantoushzadeh S, Mirnia K, Sadeghi HS, Sadeghimoghadam P, Aghaali M, et al. Neonatal Mortality Rate among Twin and Singleton Births with the Gestational Age of 34-37 Weeks: A Population-Based Study. Clin J Obstet Gynecol. 2023; 6: 088-094.

DOI: 10.29328/journal.cjog.1001134

Keywords: Twins; Perinatal mortality; Risk factors; Cesarean section; Premature birth

Abstract

Introduction: Twin pregnancy, compared to a singleton pregnancy, is associated with a higher risk of preterm birth and other neonatal complications. This study aimed to compare neonatal mortality rates and risk factors among births with the gestational age of 34 weeks - 37 weeks in twin and singleton pregnancies.

Methods: The study design was cross-sectional and population-based. We extracted the data from the birth information registry in Iran. Mothers' and neonates' information was removed from the registry systems between 2018 and 2020. We used Statistical R software to compare neonatal mortality rate, demographic variables, and risk factors between two groups of twin and singleton neonates.

Results: Out of 579,873 live births with a gestational age of 34 weeks - 37 weeks, 729 (1.4/1000) singleton and 54(0.77/1000) twins (one out of two) neonates died in the delivery room in the first hour of life. Of the neonates who left the delivery room alive, 3129 (4.9 per 1000) neonates had died (5.7/1000 singleton and 3.04/1000 twin). The neonatal mortality rate in hospitalized singleton neonates (1.85%) was higher than twin group (1.06%). After adjustment of other variables, the mortality rate in twin pregnancy was significantly lower than in singletons (p value < 1/1000), with an odds ratio of 0.47 (CI: 0.39 - 0.55). Antenatal corticosteroid treatment in the twin group was significantly higher than in singletons.

Conclusion: Twin neonatal mortality rate was lower than singletons in the neonates with gestational age 34 weeks - 37 weeks. Clinicians could consider these results for delivery timing in uncomplicated twin pregnancies. Antenatal corticosteroid therapy can be considered to reduce the mortality rate of late preterm neonates in resource-limited countries.

Introduction

Over the last 40 years, twin pregnancies have become more frequent, especially in high-income countries [1]. Between 1980 and 2009, the USA experienced an increase in twinning rates from 18.9 to 33.3 per 1000 births. The increased use of Assisted Reproductive Techniques (ARTs) is responsible for this upward trend [2]. Iran is witnessing a similar trend due to the use of ARTs [3]. It is crucial to determine the delivery time in uncomplicated twin pregnancies. The risks of late-preterm birth's adverse outcomes should be taken into account. Compared to a singleton pregnancy, a twin pregnancy is associated with a higher risk of preterm birth and other neonatal complications [4]. Prematurity complications are

the leading cause of mortalities and morbidities in multiple pregnancies [5]. Extremely premature twins don't have a higher death rate than singletons [5,6]. However, some studies have found that twins have a higher mortality rate than singletons [7]. The results of previous studies in this field, particularly in late preterm infants, are conflicting and insufficient. This study aimed to compare stillbirths and neonatal mortality in twin and singleton births with gestational age between 34 weeks - 37 weeks. Additionally, we examined the differences in mother and infant characteristics and underlying factors between twin and singleton births concerning mortality.

Methods

Study design

Between Mar 21, 2018, and Mar 21, 2020 (the first day of the Persian calendar), a cross-sectional and population-based study was carried out on all singleton and twin births with a gestational age of 34weeks+0 days to 37weeks+6day who needed NICU admission in the neonatal period. The data was extracted from 1. Birth Information Registry (Iranian Maternal and Neonatal Network (IMAN) registry, www.iman.health.gov.ir) and 2. the Specialized Newborn Care Registry (contains basic information about newborns hospitalized in the Neonatal Intensive Care Unit (NICU) and specialized neonatal department in all public and private hospitals regardless of the neonatal outcomes (death, transfer, or discharge) in Iran after merging the two datasets based on the national maternal code [8]. Iran's accreditation program for hospitals showed a data registration validity rate of around 85% [9]. Additionally, the investigator determined the gestational age from the first-trimester ultrasonography report.

Excluding criteria

Neonates who were not assigned a national code (born to mothers who were not Iranian) were omitted from both systems. The study did not include live births of triplets or higher-order multiples. Furthermore, infants with birth defects were not included.

