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Retrospective Comparative Analysis of Neonatal Mortality and Morbidity in Preterm Singleton and Multiple Births -Single Center Experience-

Mohammad Alhasoon, MD[1], Bader Alqahtani, MD[2], Mohamad Alreefi, MD[2], Abdulaziz Homedi, MD[2], Ghadah Alnami, MD[2], Saif Alsaif, MD[2], and Kamal Ali, MD(Res)[2]

Abstract

Objective. To compare mortality and major neonatal morbidities between singleton preterm infants and preterm infants of multiple gestations born <33 weeks' gestation. *Method.* Case-control study of preterm multiples and singletons <33 weeks' born at King Abdul-Aziz Medical City Riyadh (KAMC-R) between January 2017 and December 2020. Out-born infants and infants with lethal congenital abnormalities were excluded from the study. Mortality and major neonatal morbidities including bronchopulmonary dysplasia (BPD), retinopathy of prematurity (ROP), sepsis and surgical necrotizing enterocolitis (NEC) were compared between preterm singletons and multiples. *Results.* A total of 803 preterm infants were included: 567 (70.6%) were singletons, 158 (19.6%) were twins and 36 (4.5%) infants were higher multiples. Adjusted mortality before hospital discharge was significantly higher among preterm infants of multiple gestations compared to preterm singletons (12.3% vs 7.9%; *P* = .003; AOR, 2.2; 95% CI, 1.3-3.7). Retinopathy of prematurity (ROP) needing treatment was significantly higher among preterm infants of multiple pregnancies compared to preterm singletons (11% vs 6.5%, *P* = .033, AOR 1.1, 95% CI, 1.04-2.99). In addition, the incidence of bronchopulmonary dysplasia (BPD) at 36 weeks post menstrual age (PMA) (29.7% vs 20.5%; P = .003; AOR, 1.7; 95% CI, 1.2-2.5) and culture positive sepsis (24.2% vs 17.5%; *P* = .044; AOR, 1.5; 95% CI, 1.01-2.2) were significantly higher among preterm infants of multiple pregnancy. There were no differences in mortality and adverse neonatal outcomes between twins and higher multiples. *Conclusion.* Preterm infants of multiple gestations suffered higher mortality and neonatal morbidities compared to preterm singleton infants despite a higher utilization of maternal antenatal steroids and better antenatal care.

Keywords

preterm, multiples, singletons, survival, morbidity

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Introduction

The rise in multiple pregnancy birth rates over recent years can be attributed to factors such as advanced maternal age,[1,2] and the use of assisted reproductive technology.[3,4] This trend has spurred a growing interest in understanding how multiple births affect neonatal outcomes. Existing research presents mixed findings on survival outcomes of preterm multiples compared to preterm singletons. For instance, data on twins indicate that they face a higher risk of neonatal mortality compared to singletons.[5] Nevertheless, others have shown that this risk appears to fluctuate with gestational age; twins born before 28 weeks' gestation are more vulnerable, yet those born after this point tend to have a better survival rate.[6] Some studies, however, suggest that the differences in neonatal outcomes between preterm

[1]Department of Pediatrics, College of Medicine, Qassim University, Buraydah, Saudi Arabia
[2]Neonatal Intensive Care Department, King Abdulaziz Medical City-Riyadh, Ministry of the National Guard - Health Affairs, Riyadh, Saudi Arabia

Corresponding Author:
Kamal Ali, King Abdulaziz Medical City, Riyadh 11426, Saudi Arabia.
Email: alika@ngha.med.sa

singletons and multiples may not be substantial.[7,8] Notably, one study highlighted that late preterm twins have a lower incidence of neonatal mortality and intrauterine fetal death compared to singletons.[9]

Given these disparities in the literature, our study aims to scrutinize neonatal mortality and significant morbidities among infants from singleton and multiple pregnancies delivered before 33 weeks of gestation. We aim to explore the hypothesis that infants from multiple gestations born prematurely experience higher mortality and increased neonatal morbidities.

Methodology

This case-control study was conducted at King Abdulaziz Medical City (KAMC), Riyadh, Kingdom of Saudi Arabia, covering 4 years, from January 2017 to December 2020. The Neonatal Intensive Care Unit (NICU) at KAMC is a 40-bed, level III critical care unit and a 36-bed intermediate care nursery with an average of 2300 admissions per year.

