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The risks of being a preterm twin

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Abstract

Aim: Twins may have additional clinical problems compared to singletons, but there is insufficient information about whether preterm twins (especially those born before 32 weeks of gestation) are at greater risk than singletons. This study aimed to compare morbidity and mortality in twins and singletons born before 32 weeks of gestation.

Materials and Methods: Infants whose gestational age (GA) $\leq$ 32 weeks were followed in our unit between July 2017 and December 2020 were examined retrospectively. The clinical and demographic characteristics of the infants were recorded and compared between twins and singletons.

Results: 770 preterm infants were included in the study, 584 singletons and 186 twins. The singleton group had higher rates of maternal hypertension and small for GA status, while the rate of cesarean delivery was higher in the twins group ($p<0.05$). Other demographic characteristics and clinical outcomes were the same in the singleton and twin groups ($p<0.05$).

Conclusion: Preterm morbidity and mortality were similar in the twin and singleton groups in this study. This can be attributed to the similar GA and birth weight (BW) in both groups. Therefore, our results suggest that the main determinants of mortality and morbidity in preterm infants are GA and BW rather than twin pregnancy.

Introduction

Almost 1 in 10 twins is born $\leq$ 32 weeks of gestation (GW), compared to 1 in 100 singletons. The higher risk of preterm birth also increases the risk of morbidities of prematurity [1]. The risk of neonatal mortality can be up to fivefold higher for twins than singletons [2]. Late preterm infants are described as those born between 340/7 and 366/7 GW. Many studies evaluating the clinical outcomes of singletons and twins have included term or late preterm infants [3-7]. Relative adverse clinical outcomes for twins compared to singletons may vary according to gestational age (GA). Although all preterm infants are at higher risk of morbidity and mortality, it is not clear whether twin pregnancy increases this risk and the current risks for twins versus singletons born $\leq$ 32 GW, which is a higher risk group [3-7]. In addition, recent clinical studies in this population have yielded inconsistent results [1,7,8]. The frequency of preterm birth in twin pregnancies is rising substantially due to the increasing use of assisted reproductive methods and obstetric interventions to prevent stillbirth and neonatal morbidity. For this reason, it is essential to have up-to-date details about the associated risks. In addition, medical advances in the care of preterm neonates, especially those born $\leq$ 32 GW, are still ongoing. Therefore, preterm twins considered high-risk might be more likely to benefit from these medical advances [1]. The present study aimed to investigate whether the previously identified higher risk of neonatal morbidity and mortality in twins contrasted to singletons was significant in preterm infants born $\leq$ 32 GW.

Material and Methods

Patient selection and protocol

All preterm infants whose GA $\leq$ 32 weeks was born between July 2017 and December 2020 were evaluated retrospectively. Infants with major congenital anomalies and those with GA of $>$ 32 weeks were excluded. The demographic and clinical characteristics of singletons and twins were recorded. Ethics committee (88/2018, Zekai Tahir Burak Women's Health Research and Education Hospital) approval was obtained before the study, which was conducted in accordance with the Declaration of Helsinki.

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Demographic and clinical characteristics

The following data were obtained from the infants' records: GA, birth weight (BW), sex, small for gestational age (SGA; <10th percentile for BW) [9], maternal age, maternal hypertension and diabetes history, antenatal steroid (ANS) use, mode of birth (cesarean or vaginal delivery), need for resuscitation in the delivery room, 1- and 5-minute Apgar scores, early-onset neonatal sepsis (ENS; sepsis on or before postnatal day 3), late-onset neonatal sepsis (LNS; sepsis after postnatal day 3) [10], respiratory distress syndrome (RDS; need for surfactant) [11], cord blood pH, oxygen, noninvasive respiratory support (NRS), and mechanical ventilation (MV) durations, bronchopulmonary dysplasia (BPD; moderate/severe) [12], retinopathy of prematurity (ROP) requiring treatment [13], intraventricular hemorrhage (IVH; grade ≥3) [14], necrotizing enterocolitis (NEC; grade ≥2) [15], hemodynamically significant patent ductus arteriosus (PDA) [16], time to full enteral feeding, length of neonatal intensive care unit (NICU) stay, and mortality. These clinical and demographic characteristics were compared between singleton and twins.

