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Neurodevelopmental Outcome Among Multiples and Singletons: A Regional Neonatal Intensive Care Unit's Experience in Turkey

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Objective: The aim of this study was to compare the neurodevelopmental outcome at 12–18 months' corrected age between multiples and singleton preterm infants. *Methods:* We designed a prospective study of preterm infants (≤32 weeks gestation) born and hospitalized in the neonatal intensive care unit between November 2008 and November 2009, whose assessments were performed at 12–18 months' corrected age. Neurodevelopmental impairment was defined as the presence of any one of the following: moderate or severe cerebral palsy, severe bilateral hearing loss or bilateral blindness, mental developmental index score, or psychomotor developmental index score less than 70. Results were compared for both multiples and singleton infants. *Results:* One hundred and fifty-nine multiples and 211 singleton infants were assessed at 12–18 months' corrected age. The neurodevelopmental outcome including all parameters at 12–18 months' corrected age in multiples was not significantly different from singleton preterm infants. *Conclusions:* Multiple gestation in preterm infants is not associated with an increased risk of neurodevelopmental impairment at 12–18 months' corrected age compared with singleton preterm infants. For further information, long term and high participation in neurodevelopmental follow-up and evaluation at pre-school age will be needed.

■ **Keywords:** preterm, multiple birth, twin, neurodevelopmental outcome

Over the past two decades, there has been a regular increase in the incidence of preterm births all over the world, with a range of 7–13% (Hamilton et al., 2006). Most of this increase was due to an increase in multiple gestations because of the use of assisted reproductive medicine (Asztalos et al., 2001; Klebanoff & Keim, 2011; Shinwell, 2002). Currently, 3–4.5% of all births are multiple births (Martin et al., 2008). Among very low birth weight (VLBW) infants, the percentage of multiples increased from 19% to 26% between 1997 and 2002 (Fanaroff et al., 2007). Advances in neonatal intensive care have resulted in improved survival of preterm (≤32 weeks' gestational age) and VLBW infants (≤1,500 g) born from singleton and multiple gestations (Tamaru et al., 2011; Wilson-Castello et al., 2005).

Long-term morbidity of multiples may differ from singletons because of the greater incidence of prematurity and intrauterine growth retardation (IUGR) in multiples (Asztalos et al., 2001; Ingram Cooke, 2010). However, studies about morbidities have shown conflicting results related to outcomes. Some of the studies have emphasized that multiples are at greater risk for long-term problems in their growth and development, including cerebral palsy (CP), cognitive impairment, language delay, and learning disabilities (Blickstein & Keith, 2003;Bonellie et al., 2005; Ingram Cooke, 2010; Suri et al., 2001; Sutcliffe & Derom, 2006; The ESHRE Capri Workshop Group, 2000; Wadhawan et al., 2009). However, other studies have found no significant differences in the incidence of major morbidity between singletons and multiples, and it has been suggested that a higher neonatal adverse outcome rate was not seen when VLBW twins and singleton infants were studied adjusting

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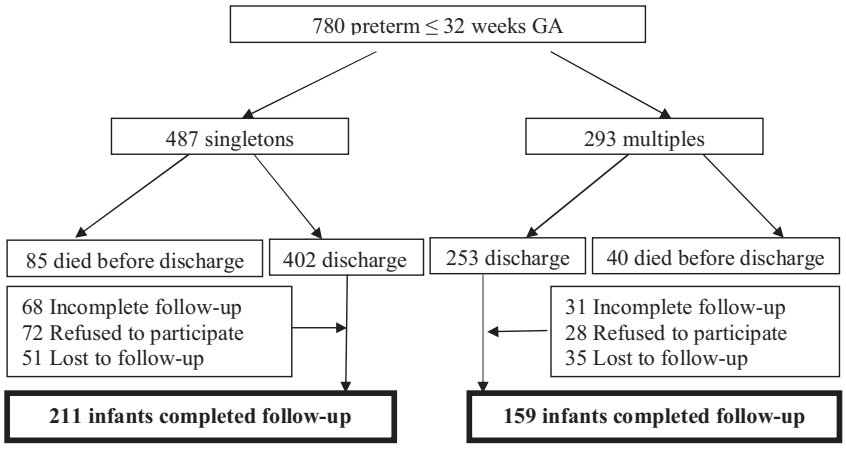

FIGURE 1
Flowchart of the study population.

for birth weight (Asztalos et al., 2001; Donovan et al., 1998; Hajnal et al., 2005).