Newborn infants (gestational age < 33 weeks) born at KAMC were included in the study. Outborn infants and those with lethal anomalies were excluded from the study. King Abdullah International Medical Research Center (KAIMRC) Institutional Review Board approved the study (IRB: RC20/283/R) and waived the patient consent as the study design was a retrospective chart review and no patients identifiables were kept in the database.

Gestational age, chorionicity, and amnionicity were determined from prenatal records. In uncertain last menstrual period, gestational age from the earliest ultrasound scan was used to determine the gestational age.

Demographic data for mothers and infants were abstracted from the prenatal and inpatient records. Maternal and neonatal variables investigated for the description of the population were: prenatal use of corticosteroids, presence of gestational diabetes and hypertension, Prolonged Rupture of Membranes (PROM) defined as "rupture of membranes more than 18 hour before delivery," mode of delivery, gender, birthweight, and gestational age at birth. The following neonatal morbidities were evaluated: Bronchopulmonary Dysplasia (BPD) at 36 weeks PMA,[10] major intraventricular hemorrhage (IVH) (grade III & IV) based on the Papile et al[11] classification, retinopathy of prematurity (ROP) based on pediatric ophthalmologic examination using the international classification of ROP,[12] that needed intravitreal injection therapy and/or laser photocoagulation, necrotizing enterocolitis (NEC) based on Bell et al's[13] classification, that needed surgical intervention with insertion of intraabdominal drain or laparotomy, cystic or diffuse periventricular leukomalacia (PVL) by ultrasound and/or MRI[14] and culture-positive sepsis of the blood, CSF, or urine. Duration of mechanical ventilation in days and the length of hospital stay to the point of home discharge were also determined. In our hospital, mothers with singleton pregnancy were seen once every 4 weeks until 28 weeks' gestation. Thereafter, they have appointments every 2 weeks until 36 weeks. After this, they were followed up weekly until delivery. On the other hand, pregnant mothers with DCDA twins were offered scans at least every 4 weeks from 24 weeks whereas mothers having MCDA or MCMA twins as well as higher multiples "as pregnancies involving triplets, quadruplets, quintuplets, and sextuplets" were offered scans at least every 2 weeks from 16 weeks of gestation.

Ethical Approval and Informed Consent

King Abdullah International Medical Research Centre (KAIMRC) approved the study with IRB number: (RC20/283/R). All methods were carried out in accordance with relevant guidelines and regulations and the study was conducted in accordance with the Declaration of Helsinki. The study was a case control study, chart review and no patients identifiable were kept. Patient consent was waived by the ethical committee.

Statistical Analysis

Data were tested for normality using the Kolmogorov-Smirnov (KS) test and found to be normally distributed. Comparisons of survival and adverse neonatal outcomes were made between preterm infants with multiple gestations versus those preterms of singleton gestation. Furthermore, we compared the outcomes of preterm twins versus preterm of higher multiple gestations. Finally, a subgroups analysis for preterms (multiples and singletons) was carried out for 2 gestational age groups (above and below 29 weeks' gestation).

Comparison of categorical variables was analyzed with bivariate analysis using chi-square test and description of unadjusted odds ratios (ORs). This was followed by multivariable logistic regression and presentation of adjusted Odds Ratios (AOR) with 95% confidence intervals (CI) to minimize confounding. All risk factors with a significant ($P < .05$) association in the bivariate analysis were included in the multivariable analysis. The following covariables were considered for the multivariable models: gender, gestational age (to remove the effect of collinearity with birthweight), prenatal corticosteroids, maternal arterial hypertension, maternal diabetes, and cesarean delivery. A comparison of means was analyzed