Primary outcome

Neonatal mortality was the main outcome of interest. The mortality rate was determined by the number of deaths per 1000 infants, including stillbirths. The mortality rate was divided based on time of occurrence: antepartum (stillbirth), early neonatal death in the delivery room, and late neonatal death after NICU admission. Neonatal death is characterized as a demise from birth to 28 days of age.

Data collection

The information such as the mothers' demographic characteristics, infant's birth characteristics, mode of delivery, birth date, number of parity and gravidity, parental consanguinity, abortion history, gestational weeks, mother's medical history, and risk factors for pregnancy and childbirth, were reported and evaluated among hospitalized neonates.

Statistics

Data analysis was performed with the statistical R software. Chi-square, t-test, univariate logistic regression, and backward stepwise multivariate logistic regression were used to compare the two groups' demographic variables and risk factors. Multivariable logistic regression was performed to adjust for confounding factors, such as maternal age, delivery type, birth weight, and corticosteroid administration. The level of significance was established at $\alpha = 0.05$.

Ethics: The Research Ethics Committees of Imam Hospital Complex at Tehran University of Medical Sciences approved the study (IR.TUMS.IKHC.REC.1400.256).

Results

The total number of neonates from 2018 to 2020 was 633,438 after the datasets were merged. A total of 579,873 neonates met the inclusion criteria. This survey recorded 4640 stillbirths (91/1000 births) and 177,736 neonates hospitalized. Of the total, 88.79% (157,815) were singletons, and 11.21% (19,921) were twins. The association between mortality and each candidate predictor is summarized in Table 1. C-sections accounted for 67.92% (120,730) of all deliveries. The rate of cesarean deliveries was higher for twin births than for singletons. Among the singleton group, C-sections were used to deliver 64% of neonates, while in the twin group, the percentage was 95%. The mean birth weight among twins was 2284.84 ± 1945.6 grams, and the mean birth weight of singletons was 2753.85 ± 2427.44 grams. The median birth weight of singletons was 2760 grams. In the twin group, 28.4% were given antenatal corticosteroid treatment, compared to 16.8% in singletons (Figure 1).

Table 1 compares variables related to the mother and neonates and delivery conditions separately for singletons and twins in both the surviving and dead groups. Table 2 shows the outcomes of univariate logistic regression analyses for factors associated with mortality for singletons and twins separately. Gestational age, weight, prior pregnancy, consanguinity of parents, and Apgar score were significant mortality risk factors in hospitalized babies common to singletons and twins (p values < 0.05). Delivery type,

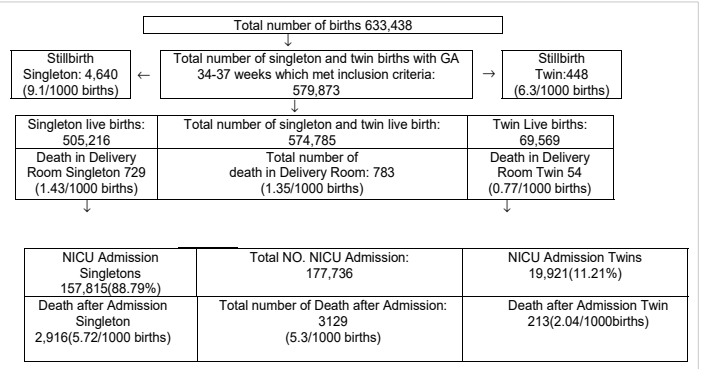

Figure 1: Study flowchart.

Table 1: Comparison of clinical and demographic characteristics in late preterm birth between singleton and twin pregnancies (survived and died).