The objective of our study was to present the neurodevelopmental outcome of a single-center cohort of multiple preterm infants born at ≤32 weeks gestational age in a one-year period in Turkey and compare the neurodevelopmental outcome among those and singleton preterm infants.

Materials and Methods

This was a prospective cohort study of preterm infants (≤32 weeks gestational age) born and hospitalized at Zekai Tahir Burak Maternity Teaching Hospital neonatal intensive care unit (NICU) between November 2008 and November 2009. Infants ($n = 370$) were categorized into two groups: singletons and multiple births. Data on infant perinatal characteristics were collected from the medical records. The infants were followed up to 12–18 months' corrected age (CA) by a neonatologist and a pediatrician.

The outcome of our study was the neurodevelopmental comparison of the two groups. A comprehensive assessment at 12–18 months' CA was performed, consisting of the following evaluation: hearing, vision, neurologic, and development.

Hearing status was obtained by audiological test results. Eye examinations were performed by an ophthalmologist who was expert in assessing VLBW preterm infants. Physical and neurological examinations were performed by a pediatrician, and the presence of CP, bilateral blindness or deafness was recorded. Diagnosis of CP, including diplegia, quadriplegia, and hemiplegia, was based on the presence of hypertonicity, hyperreflexia, and dystonic or spastic movement in the involved extremities. Developmental assessment was performed with the Bayley Scales of Infant Development II for subjects up to 42 months (Bayley, 1993), and the Mental Developmental Index (MDI) and Psychomotor Developmental Index (PDI) were also used. Neurodevelopmental impairment was defined as the presence of any one of the following: CP, bilateral blindness, bilateral deafness, MDI or PDI scores on the Bayley II Scales of Infant Development < 70. All evaluations were performed by certified and experienced examiners who were blinded to both groups.

The study protocol was approved by the local ethical committee and study participation by written consent was obtained from all parents.

Statistical Analysis

Statistical analysis was performed with the SPSS 16.0 statistical package. The χ^2 test was used for categorical variables and a t test was used for continuous variables. A p value of <.05 was considered significant.

Results

A total of 780 preterm infants born at ≤32 weeks gestational age were admitted to our NICU during the study period. Of these, 487 were singletons and 293 were multiples. During the NICU stay, 85 singletons and 40 multiples died. The developmental test could not be performed for 191 singletons and 94 multiples, either because of incomplete follow-up (68 singletons and 31 multiples) or because the parents did not wish to participate (72 singletons and 28 multiples) or because of lost follow-up (51 singletons and 35 multiples). As a result, 211 singletons and 159 multiples were approached for this prospective follow-up study and assessed at 12–18 months' CA (Figure 1).

In the singleton group ($n = 211$), the mean birth weight was 1,200 ± 271 g and 53 (25.1%) infants were ≤1,000 g. Their mean gestational age was 29.0 ± 2.3 weeks and 93 (44.1%) infants were of ≤28 weeks gestation. In the multiples group ($n = 159$), the mean birth weight was 1,311 ± 316 g and 29 (18.2%) infants were ≤1,000 g. Their mean gestational age was 29.8 ± 2.1 weeks and 49 (30.8%) were