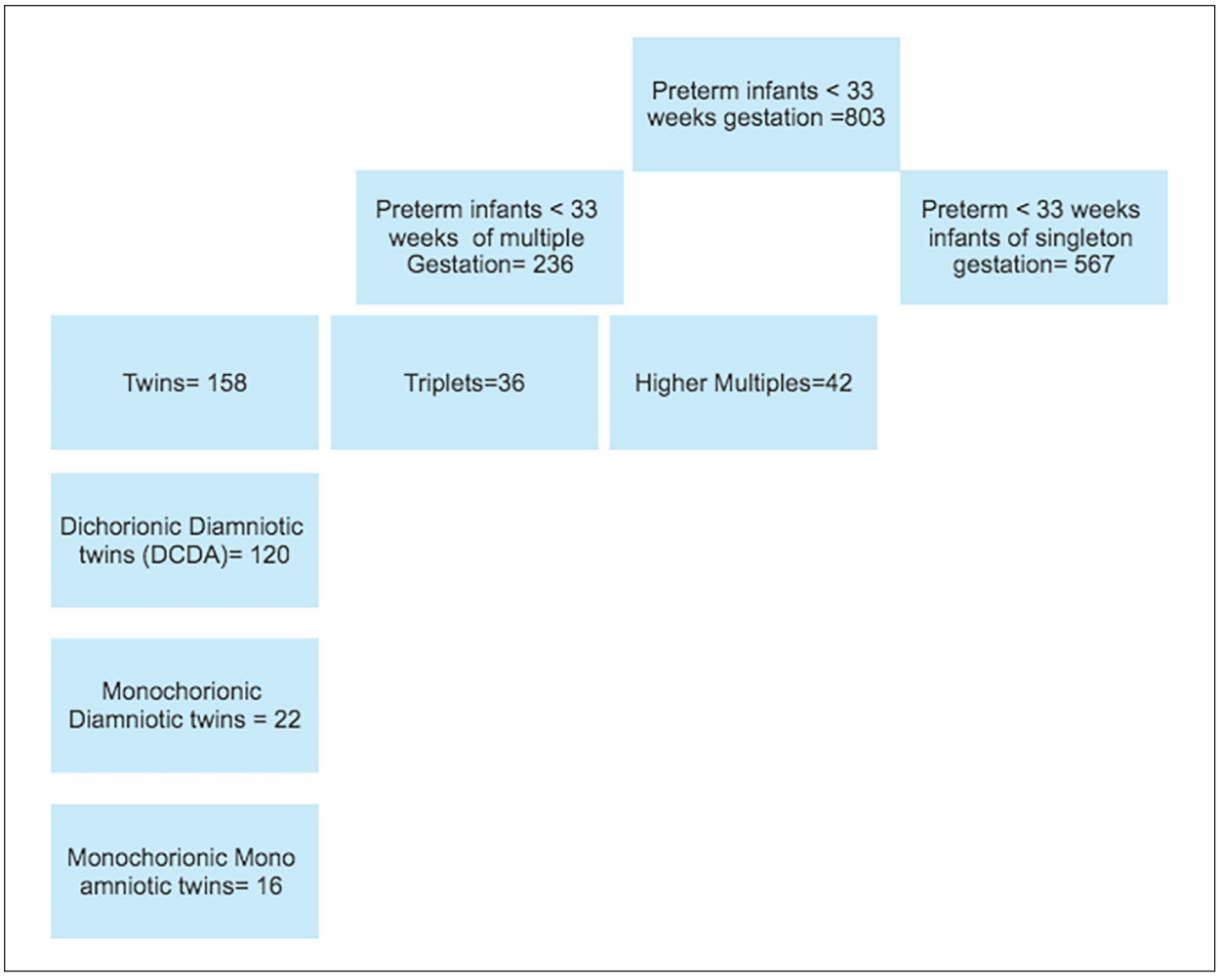

Figure 1. Study diagram of the infants included in the study.
Abbreviations: DCDA, dichorionic diamniotic; MCDA, monochorionic diamniotic; MCMA, monochorionic monoamniotic.

using independent, two-sided *t*-tests. Statistical Package for the Social Sciences (SPSS) version 26.0 was used for analysis.

Results

Eight hundred three preterm infants <33 weeks' gestation were born during the 4-years study period, of which 567 (70.6%) were preterm singletons and a further 236 (29.4%) were preterm multiples. Of the 236 preterm infants in the multiple gestation group, 19.6% were twins, 4.5% were triplets, 4.5% were quadruplets, and 0.7% were of a sextuplet pregnancy (Figure 1).