Sample size

Sample size calculation was based on the morbidity and mortality variable. The power calculation was performed according to the data from a previous study which was conducted in the relationship of neonatal morbidity in twins and singletons [4]. The total sample size of 242 (121 for twin group, 121 for singleton group) will be sufficient to detect power of 80% and a significance level of 5%.

Statistical analysis

Demographic and clinical data were transferred from medical records to computer and resolved using SPSS (Statistical Package for the Social Sciences) version 16.0 statistical software (SPSS Inc, Chicago, IL). Measured data were tested for normal distribution using both graphical analyses and the Shapiro-Wilk test. Normally distributed variables were presented as mean and standard deviation, non-normally distributed variables as median, minimum, and maximum values. Continuous variables were compared using Student t-test or Mann-Whitney U test, and nominal variables were analyzed using χ^2 or Fisher's exact test as appropriate. A p-value of <0.05 was assessed as statistically significant.

Results

Of 779 infants born at a GA of ≤32 weeks during the study period, 9 were excluded due to major congenital anomalies. Therefore, a total of 770 preterm infants (mean GA: 28.4 ± 1.2 weeks, mean BW: 1061 ± 235 g) were included in our study. Of these, 584 were singletons, and 186 were twins. In our study, twins accounted for 24.1% (186/770) of births ≤ 32 GW. Rates of maternal hypertension and SGA status were significantly higher in the singleton group than in the twin group (p<0.001 and p=0.002, respectively). Caesarean delivery was significantly more common in the twin group compared to the singleton group (p<0.001). There were no dissimilarities between singletons and twins in the other demographic and clinical characteristics (p>0.05). The characteristic of demographics is shown in Table 1 and the characteristic of clinical in Table 2.

Discussion

Although it is well established that twins have a higher rate of adverse clinical outcomes than singletons and that infants born ≤ 32 GW are at higher risk for many morbidities, there is still uncertainty about the risks associated with being a preterm twin [1,3,6,17]. In our study, twins born ≤ 32 GW had lower rates of SGA and maternal hypertension and a higher rate of cesarean birth compared to singletons. Other demographic characteristics and clinical outcomes were similar in singletons and twins. The frequency of maternal hypertension is reported to be higher in twin pregnancies than singleton pregnancies, even increasing up to twofold. However, this result was obtained by evaluating infants born at or near term [18]. There is less information about the risk of gestational hypertension for extremely low birth preterm twins. Different results have been reported regarding the prevalence of hypertension for twins and singletons born before 35 GW [3,4,17]. A study examining preterm neonates born before 31 GW also showed that rates of hypertension and SGA were lower in twin pregnancies, similar to our results [1]. These contradictory results may be due to the difference in GA, because the frequency of gestational hypertension and subsequent SGA of the newborn increases after 34 weeks of gestation [17-19]. Therefore, twins born ≤ 32 GW should be evaluated separately. According to our results, the higher frequency of maternal hypertension in singletons than twins may arise as a result of risk factors such as early delivery due to hypertension, preeclampsia history in previous pregnancies and in the family, or the presence of renal disease [17,18]. In addition, the lower rates of maternal hypertension and SGA status in twins may be due to placental factors. In twins, placental vascular lesions associated with placental hemorrhage, low rates of retroplacental hemorrhage and placental maternal vascular malperfusion, and high rates of cesarean delivery may affect the frequency of placental pathology lesions. Therefore, the etiopathogenesis of preterm birth in twin pregnancies may occur through mechanisms different from those involved in singleton pregnancies [20]. As our data does not include placental evaluation and some other risk factors, we cannot comment on the results. Although placental histopathological findings and other possible additional risk factors that we could not evaluate may be associated with negative outcomes, there was no dissimilarity between the groups in our study in terms of negative neonatal outcomes. The similar clinical outcomes suggest that GA and BW are the dominant factors associated with neonatal outcomes [20]. Infants born by cesarean section have higher morbidity than infants of the same GA born vaginally [6]. However, our results indicated that all morbidity and mortality, including respiratory morbidities, were similar in the singleton group and the twin group, which had a high cesarean rate. In late preterm twins, respiratory and other morbidities may increase with the higher cesarean rate. This is because the main cause of respiratory distress in late preterm infants