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TABLE 1

Perinatal Characteristics of Infants

Variables	Singleton ($N = 211$)	Multiples ($N = 159$)	p
RDS, *n* (%)	113 (53.5%)	71 (44.6)	.1
PDA, *n* (%)	80 (37.9%)	55 (34.6%)	.51
NEC, *n* (%)	23 (10.9%)	15 (9.4%)	.23
Sepsis, *n* (%)	112 (53.1%)	91 (57.2%)	.68
BPD, *n* (%)	33 (15.6%)	13 (8.2%)	.053
IVH Grade 3–4, *n* (%)	4 (1.9%)	5 (3.1%)	.35
Hydrocephalus, *n* (%)	4 (1.9%)	3 (1.9%)	.45
Retinopathy, *n* (%)	99 (46.9%)	61 (38.4%)	<.05

Note: BPD = bronchopulmonary disease; IVH: intraventricular hemorrhage; NEC = necrotizing enterocolitis; PDA = patent ductus arteriosus; RDS = respiratory distress syndrome.

≤28 weeks gestation. The mean birth weight and gestational age were significantly lower in the singletons group than in the multiples ($p < .01$ and $p < .05$).

Table 1 shows perinatal characteristics of the study infants. There were no significant differences in perinatal characteristics such as respiratory distress syndrome (RDS), patent ductus arteriosus (PDA), necrotizing enterocolitis (NEC), sepsis, bronchopulmonary disease (BPD), grade 3–4 intraventricular hemorrhage (IVH), and hydrocephalus between the two groups, except that preterm infants in the singleton group were more likely to have retinopathy than in the multiples group ($p < .05$).

Of the surviving infants, 211 (52.5%) singleton and 159 (62.8%) multiple preterm infants were assessed at a mean age of 16.7 ± 2.1 months. The mean of the MDI scores was 96.1 ± 21.1 in the singleton group and 99.0 ± 20.4 in the multiples group. The mean of the PDI scores was 94.3 ± 21.9 in the singleton group and 89.7 ± 22.7 in the multiples group. There were no significant differences between groups for mean MDI and PDI scores ($p = .58$ and .079, respectively).

The neurosensory outcomes of the singletons and multiples at 12–18 months' CA are shown in Table 2. Cerebral palsy was present in 7 (3.3%) of 211 singletons and in 7 (4.4%) of 159 multiples; no significant difference was found between the groups ($p = .60$) for CP rate. In our cohort, there was no infant who was diagnosed as blind or deaf. Fifteen percent of singletons and 8.2% of multiples had MDI scores <70. Twenty percent of singletons and 18.2% of multiples had PDI scores <70. Among those with MDI scores and PDI scores <70, the number of infants did not differ in singletons compared to multiples ($p = .089$, $p = .067$). The proportion of patients who had neurodevelopmental impairment at 12–18 months' CA (CP, deafness or blindness, MDI < 70, PDI < 70) was 26.5% in singletons and 18.2% in multiples; the difference was not statistically significant ($p = .06$).

Discussion

Multiple gestation is associated with a higher prematurity rate and a higher incidence of VLBW. In many of the studies, infants born from multiple gestation have been shown to have a higher incidence of adverse outcomes, including an increase in the prevalence of CP and cognitive impairment (Blickstein, 2002; Blickstein & Keith, 2003; Doyle, 1996; Ingram Cooke, 2010; Martin & Park, 1999; Mazhar et al., 2002; The ESHRE Capri Workshop Group, 2000; Wadhawan et al., 2009).

In our study of a cohort of multiples and singletons born at ≤32 weeks gestational age at a big maternity center in Turkey over a one-year period, we examined the outcomes of the group at 12–18 months' CA. Our results showed that for CP and neurodevelopmental impairment, there were no significant differences between singletons and multiples ($p = .60$ and .06); that is, multiple birth did not influence neurodevelopmental outcome in the preterm infants born at ≤32 weeks gestational age.