Maternal hypertension ($P = .009$) and maternal PROM ($P < .001$) were significantly higher among mothers of infants in the preterm singleton pregnancy group. On the other hand, antenatal corticosteroids (75% vs 61.5%, $P = .001$), use of assisted reproductive therapy (49.6% vs 5.3%, $P < .001$), and delivery by cesarean section (83.9% vs 58.9%, $P < .001$) were all significantly higher among mothers of infants in the multiple pregnancy group. There were no statistically significant differences in gender, gestational age at birth, birthweight, and maternal diabetes between the 2 groups (Table 1).

Adjusted mortality before hospital discharge was significantly higher among preterm infants of multiple gestations compared to preterm singletons (12.3% vs 7.9%; $P = .003$; OR, 2.2; 95% CI, 1.3-3.7). Retinopathy of prematurity (ROP) needing treatment was significantly higher among preterm infants of multiple pregnancies compared to preterm singletons (11% vs 6.5%, $P = .033$, OR 1.1, 95% CI 1.04-2.99). In addition, the incidence of BPD at 36 weeks PMA (29.7% vs 20.5%; $P = .003$; OR, 1.7; 95% CI, 1.2-2.5) and culture positive sepsis (24.2% vs 17.5%; $P = .044$; OR, 1.5; 95% CI, 1.01-2.2) were

Table 1. Maternal and Infant's Characteristics.

Characteristics	Singletons (567)	Multiples (236)	*P*-value
Maternal hypertension (n, %)	96 (16.93)	23 (9.74)	.009
Maternal diabetes (n, %)	99 (17.46)	35 (14.83)	.357
Maternal prolonged rupture of membranes (n, %)	175 (30.86)	42 (17.79)	<.001
Maternal antenatal steroids (n, %)	348 (61.375)	177(75)	.001
Cesarean section delivery (n, %)	334 (58.9)	198 (83.89)	<.001
Assisted conception (n, %)	30 (5.29)	117 (49.57)	<.001
Maternal age (years) (Mean, SD)	30.5 (6.6)	30.2 (5.6)	.424
Gender (male) (n, %)	(315, 55.55)	(137, 58.05)	.516
Gestational age (weeks) (Mean, SD)	29 (3.3)	29 (3.0)	.952
Birth weight (grams) (Mean, SD)	1282 (438)	1259 (448)	.514

Table 2. Survival and Neonatal Outcomes in Preterm Births: Adjusted and Unadjusted Analyses Between Multiples and Singletons.

Outcome	Singleton (n = 567)	Multiple (n = 236)	Unadjusted *P*-value	Unadjusted OR (95% CI)	Adjusted OR (95% CI), *P*-value
Mortality (n, %)	45 (7.93)	29 (12.28)	.034	1.7 (1.04-2.75)	2.2 (1.3-3.7), .003
Major IVH (n, %)	77 (13.58)	34 (14.4)	.757	1.1 (0.69-1.65)	1.3 (.79-2.02), .327
PVL (n, %)	46 (8.11)	24 (10.16)	.347	1.3 (0.76-2.15)	1.2 (.72-2.15), .438
ROP (n, %)	37 (6.52)	26 (11)	.031	1.8 (1.04-3.0)	1.1 (1.04-2.99), .033
Surgical NEC (n, %)	25 (4.4)	14 (5.93)	.360	1.4 (0.69-2.7)	1.5 (.74-1.9), .286
BPD (n, %)	116 (20.45)	70 (29.66)	.005	1.6 (1.15-2.3)	1.7 (1.2-2.5), .003
Sepsis (n, %)	99 (17.46)	57 (24.15)	.030	1.5 (1.03-2.2)	1.5 (1.01-2.2), .044

Adjustments were made for antenatal steroids, maternal hypertension, maternal PROM and mode of delivery.
Abbreviations: IVH, intraventricular hemorrhage; PVL, periventricular leukomalacia; ROP, retinopathy of prematurity; NEC, necrotizing enterocolitis; BPD, bronchopulmonary dysplasia.

significantly higher among preterm infants of multiple pregnancy (Table 2). There were no statistically significant differences between preterm infants of multiple and singleton pregnancies regarding the occurrence of severe IVH, cystic PVL, and surgical NEC (Table 2).