Variables	Single		*p* - value	Twin		*p* - value
	survived	died		survived	died	
Delivery type						
vaginal birth	55080(98.4%)	875(1.6%)	0.000	1043(99.2%)	8(0.8%)	0.007
C-section	99819(98%)	2041(2%)		18665(98.9%)	205(1.1%)	
Gestational age, week	Median (36.00), IQR (2)			Median (35.0), IQR (2)		
34	19573(96.7%)	662(3.3%)	0.000	5289(98.6%)	76(1.4%)	0.001
35	26171(97.7%)	618(2.3%)		5265(98.8%)	66(1.2%)	
36	39284(98.2%)	704(1.8%)		5020(99.3%)	37(0.7%)	
37	69872(98.7%)	932(1.3%)		4134(99.2%)	34(1.1%)	
Weight (gram)	Mean (2753.854) Median 2760	Mean (2427.438) Median 2470	0.000	Mean (2284.841)	Mean (1945.601)	0.000
very low birth weight (<1500)	1284(87.1%)	190(12.9%)	0.000	449(91.8%)	40(8.2%)	0.000
low birth weight (<2500)	42326(97.1%)	1277(2.9%)		13260(99%)	140(1%)	
normal birth weight (<=4000)	108895(98.7%)	1414(1.3%)		5994(99.5%)	213(0.5%)	
Corticosteroid administration						
has not taken	92580(98.3%)	1610(1.7%)	0.000	9649(99%)	97(1%)	0.304
full	16485(98.2%)	296(1.8%)		4002(98.9%)	43(1.1%)	
imperfect	9552(97.7%)	225(2.3%)		1598(98.6%)	23(1.4%)	
Maternal age (years)	30.48 ± 6.24			30.28±5.93		
<20	6654(97.7%)	155(2.3%)	0.001	486(98.2%)	9(1.8%)	0.307
20–29	59858(98%)	1197(2%)		8456(99%)	86(1%)	
30–39	77314(98.3%)	1359(1.7%)		9605(98.9%)	108(1.1%)	
≥40	11074(98.2%)	205(1.8%)		1158(99.1%)	10(0.9%)	
Prior pregnancies	Median(0.9981), IQR (2)			Median(0.7342), IQR (1)		
None	59249(98.5%)	914(1.5%)	0.000	10021(99%)	101(1%)	0.000
1	55498(98.4%)	931(1.6%)		6291(99.1%)	59(0.9%)	
2	27735(97.8%)	625(2.2%)		2452(99%)	26(1%)	
≥3	12418(96.5%)	446(3.5%)		944(97.2%)	27(2.8%)	
Consanguinity of parents						
No	129460(98.4%)	2078(1.6%)	0.000	16574(99.1%)	152(0.9%)	0.000
Yes	25440(96.8%)	838 (3.2%)		3134(98.1%)	61(1.9%)	
Childbirth Preparation Classes						
No	141867(98.1%)	2730(1.9%)	0.000	18477(99%)	194(1%)	0.145
Yes	13033(98.6%)	186(1.4%)		1231(98.5%)	19(1.5%)	
Year						
2018	55264 (98.1%)	1078(1.9%)	0.012	6602(99%)	70(1%)	0.421
2019	53495 (98.3%)	930(1.7%)		6944(99%)	68(1%)	
2020	46141 (98.1%)	908(1.9%)		6162(99%)	75(1.2%)	
Artificial Insemination						
No	153023(98.1%)	2893(1.9%)	0.047	18040(98.9%)	198(1.1%)	0.537
Yes	1877(98.8%)	23(1.2%)		1668(99.1%)	15(0.9%)	
Apgar score	Median (9.00), IQR (1)			Median (9.00), IQR (1)		
0-3	1382 (71.6%)	547(28.4%)	0.000	176(88.4%)	23(11.6%)	0.000
4-6	5516 (90.4%)	584(9.6%)		878(96%)	37(4%)	
7-10	147998(98.8%)	1785(1.2%)		18654(99.2%)	153(0.8%)	

corticosteroid administration, and participation in childbirth Preparation Classes were considerable risk factors of mortality in hospitalized babies for singletons ($p < 0.001$) but not twins ($p > 0.05$). Table 3 shows the outcomes of multivariate logistic regression analyses for singletons and twins separately and for all neonates with gestational age 34 weeks - 37 weeks (twins as a reference group). Starting with the most comprehensive model, including all risk factors (full model), we used a backward stepwise selection process.

Discussion

The rate of stillbirth and death in the delivery room was significantly higher in the singletons group. In hospitalized neonates, the neonatal mortality rate was higher in the singletons (1.85%) than in twins (1.06%). The mortality rate was higher in the singleton group (12.9%) than in the twin group (8.2%) for very low birth weight neonates. The odds ratio of mortality in very low birth weight neonates in the twin group was higher than in the singleton group (16.18 *vs.* 11.39), but for low birth weight neonates, the odds ratio in the singleton group was higher (2.32 *vs.* 1.91). The mortality rate was lower in the artificial insemination group than in the others. After adjusting for other variables, the multivariate regression analysis showed that hospitalized neonates in twin pregnancies had a lower mortality rate than singletons, with an odds ratio of 0.47 (CI: 0.39, 0.55). In neonates with

Table 2: Univariate analysis of associated factors related to neonatal mortality rate by separate logistic regression models for singletons and twins born with gestational age 34 - 37 weeks in Iran, 2018–2020.