Table 1. Demographic Characteristics

Variable	Singletons (n = 584, 75.9%)	Twins (n = 186, 24.1%)	p
Maternal age, years[a]	28.5 ± 6.4	28.7 ± 6.1	0.683
Gestational age, weeks[a]	28.4 ± 1.2	28.3 ± 1.1	0.133
Birth weight, g[a]	1049 ± 230	1090 ± 214	0.141
Male sex, n (%)	291 (49)	101 (54.3)	0.069
SGA, n (%)	69 (11.8)	13 (6.9)	0.002*
Maternal hypertension, n (%)	143 (24.4)	3 (1.6)	<0.001*
Maternal diabetes, n (%)	28 (4.8)	6 (3.2)	0.163
Antenatal steroid, n (%)	403 (69)	122 (65.5)	0.099
Need for delivery room resuscitation, n (%)	145 (24.8)	50 (26.8)	0.089
Cesarean delivery, n (%)	474 (81.1)	177 (95.1)	<0.001*

*Statistically significant (p<0.05), [a] Mean ± standard deviation, SGA: Small for gestational age

Table 2. Clinical Characteristics

Variable	Singletons (n = 584, 75.9%)	Twins (n = 186, 24.1%)	p
1-minute Apgar score[a]	5 (1-7)	5 (1-7)	0.714
5-minute Apgar score[a]	8 (2-9)	7 (3-9)	0.458
ENS, n (%)	15 (2.5)	4 (2.1)	0.833
LNS, n (%)	89 (15.2)	31 (16.6)	0.162
RDS, n (%)	346 (59.2)	113 (60.7)	0.244
Cord blood pH[b]	7.22 ± 0.09	7.22 ± 0.08	0.461
Oxygen support duration, days[b]	25.1 ± 16.1	23.6 ± 12.6	0.114
NRS duration, days[b]	8 ± 7.7	7.9 ± 6.4	0.184
MV duration, days[b]	4.3 ± 3.6	3.8 ± 2.3	0.091
Moderate/severe BPD, n (%)	101 (17.3)	35 (12.2)	0.246
ROP, n (%)	60 (10.2)	16 (8.6)	0.326
IVH (stage ≥3), n (%)	42 (7.2)	15 (8)	0.415
NEC (stage ≥2), n (%)	14 (2.4)	3 (1.6)	0.219
PDA, n (%)	222 (38)	76 (40.8)	0.197
Time to full enteral feeding, days[b]	16.4 ± 7.5	15.8 ± 6.1	0.148
Length of NICU stay, days[b]	56.5 ± 31.8	52.3 ± 29.5	0.182
Mortality, n (%)	98 (16.8)	31 (16.6)	0.942

[a]Median (minimum–maximum), [b]Mean ± standard deviation, BPD: Bronchopulmonary dysplasia, ENS: Early-onset neonatal sepsis, LNS: Late-onset neonatal sepsis, IVH: Intraventricular hemorrhage, MV: Mechanical ventilation, NEC: Necrotizing enterocolitis, NRS: Noninvasive respiratory support, PDA: Patent ductus arteriosus, RDS: Respiratory distress syndrome, ROP: Retinopathy of prematurity, NICU: Neonatal intensive care unit.