Subgroup analysis of singletons and multiples born <29 weeks' gestation showed that 208 singletons and a further 78 multiples were born during the study period. In this subgroup, maternal hypertension was significantly higher among mothers of preterm singletons (16.8% vs 3.4%, $P = .002$). On the other hand, antenatal steroids uptake (74.4% vs 60.1%, $P = .013$), delivery by cesarean section (77% vs 51.9%, $P < .001$) and rates of assisted conception (52.9% vs 6.7%, $P < .001$) were significantly higher among multiples compared to singletons (Table 3). In this subgroup, birthweight was significantly lower among preterm multiples compared to singletons (796 g vs 891 g, $P < .001$) (Table 3). Morality before hospital discharge was significantly higher among preterm multiples compared to preterm singletons born at a gestational age between 23 + 0 and 28 + 6 weeks (26.4% vs 13.9% $P = .003$; OR, 2.9; 95% CI, 1.4-5.9). Furthermore, rates of PVL ($P = .041$; OR, 2.2; 95%, 1.03-4.7), ROP needing treatment ($P = .005$, OR 2.7, 95% CI, 1.4-5.3), BPD at 36 weeks, PMA ($P = .002$; OR, 2.5; 95% CI, 1.4-4.3) and culture-positive sepsis ($P = .034$; OR, 1.8; 95% CI, 1.04-3.2) were significantly higher among preterm infants of multiple pregnancies in comparison to preterm singletons (Table 4). Duration of mechanical ventilation (24 days vs 17 days, $P = .013$) and length of hospital stay (90 days vs 75 days, $P = .001$) were significantly longer among multiples compared to singletons born at a gestational age between 23 + 0 and 28 + 6 weeks.

Subgroup analysis of singletons and multiples born >29 weeks showed that there were 360 singletons and a further 149 multiples born during the study period. In this subgroup, maternal PROM was significantly higher among mothers of preterm singletons (29.7% vs 14.1%, $P < .001$). On the other hand, antenatal steroids uptake (75.2% vs 62.4%, P = .03), delivery by cesarean section (87.9% vs 63.1%, $P < .001$), and rates of assisted conception (47.7% vs 4.4%, $P < .001$) were significantly higher among multiples compared to singletons (Table 5). There were no statistically significant differences in mortality

Table 3. Maternal and infants' characteristics (for infants <29 weeks' gestation).

characteristics	Singleton < 29 weeks (n = 208)	Multiple < 29 weeks (n = 87)	*P*-value
Maternal hypertension (n, %)	35 (16.82)	3 (3.44)	.002
Maternal diabetes (n, %)	32 (15.38)	13 (14.94)	.923
Maternal prolonged rupture of membranes (n, %)	68 (32.69)	21 (24.13)	.144
Complete antenatal steroids (n, %)	125 (60.09)	65 (74.71)	.013
Cesarean section delivery (n, %)	108 (51.92)	67 (77)	<.001
Assisted conception (n, %)	14 (6.73)	46 (52.87)	<.001
Maternal age-years (Mean, SD)	30.2 (6.5)	29.0 (5.8)	.126
Gender (male) (n, %)	95 (45.67)	59 (67.81)	.001
Gestational age (weeks) (Mean, SD)	26.3 (1.7)	25.6 (1.9)	.001
Birthweight (grams), (Mean, SD)	891 (230)	796 (240)	.002

Table 4. Survival and Neonatal Outcomes in Preterm Births <29 weeks': Adjusted and Unadjusted Analyses Between Multiples and Singletons.

Outcome	Singletons <29 weeks (n = 208)	Multiples <29 weeks (n = 87)	Unadjusted *P*-value	Unadjusted OR (95% CI)	Adjusted OR (95% CI), *P*-value
Mortality (n, %)	29 (13.94)	23 (26.43)	.010	2.2 (1.2-4.1)	2.9 (1.4-5.9), .003
Major IVH (n, %)	54 (25.96)	30 (34.48)	.139	1.5 (0.87-2.6)	1.4 (.8-3.5), .269
PVL (n, %)	20 (9.61)	21 (24.13)	.001	2.9 (1.5-5.9)	2.2 (1.03-4.7), .041
ROP (n, %)	33 (15.86)	25 (28.73)	.011	2.1 (1.2-3.9)	2.7 (1.35-5.3), .005
Surgical NEC (n, %)	17 (8.17)	9 (10.34)	.549	1.3 (0.55-3.0)	1.3 (.49-3.2), .638
BPD (n, %)	87 (41.82)	55 (63.21)	.001	2.4 (1.4-3.97)	2.45 (1.4-4.3), .002
Sepsis (n, %)	61 (29.32)	39 (44.82)	.010	1.9 (1.2-3.3)	1.8 (1.04-3.2), .034