Variables		Singletons	Twins
		Odds ratio (95% CI)	Odds ratio (95% CI)
Gestational Age	34 (ref)		
	35	0.69 (0.62, 0.78)***	0.87 (0.62, 1.21)
	36	0.52 (0.47, 0.59) ***	0.51 (0.34, 0.75) ***
	37	0.39 (0.35, 0.43) ***	0.57 (0.37, 0.85) **
Weight	normal weight(ref)		
	very low birth weight	11.39(9.67,13.35) ***	16.18 (10.11,26.04) ***
	low birth weight	2.32 (2.15, 2.50) ***	1.91 (1.32,2.85) ***
Delivery type	vaginal birth (ref)		
	C-section	1.28 (1.18,1.39) ***	1.43 (0.75,3.17)
Corticosteroid administration	has not taken(ref)		
	full	1.03 (0.90, 1.16)	1.06 (0.73,1.52)
	imperfect	1.35 (1.17, 1.55) ***	1.43 (0.88,2.22)
Maternal age (years)	<20 (ref)		
	20–29	0.85 (0.72,1.02)	0.54 (0.29,1.17)
	30–39	0.75 (0.64,0.89) **	0.60 (0.32,1.29)
	≥40	0.79 (0.64,0.98) *	0.46 (0.18,1.18)
Prior pregnancies	None (ref)		
	1	1.08 (0.99,1.19)	0.93 (0.67,1.28)
	2	1.46 (1.31,1.61) ***	1.05 (0.66,1.56)
	≥3	2.32 (2.07,2.60) ***	2.83 (1.81,4.29) ***
Consanguinity of parents	No(ref)		
	Yes	2.05 (1.89,2.22) ***	2.12 (1.56,2.84) ***
Childbirth Preparation Classes	No(ref)		
	Yes	0.74 (0.63,0.85) ***	1.47 (0.88,2.22)
Year	2018(ref)		
	2019	0.89 (0.81,0.97) *	0.92 (0.65,1.129)
	2020	1.00 (0.92,1.10)	1.14 (0.82,1.59)
Apgar score	0-3(ref)		
	6-Apr	0.26 (0.23,0.30) ***	0.32 (0.18,0.56) ***
	10-Jul	0.03 (0.02,0.03) ***	0.06 (0.04,0.10) ***
Artificial Insemination	No(ref)		
	Yes	0.64 (0.41,0.95) *	0.81 (0.46,1.33)

Signif. codes: 0 '***' 0.001 '**' 0.01 '*' 0.05 '.' 0.1 ' '

gestational age 34 weeks - 37 weeks, twins have a significantly different mortality rate than singletons. The stillbirth, delivery room death, and neonatal mortality rates were lower in twins than in singletons. Mortality rates decline as gestational age increases in both groups. There are numerous explanations for our findings. Our study had a larger sample size compared to earlier ones. A slight difference between the groups can be detected. Antenatal corticosteroids may have been administered more to twins due to their increased risk of preterm birth [10]. In this study, the use of antenatal corticosteroids was more frequent in the twin group. Previous studies have yielded conflicting results. Research shows late preterm singleton infants have a greater mortality risk than term infants. Morbidity risk decreases as gestational age increases [11-15]. Studies have revealed that premature neonates in multiple gestations have a higher risk of morbidity and mortality than full-term neonates [15-17]. No contrast in mortality rates between twins and singletons was found in previous studies [18-20]. Studies reporting equivalent outcomes among singletons and twins in the late preterm often had small sample sizes [21,22]. In a study of 165,894 neonates, Clara Ward et al. found no difference in mortality rates between twins and singletons. A study discovered that twins in the late preterm are at a higher risk of neonatal morbidity. They failed to consider crucial factors like indication for delivery, mode of delivery, or antenatal corticosteroid administration [15]. In a study of 1015 late preterm neonates by Vachharajani, et al. singletons had a higher need for ventilation, but there was no difference in respiratory morbidity between singletons and twins [18]. Our study is consistent with Garite et al.'s findings that neonatal outcomes of multiple gestations are comparable to singletons in a survey of 14,457 twin and triplet births with gestational age between 23 to 35 weeks. According to the study, gestational age and growth restriction are the primary factors leading to mortality in multiple births [23]. According to other studies, twin and triplet neonates have comparable outcomes to singleton [21,24,25]. In a retrospective study conducted by Blank Vask, et al. on 152,120 singleton and 51,658 twin babies whose gestational age was 28 - 43 weeks, results revealed that the rate of stillbirth and neonatal mortality up to the gestational age 37 weeks was higher in twins compared to singletons [26]. Twin fetuses have a clinical impression of accelerated pulmonary maturation, resulting in earlier delivery terms for twins than singleton fetuses. This hypothesis was not supported by some studies [27]. The rate of cesarean sections is higher in neonates born as twins.