is transient tachypnea of the newborn due to the inability to excrete fetal lung fluid, and cesarean delivery rises the risk of transient tachypnea of the newborn [6,21]. However, the main cause of respiratory morbidity in preterm infants born ≤ 32 GW is the lack of surfactant production due to lung immaturity and the resulting RDS [3,4,8]. Therefore, these very preterm infants have a greater need for respiratory support due to RDS compared to late preterm and term infants. This results in increases in morbidities of prematurity (PDA, BPD, ROP, IVH, NEC, length of hospital stay, and mortality. In the very preterm group especially, GA and BW are the main factors influencing infants' clinical outcomes rather than twin or singleton status [7]. Therefore, the fact that GA and BW were similar in both groups may explain why we did not observe a difference in clinical outcomes [8,22]. Twins born between 22 and 37 GW may have lower mortality compared to singletons at the same GA [17,23,24]. On the contrary, some preterm studies have shown that being a singleton or twin does not affect mortality [1,19,20]. In fact, the main reason for these different results is that the twins and singletons included the groups had different GA and BW. This is the primary reason for the different results in twin and singleton studies, especially in very preterm (GA ≤ 32 weeks) infants. Evaluations should compare twins and singletons matched for GA and BW [8]. In this respect, as indicated by our study results, preterm infants born at similar GA and BW and receiving the same standard of postnatal care may have similar clinical outcomes regardless of being twins or singletons [5,25]. Furthermore, over the years, technological advances have contributed to improvements in clinical outcomes. For example, advances in MV and NRS practices, ANS use, developments in twin-twin transfusion therapy, and determining the appropriate target oxygen saturation level have significantly reduced morbidity and increased survival among preterm infants [8,26]. Therefore, it is necessary to determine whether these evolving approaches have changed the clinical outcomes of twins and singletons. The power of our study is the size of our example population. One of the limitations

of our study is that it was conducted in a single center. Thus, our findings demonstrate the results of patients with more uniform treatments and treatment strategies compared to a multicenter study. In addition, we were unable to evaluate data related to neurodevelopmental outcomes. Another limitation is the retrospective study design. In conclusion, this study evaluating preterm infants born ≤ 32 GW revealed no difference between twins and singletons in terms of morbidities, prematurity, or mortality. This may be due to advances in current treatment approaches in prenatal and postnatal care and/or the similar GA and BW in the groups. Nonetheless, preterm infants, especially twins, may face a higher incidence of neonatal morbidity and more extended hospital stays. The indication for preterm delivery should be well justified; if not safe for mother and baby, it should be avoided. The pregnancy should be continued for as long as it remains beneficial for the mother and fetus.

Ethics approval

Ethics committee (Zekai Tahir Burak Womens Health Education and Research Hospital, 88/2018) approval was obtained before the study, which was conducted in accordance with the Declaration of Helsinki.