Adjustments were made for gender, antenatal steroids, maternal hypertension and mode of delivery.
Abbreviations: IVH, intraventricular hemorrhage; PVL, periventricular leukomalacia; ROP, retinopathy of prematurity; NEC, necrotizing enterocolitis; BPD, bronchopulmonary dysplasia..

Table 5. Maternal and Infants' Characteristics (for Infants Born >29 weeks' Gestation).

Characteristics	Singleton > 29 weeks (n = 360)	Multiple > 29 weeks (n = 149)	*P*-value
Maternal hypertension (n, %)	61 (16.94)	20 (13.42)	.323
Maternal diabetes (n, %)	67 (18.61)	22 (14.76)	.293
Maternal prolonged rupture of membranes (n, %)	107 (29.72)	21 (14.09)	<.001
Complete antenatal steroids (n, %)	224 (62.22)	112 (75.16)	.030
Cesarean section delivery (n, %)	227 (63.05)	131 (87.91)	<.001
Assisted conception (n, %)	16 (4.44)	71 (47.65)	<.001
Maternal age (years) (Mean, SD)	30.7 (6.6)	30.8 (5.3)	.869
Gestational age (weeks) (Mean, SD)	30.7 (1.2)	31.1 (0.94)	.007
Gender (male) (n, %)	221 (61.38)	78 (52.34)	.074
Birthweight (grams) (Mean, SD)	1508 (365)	1530 (293)	.461

and major neonatal morbidities between preterm multiples and singletons born <29 weeks' gestation (Table 6). The duration of mechanical ventilation did not differ between the 2 groups (13.5 vs 11, $P = .43$). The length of hospital stay was however significantly longer in preterm singletons compared to preterm multiples in infants born between 29 + 0 and 32 + 6 weeks (35 vs 30 days, $P = .003$).

Of the multiple pregnancy group infants, 158 (12%) were twins and 78 (5.1%) were of higher multiples. Uptake of antenatal corticosteroids (85.9% vs 69.6%,

Table 6. Survival and Neonatal Outcomes in Preterm Births >29 weeks': Adjusted and Unadjusted Analyses Between Multiples and Singletons.

Outcome	Singletons > 29 weeks (n = 360)	Multiples > 29 weeks (n = 149)	Unadjusted *P*-value	Unadjusted OR (95% CI)	Adjusted OR (95% CI), *P*-value
Mortality (n, %)	16 (4.44)	6 (4)	.833	0.90 (0.35-2.35)	1.14 (.41-3.16), .80
Major IVH (n, %)	23 (6.38)	4 (2.68)	.090	2.47 (0.84-7.28)	1.6 (.52-5.04), .39
PVL (n, %)	26 (7.22)	3 (2)	.036	3.78 (1.12-12.71)	3.2 (.92-10.8), .065
ROP (n, %)	4 (1.11)	1 (0.67)	.647	1.66 (0.18-15.0)	1.07 (.09-10.8), .99
Surgical NEC (n, %)	8 (2.22)	5 (3.35)	.461	0.655 (0.21-2.03)	2.4 (.67-8.2), .18
BPD (n, %)	30 (8.33)	15 (10.06)	.531	0.81 (0.42-1.55)	1.4 (.69-2.7), .35
Sepsis (n, %)	38 (10.55)	18 (12.08)	.671	0.86 (0.47-1.56)	1.3 (.71-2.5), .37

Adjustments were made for antenatal steroids, maternal PROM, and mode of delivery.
Abbreviations: IVH, intraventricular hemorrhage; PVL, periventricular leukomalacia; ROP, retinopathy of prematurity; NEC, necrotizing enterocolitis; BPD, bronchopulmonary dysplasia..

Table 7. Maternal and Infants' Characteristics (Twins vs Higher Multiples).