Table 3: Multivariate analysis of associated factors related to late preterm mortality by separate logistic regression models for singletons and twins born in Iran, 2018–2020 (*Stepwise Logistic Regression: backward*).

stage	Variables		Singletons	Twins	Total
			Odds ratio(95% CI)	Odds ratio(95% CI)	Odds ratio(95% CI)
Full model	Singletons(ref)	Fetal number	-	-	
	Twins				0.46(0.39,0.55) ***
	34 (ref)	Gestational Age			
	35		0.95 (0.82, 1.09)	0.98 (0.67, 1.44)	0.95(0.83,1.08)
	36		0.96 (0.83, 1.10)	0.64 (0.39, 1.04)	0.93(0.82,1.07)
	37		0.86 (0.75, 1.00) .	0.82 (0.48, 1.36)	0.86(0.75,0.98) *
	normal weight (ref)	Weight			
	very low weight		6.01(4.81,7.48) ***	8.44 (4.75,15.0) ***	6.59(5.37,8.04) ***
	low weight		1.82 (1.65, 2.02) ***	1.36 (0.89,2.14)	1.79(1.62,1.97) ***
	vaginal birth (ref)	Delivery type			
	C-section		1.02(0.93,1.13)	1.38 (0.68,3.29)	1.03(0.94,1.14)
	has not taken (ref)	Corticosteroid administration			
	full		0.93 (0.81, 1.06)	1.05 (0.71,1.52)	0.95(0.83,1.07)
	imperfect		0.91 (0.78, 1.06)	1.05 (0.63,1.66)	0.92(0.79,1.07)
	<20 (ref)	Maternal age (years)			
	20–29		0.91 (0.73,1.13)	0.64 (0.30,1.58)	0.88(0.72,1.10)
	30–39		0.65 (0.52,0.82) ***	0.61 (0.28,1.53)	0.65(0.52,0.81) ***
	≥40		0.53 (0.40,0.71) ***	0.42 (0.15,1.28)	0.53(0.40,0.69) ***
	None (ref)	Prior pregnancies			
	1		1.27 (1.13,1.43) ***	1.11 (0.75,1.63)	1.25(1.12,1.40) ***
	2		1.80 (1.57,2.06) ***	1.18 (0.68,1.99)	1.74(1.53,1.98) ***
	≥3		2.43 (2.07,2.85) ***	2.30 (1.25,4.04) **	2.42(2.07,2.83) ***
	No (ref)	Consanguinity of parents			
	Yes		1.73 (1.56,1.91) ***	1.97 (1.38,2.79) ***	1.75(1.59,1.93) ***
	No (ref)	Childbirth Preparation Classes			
	Yes		0.78 (0.65,0.94) .	1.56 (0.86,2.62)	0.82(0.69,0.98) *
	2018 (ref)	Year			
	2019		0.85 (0.76,0.95) **	0.95 (0.64,1.40)	0.86(0.77,0.95)
	2020		0.95 (0.85,1.06	0.95 (0.64,1.41)	0.95(0.85,1.05) **
	0-3 (ref)	Apgar score			
	6-Apr		0.28 (0.24,0.33) ***	0.30 (0.16,0.59) ***	0.28(0.24,0.32) ***
	10-Jul		0.04 (0.03,0.04) ***	0.08 (0.05,0.14) ***	0.04(0.04,0.05) ***
	No(ref)	Artificial Insemination			
	Yes		0.91 (0.54,1.43)	1.00 (0.53,1.75)	0.96(0.65,1.37)
	R^2		0.14	0.1	0.14
Final model	Singletons(ref)	Fetal number	-	-	
	Twins				0.47(0.39,0.55) ***
	normal weight (ref)	Weight			
	very low weight		6.25(5.03,7.72) ***	9.60 (5.55,16.6) ***	6.91(5.67,8.37) ***
	low weight		1.88(1.72,2.07) ***	1.48 (0.99,2.29)	1.86(1.69,2.03) ***
	No (ref)	Childbirth Preparation Classes			
	Yes		0.78(0.65,0.94) *	1.58 (0.87,2.65)	0.83(0.69,0.98) *
	<20 (ref)	Maternal age (years)	0.90(0.73,1.13)	-	
	20–29		0.65(0.52,0.82) ***		0.88(0.72,1.10)
	30–39		0.53(0.40,0.71) ***		0.65(0.52,0.81) ***
	≥40				0.53(0.40,0.69) ***
	2018 (ref)	Year		-	
	2019		0.85(0.76,0.95) **		0.86(0.77,0.95) **
	2020		0.95(0.85,1.06)		0.95(0.85,1.05)
	0-3 (ref)	Apgar score			
	6-Apr		0.28(0.24,0.33) ***	0.31(0.16,0.60) ***	0.28(0.24,0.32) ***
	10-Jul		0.04(0.03,0.04) ***	0.08(0.05,0.14) ***	0.04(0.03,0.05) ***
	None (ref)	Prior pregnancies			
	1		1.28(1.14,1.44) ***	1.06(0.72,1.52)	1.26(1.13,1.41) ***
	2		1.82(1.59,2.08) ***	1.11(0.65,1.80)	1.76(1.55,2,00) ***
	≥3		2.46(2.10,2.88) ***	2.06(1.17,3.44) **	2.45(2.10,2.85) ***
	No (ref)	Consanguinity of parents			
	Yes		1.72(1.56,1.91) ***	2.04(1.43,2.87) ***	1.75(1.58,1.93) ***
	R2		0.14	0.1	0.14