References

1. Papiernik E, Zeitlin J, Delmas D, et al. Differences in outcome between twins and singletons born very preterm: results from a population-based European cohort. Hum Reprod 2010;25:1035-43.
2. Anthony S, Jacobusse GW, van der Pal-de Bruin KM, et al. Do differences in maternal age, parity and multiple births explain variations in fetal and neonatal mortality rates in Europe?-Results from the EURO-PERISTAT project. Paediatr Perinat Epidemiol 2009;23:292-300.
3. Zdanowicz JA, Sommer E, Raio L, et al. Do late preterm twins face an increased neonatal morbidity compared with singletons? Swiss Med Wkly 2018;148:w14581.
4. Simchen MJ, Okrent Smolar AL, Dulitzky M, et al. Neonatal morbidities and need for intervention in twins and singletons born at 34-35 weeks of gestation. J Perinat Med 2016;44:887-892.
5. Salem SY, Kibel M, Asztalos E, et al. Neonatal Outcomes of Low-Risk, Late-Preterm Twins Compared With Late-Preterm Singletons. Obstet Gynecol 2017;130:582-590.
6. Ribicic R, Kranjcec I, Borosak J, et al. Perinatal outcome of singleton versus twin late preterm infants: do twins mature faster than singletons? J Matern Fetal Neonatal Med 2016;29:1520-4.
7. Tseng HC, Sung FC, Mou CH, et al. Population based retrospective cohort study on risk of retinopathy of prematurity in twins. PLoS One 2020;15:e0230346.
8. Chen HY, Chauhan SP. Risk of Neonatal and Infant Mortality in Twins and Singletons by Gestational Age. Am J Perinatol 2019;36:798-805.
9. Lubchenco LO, Hansman C, Dressler M, et al. Intrauterine Growth as Estimated from Liveborn Birth-Weight Data at 24 to 42 Weeks of Gestation. Pediatrics 1963;32:793-800.
10. Wynn JL, Wong HR, Shanley TP, et al. Time for a neonatal-specific consensus definition for sepsis. Pediatr Crit Care Med 2014;15:523-8.
11. Bozkaya D, Dizdar EA, Korkut S, et al. Evaluation of Different Types of Natural Surfactants by Lung Ultrasound in Respiratory Distress Syndrome. Am J Perinatol. 2021;38:590-596.
12. Tayman C, Cakir U, Yucel C, et al. Is Endocan a Novel Diagnostic Marker for the Severity of Bronchopulmonary Dysplasia in Very Low Birth Weight Infants? Arch Bronconeumol 2019 ;55:465-471.
13. International Committee for the Classification of Retinopathy of Prematurity. The International Classification of Retinopathy of Prematurity revisited. Arch Ophthalmol 2005;123:991-9.
14. Allan WC, Volpe JJ. Periventricular-intraventricular hemorrhage. Pediatr Clin North Am 1986;33:47-63.
15. Bell MJ, Ternberg JL, Feigin RD, et al. Neonatal necrotizing enterocolitis. Therapeutic decisions based upon clinical staging. Ann Surg 1978;187:1-7.
16. Cakir U, Tayman C, Karacaglar NB, et al. Comparison of the effect of continuous and standard intermittent bolus paracetamol infusion on patent ductus arteriosus. Eur J Pediatr 2021;180:433-440.
17. Topcuoğlu S, Yavuzcan Öztürk D, Gürsoy T, et al. Comparison of singleton, twin and triplet pregnan-cy outcomes of preterm infants delivered before 34 weeks of gestation. Zeynep Kamil Tıp Bülteni 2014; 45:38-43.
18. Sibai BM, Hauth J, Caritis S, et al. Hypertensive disorders in twin versus singleton gestations. National Institute of Child Health and Human Development Network of Maternal-Fetal Medicine Units. Am J Obstet Gynecol 2000;182:938-42.
19. Walker AR, Waites BT, Caughey AB. Twins versus singleton pregnancies: outcomes in small for gestational age late preterm deliveries. J Matern Fetal Neonatal Med 2020;33:895-900.
20. Weiner E, Dekalo A, Feldstein O, et al. The placental factor in spontaneous preterm birth in twin vs. singleton pregnancies. Eur J Obstet Gynecol Reprod Biol 2017;214:1-5.
21. Mor N, Machtinger R, Yinon Y, et al. Outcome of two sequential singleton pregnancies and twin pregnancies among primiparous women at advanced age undergoing IVF. Arch Gynecol Obstet 2020;302:1113-1119.
22. Blondel B, Kogan MD, Alexander GR, et al. The impact of the increasing number of multiple births on the rates of preterm birth and low birthweight: an international study. Am J Public Health 2002;92:1323-30.
23. Esteves-Pereira AP, da Cunha AJLA, Nakamura-Pereira M, et al. Twin pregnancy and perinatal outcomes: Data from 'Birth in Brazil Study'. PLoS One 2021;16:e0245152.
24. Minakami H, Sato I. Reestimating date of delivery in multifetal pregnancies. JAMA 1996;275:1432-4.
25. Tyson JE, Parikh NA, Langer J, et al. Intensive care for extreme prematurity--moving beyond gestational age. N Engl J Med 2008;358:1672-81.
26. Yarci E, Alyamac Dizdar E, Oncel MY, et al. Successful management of twin anemia/polycythemia sequence by syngeneic partial exchange transfusion. Fetal Diagn Ther 2014;36:251-4.