Characteristics	Twins (n = 158)	Higher multiples (n = 78)	*P*-value
Maternal hypertension (n, %)	19 (12)	4 (5.12)	.093
Maternal diabetes (n, %)	25 (15.82)	10 (12.82)	.542
Maternal prolonged rupture of membranes (n, %)	31 (19.62)	11 (14.1)	.297
Complete antenatal steroids (n, %)	110 (69.62)	67 (85.89)	.003
Cesarean section delivery (n, %)	122 (77.21)	76 (97.43)	<.001
Gender (male) (n, %)	92 (58.22)	45 (57.69)	.937
Gestational age (weeks) (Mean, SD)	29.1 (2.7)	28.9 (3.4)	.652
Birthweight (grams) (Mean, SD)	1298 (441)	1182 (457)	.068

$P = .003$) and delivery by cesarean section (97.4% vs 77.2%, $P < .001$) were significantly higher among infants of the higher multiples compared to twins. There were no statistically significant differences between twins and higher multiples with regard to maternal hypertension, maternal diabetes, and maternal PROM. Gestational age at birth, birthweight, and gender did not differ between the 2 groups (Table 7). There were no statistically significant differences in the adjusted mortality and all major neonatal morbidities between twins and higher multiples (Table 8).

Discussion

This single-center case-control study of 236 multiple and 567 singleton preterm infants born <33 weeks' gestation compared neonatal mortality and major neonatal morbidities between preterm infants of singleton and multiple pregnancies.

Our study showed a significantly higher neonatal mortality rate for preterm's of multiple pregnancies compared to preterm's singletons at gestational age <33 weeks. This finding of higher mortality among preterms of multiple pregnancy is similar to large international databases from Europe[15] and the USA.[16] Nevertheless, other studies have shown no differences in mortality between preterm singletons and multiples.[17,18] On the other hand, contrary to our findings, others have reported lower neonatal mortality among preterm multiples compared to singletons.[19]

With regard to neonatal morbidities, we report a significantly higher incidence of BPD among preterm multiples compared to a singleton at a gestational age between 23 and 28 + 6 weeks. In addition, we also found that preterm multiples born before 29 weeks' gestation required a longer duration of mechanical ventilation, which is likely to reflect the severity of the initial respiratory distress syndrome among these infants. These findings agree with a recent multicenter national study that showed similar adverse short- and long-term respiratory outcomes among preterm multiples.[20] Others have shown lower rates of BPD among twins compared to singleton preterm born between 22- and 31-weeks' gestation despite a higher incidence of RDS among the preterm multiples group.[21] Furthermore, we have found that the risk of severe ROP needing therapy was significantly higher in preterm multiples compared to singletons at gestational age <29 weeks. This risk remained significant after adjustments for differences in birthweight, antenatal steroids

Table 8. Survival and Neonatal Outcomes in Preterm Births (Twins vs Higher Multiples): Adjusted and Unadjusted Analyses Between Twins and Higher Multiples.

Outcome	Twins (n = 158)	Higher multiples (n = 78)	Unadjusted *P*-value	Unadjusted OR (95% CI)	Adjusted OR (95% CI), *P*-value
Mortality (n, %)	17 (10.75)	12 (15.38)	.238	0.65 (0.3-1.4)	1.95 (.79-4.80), .145
Major IVH (n, %)	20 (12.65)	14 (17.94)	.250	1.5 (0.73-3.3)	.69 (.31-1.55), .376
PVL (n, %)	18 (11.39)	6 (7.69)	.400	0.66 (0.52-1.7)	1.7 (.62-4.69), .305
ROP (n, %)	14 (8.86)	12 (15.38)	.119	1.91 (0.84-4.4)	.42 (.16-1.09), .075
Surgical NEC (n, %)	9 (5.69)	5 (6.41)	.799	1.2 (0.37-3.6)	.52 (.14-1.94), .334
BPD (n, %)	49 (31)	21 (26.92)	.576	0.84 (0.46-1.5)	1.28 (.59-2.43), .458
Sepsis (n, %)	35 (22.15)	22 (28.20)	.270	1.42 (0.76-2.6)	.740 (.38-1.45), .381

Abbreviations: IVH, intraventricular hemorrhage; PVL, periventricular leukomalacia; ROP, retinopathy of prematurity; NEC, necrotizing enterocolitis; BPD, bronchopulmonary dysplasia..