Signif. codes: 0 '***' 0.001 '**' 0.01 '*' 0.05 '.' 0.1 ' ' 1

Respiratory disorder is a crucial problem for twin neonates [28]. Amniotic fluid samples from 454 singletons and 398 twin pregnancies were analyzed by Tsuda et al. According to a study, twin fetuses experience more rapid lung fluid absorption and maturation than singletons [29]. According to their findings, neonatal respiratory distress syndrome and transient tachypnea in newborns at 38 weeks gestation in singleton pregnancies are comparable to that at 36 weeks gestation in twin pregnancies [28]. It is recommended to deliver uncomplicated twin pregnancies earlier to prevent intrauterine death in the last weeks of gestation due to their higher risk than singleton pregnancies [30] and lower neonatal mortality rate during the late preterm period [30]. Antepartum corticosteroids reduce morbidity and mortality of preterm babies under 34 weeks gestation. Recent studies suggest that the beneficial effects of giving antenatal corticosteroids may also extend to late preterm and early-term infants. In most studies conducted in late preterm infants, antenatal corticosteroids reduce the chance of short-term respiratory complications but do not affect the mortality rate [31]. Antenatal corticosteroid benefits in twin pregnancies have been studied less than in singleton pregnancies. Guidelines for administering antenatal corticosteroids in twin pregnancies are based on evidence from singleton pregnancies [31-32]. While studies show varying perinatal mortality rates for twins compared to singletons, recent years have seen a greater reduction in stillbirth and neonatal death rates for twins than for singletons. This achievement owes to the critical role of fetal monitoring in twin pregnancies. The presence of specific guidelines for managing high-risk and twin pregnancies and the ability to treat complications like twin-twin transfusion syndrome during the fetal period are crucial factors [33-35]. Most studies like ours have examined twin mortality overall without considering the impact of chronicity, and the mortality rate of twins has not been explored by zygosity [33].

Study limitations

The study excluded non-Iranian mothers and out-of-hospital deaths and births. Therefore, the results did not reflect the immigrant population in Iran. We accounted for critical factors in this setting (delivery method, antenatal corticosteroid use, and assisted reproductive technology) and applied multivariable logistic regression to account for possible variables.

Conclusion

Our study shows that twins have a lower mortality rate than singletons who delivered between 34 to 37 weeks of gestational age. Delivery timing in uncomplicated twin pregnancies could be affected by these results. Moreover, the roles of antepartum corticosteroids and better prenatal care were considered to improve the outcomes of singleton, such as twin pregnancies which caused a decrease in stillbirth and neonatal death between them. Healthcare providers and policymakers could use these results and demonstrations to make appropriate decisions in the healthcare system to develop and improve maternal-fetal health among developing countries like Iran, and it could be guided to further studies in this field.

Acknowledgments

We thank Iran's Neonatal Health Office of Health and Medical Education Ministry.

Funding: Tehran University of Medical Sciences

Availability of data and materials: In this study, we used Iranian Maternal and neonatal records (IMAN registry) data; administrative permissions are required to access the dataset.

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