Our findings are consistent with studies published by the following authors, who compared the outcomes of singletons and multiples preterm infants. Donovan et al. (1998) examined the outcomes of singletons and multiples born at <28 weeks gestational age and with birth weights of 401–1,500 g. The authors found no significant differences in the incidence of major morbidity and mortality. They suggested that a higher neonatal adverse outcome rate was not seen when VLBW twins and singleton infants were studied adjusting for birth weight using the National Institute of Child Health and Human Development

TABLE 2

Long-Term Outcomes of Study Infants at 12–18 Months Corrected Age

	Singleton		Multiples ($n = 159$)			
Variables	All singletons ($n = 211$)	≤1,000 g singletons ($n = 53$)	All multiples ($n = 159$)	≤1,000 g multiples ($n = 29$)	p	
CP, *n* (%)	7 (3.3%)	5 (9.4%)	7 (4.4%)	2 (6.8)	.60	.058
Blind, *n* (%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0	0
Deaf, *n* (%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0	0
MDI < 70, *n* (%)	32 (15.2%)	9 (16.9%)	13 (8.2%)	4 (13.7%)	.089	.73
PDI < 70, *n* (%)	42 (19.9%)	17 (32.1%)	29 (18.2%)	10 (34.4%)	.067	.74
MDI + PDI < 70, *n* (%)	19 (9.0%)	8 (15.1%)	11 (6.9%)	6 (20.6%)	.46	.55
Neurodevelopmental impairment, *n* (%)	56 (26.5%)	20 (37.7%)	29 (18.2%)	12 (41.3%)	.06	.65

Note: CP = cerebral palsy; MDI = Mental Developmental Index; PDI = Psychomotor Developmental Index.

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(NICHD) database (Donovan et al., 1998). Asztalos et al. (2001) evaluated 52 twins and 101 singleton infants born between 24 and 30 weeks gestational age. Their primary outcome was death or the presence of a severe neurodevelopmental deficit at 18–24 months' CA. The incidence of death or severe disability was 29.7% in twins versus 22.8% in singletons ($p = .337$). They reported that severe neurodevelopmental morbidity was not significantly higher in twins than in singletons in their cohort (Asztalos et al., 2001). Hajnal et al. (2005) examined the neurodevelopmental outcome of multiples and singletons born <1250 g at two years' CA. The Bayley Scales of Infant Development and a standardized neurologic examination were administered. They found that the neurodevelopmental outcome of multiple births was similar to that of singletons (Hajnal et al., 2005).

On the contrary, there are some studies indicating differences between the multiplets and singletons in long-term outcome. Wadhawan et al. (2009) conducted a retrospective study to evaluate the incidence of neurodevelopmental impairment at 18–22 months' CA between twins and singletons of extremely low birth weight (ELBW). The cohort of infants consisted of 7,630 singleton infants and 1,376 twins. The authors indicated that twin gestation in ELBW infants was associated with an independent, increased risk of neurodevelopmental impairment at 18–22 months' CA compared with singleton-gestation infants (Wadhawan et al., 2009). In another study of Wadhawan et al., ELBW (birth weight 401–1,000 g) multiple births born were assessed for neurodevelopmental impairment at 18–22 months' CA. Their results showed that the risk of neurodevelopmental impairment was increased in triplets or higher order multiples when compared with singletons (adjusted odds ratio: 1.7; Wadhawan et al., 2011).

In our study, it was shown that multiple births did not influence neurodevelopmental outcome in preterm ≤32 weeks gestational age. However, we think that if the groups were equal in variables such as BW and GA, the developmental results may have been influenced in favor of singletons. It should be taken into consideration that neurological handicaps and mental retardation may become prominent several years after birth, so an assessment at the age of 5–7 years is preferable.

Although this is the first long-term comparison between singletons and multiples in Turkey, our study had few limitations. First, our study was a small cohort of VLBW patients and, second, it had low response rate of follow-up (47.4%). This may raise a concern about the possibility of a non-response bias.

In conclusion, in our population of preterm infants at ≤32 weeks gestational age, there were no significant differences between multiples and singleton infants for neurodevelopmental outcome at 12–18 months' CA. We suggest that a longer and more participatory follow-up and assessment at pre-school age is undertaken.

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