use, maternal hypertension and PROM. This suggests that multiple pregnancy increases the risk of severe ROP. Our finding of increased ROP among preterms of multiple gestations agrees with results from other studies.[22] Yet, our finding of higher rates of severe ROP among preterm multiples contrasts data from other studies showing no association between multiple births and the incidence and severity of ROP.[23,24] Interestingly, others have shown a higher risk of severe ROP among singletons preterms in comparison to preterm multiples.[25]

In our study, we report higher rates of PVL on USS/MRI in preterm multiples born at gestational age <29 weeks compared to singletons. Nevertheless, major IVH (grades 3 and 4) was not significantly different between multiples and singletons in the same gestational age group. This finding is similar to a recent large trial that reported a higher incidence of major neurological injury among twin preterm infants compared to preterm singletons.

With regard to LOS, our study has shown that although LOS was longer for multiples born at GA <29 weeks, those preterm multiples born >29 weeks' gestation had a significantly shorter LOS in comparison to singletons of a similar gestation. In a study of late preterm infants of multiple gestations, the LOS for multiples born at 34 weeks but not 35 and 36 weeks was significantly longer for multiples compared to singletons of matched gestation.[26] Indeed, the age range of preterm infants included in that study was not similar to our study, which did not include late preterm infants. Nevertheless, another study from Canada with a similar gestational age profile to our study did not show differences in LOS between multiple and singleton preterm infants.[27]

We report higher rates of culture-positive sepsis in preterm multiples born at GA <29 weeks compared to singletons of a similar gestation. This contradicts a recent study that showed a lower risk of sepsis in preterm multiples. Other studies that examined the sepsis outcome concerning multiple gestations did not find differences between singletons and multiples.[28,29] There were no statistically significant differences in the incidence of surgical NEC between preterm infants of singleton and multiple pregnancies in our study.

Interestingly, the survival and major neonatal morbidities of moderately preterm infants (29-32 weeks gestations) of multiple pregnancies were similar to the singletons born in the same gestational age group. Furthermore, our study has not detected any statistically significant differences in mortality and major morbidities between preterm twins and those preterm infants of higher multiples.

Our study has some strengths and limitations. First, this was a retrospective study, and the data for both mothers and infants were obtained from charts and medical records. Therefore, there was reliance on accurate record keeping and some maternal and infant data were missing for the study population. Secondly, this data reflects the experience of a single institution. Therefore, extrapolations and interpretations of our results must be made with caution. Thirdly, the multiple pregnancy group in our study is a heterogenous group with different subsets of twins, triplets and higher multiples. Given the relatively small number of triplets and higher multiples compared to twins we were unable to study the different sets of multiple pregnancy separately.

This study compared neonatal mortality and major morbidities between singleton infants and multiple births. Our analysis controlled for baseline characteristics and identified variables that could affect the neonatal outcome, such as maternal hypertension, maternal antenatal corticosteroid uptake and mode of delivery. We believe these results are valuable in counseling parents in the case of multiple gestation pregnancies.

Conclusion

We have shown that despite a higher uptake of maternal antenatal corticosteroids therapy, preterm infants of

multiple suffered higher mortality and greater adverse early neonatal morbidities in comparison to preterm singletons of similar gestation. We recommend that such high-risk pregnancies should have close antenatal surveillance, advanced delivery planning and thorough neonatal intensive care in an effort to reduce perinatal morbidity and adverse early neonatal outcomes.

Author Contributions

MA: Contributed to conception and design; Drafted the manuscript; Gave final approval. BA: Drafted the manuscript; Gave final approval. MA: Drafted the manuscript; Gave final approval. AH: Drafted the manuscript; Gave final approval. GA: Gave final approval. SA: Gave final approval. KA: Contributed to analysis; critically revised the manuscript; Gave final approval; Agrees to be accountable for all aspects of work ensuring integrity and accuracy.

Consent for Publication

All of the authors in this study have consented for publication of this study

Availability of Data and Materials

The datasets used and analyzed during this current study is available from the corresponding author on reasonable request.

Declaration of Conflicting Interests

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ORCID iDs

Mohammad Alhasoon https://orcid.org/0000-0002-1945-9263

Kamal Ali https://orcid.org/0000-0002-5516-717X

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