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Original article

Comparison of 24 months neurodevelopmental outcome in twins and singletons ≤ 34 weeks gestation at birth

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Abstract

The aim of this study was to screen neurodevelopmental impairment of preterm twins born at less than 34 weeks of gestation, compare them with the outcome of preterm singletons, and to determine potential neonatal factors adversely related to motor and cognitive outcome.

Twins of 25-34 weeks gestation were included in the study. In total, 46 twins were matched with 46 singletons and were followed prospectively to 24 months corrected age. Obstetrical and neonatal data were recorded. All infants were assessed using the Bayley Scales of Infant and Toddler Development III

For all morbidities, a significant difference could not be demonstrated.

At 24 month follow up there was no significant difference in the cognitive outcome for the twins compared to singletons [98.6 (± 10.4) vs 97.8 (± 9.7), respectively]. There was also no significant difference in the motor outcome for the twins compared to singletons [94.8 (± 12.4) vs 98.1 (± 9.6.), respectively].

For the twins, we found a link between pre-eclampsia and abnormal cognitive ($p = 0.012$) and motor ($p = 0.030$) results.

With the number of twins steadily increasing, close developmental monitoring and probably early intervention services are needed to determine future directions for research.

Keywords

Infant, preterm, twins, singleton, neurodevelopmental outcome, Bayley III.

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Introduction

There has been growing concern in recent years about the escalating multiple birth rate arising from the increasing use of assisted reproduction procedures [1]. Multiple fetus pregnancies account for an increasing percentage of Low Birth Weight infants (LBW) and preterm delivery with its associated increase in perinatal mortality and morbidity [2, 3]. Preterm, LBW infants are at higher risk of infant mortality and neurodevelopmental difficulties [4]. Disabilities can be isolated or associated with cerebral palsy, attention deficit disorder, and cognitive defect [5]. Isolated cognitive defects are often misdiagnosed except when a young child has had early neurodevelopmental screening [5, 6].

Although the hazards of delivery of twins are now largely avoided through wider use of caesarean section [7], concern remains that twins have higher short and long term morbidity when compared with singletons. Twin pregnancies are associated with obstetrical and neonatal risks. Neurological complications are more frequent in twins [8, 9]. In addition to preterm birth and low BW, factors likely to be affecting these outcomes in twins include the greater likelihood of intrauterine growth restriction, zygosity and even the presence of a same age sibling in the family group during childhood [10].

Population based studies from large databases have shown a fivefold higher risk of cerebral palsy (CP) in twins as compared with CP rates in singletons [11]. Although prematurity and low birth weight (BW) play a role, they may not account entirely for the increased risk [12]. A study from Child Health and Human Development (NICHD) network reported that the short-term neonatal outcomes of very low BW twins (BW: < 1500 g) are similar to singleton infants in the same BW category [13]. Another study [14] showed similar results for short-term morbidities in very LBW twins and singletons.

Moreover, no differences persisted in the incidences of most neonatal complications, and the multiples achieved most milestones at the same time as the singletons [15]. A bimodal distribution was described for CP rates with similar rates in twins and singletons in those born at less than 32 weeks gestation, but progressively higher rates of CP in twins as the gestation moved towards term [16].

With the increasing numbers of smaller and immature infants of twin pregnancies, it is important to know whether the advances in obstetrical management and subsequent neonatal care of the very low BW twin infant are leading to improved neurodevelopmental outcomes than previously reported.

The aim of this study was therefore to screen neurodevelopmental impairment of preterm twins born at less than 34 weeks of gestation, compare them with the outcome of preterm singletons, and to determine potential neonatal factors adversely related to motor and cognitive outcome.

Methods

Participants

The study was approved by hospital's ethical committee and informed consent was given by the parents. Twins of 25-34 weeks gestation, born between December 2008 and June 2010 and admitted to our level III Neonatal Intensive Care Unit, were included. Infants with chromosomal anomalies and major genetics syndromes were excluded from the study. Each twin was matched with a singleton infant of the same gender and within 1 week of the same GA at birth.

In total, 46 twins were matched with 46 singletons and were followed prospectively to 24 months corrected age.

Demographics

Obstetrical and neonatal data were recorded prospectively. Maternal data included the following variables: way of conception, pregnancy induced hypertention, premature rupture of membranes, intrauterine growth retardation, steroids. Neonatal data included: GA, BW, Apgar scores, small for GA (SGA), need for surfactant, respiratory distress syndrome (RDS), patent ductus arteriosus (PDA), sepsis, intraventricular hemorrhage (IVH), periventricular leukomalacia (PVL), necrotizing enterocolitis (NEC), bronchopulmonary dysplasia (BPD), days on O2, days on mechanical ventilation (MV), retinopathy of prematurity [17] and days of hospitalization.

Clinical diagnoses made according to standard definitions. GA was determined by either date of last menstrual period or early ultrasound (< 20 weeks gestation). RDS requiring oxygen therapy is present beyond the first 24 hours of life, may require surfactant, and has typical radiographic signs [18]. PDA was defined as a clinical murmur, hyperdynamic precordium and peripheral pulses,

widened pulse pressures, hemodynamic finding on 2-D echocardiography, may require treatment or ligation. IVH confirmed by cranial ultrasound: grade 1 involving germinal matrix hemorrhage, grade 2 IVH involving 10-50% of ventricular are, grade 3 involving IVH occupying > 50% of the ventricular area, grade 4 involving hemorrhagic involvement of adjacent white matter [19]. PVL confirmed by cranial ultrasound: evidence of white matter injury [19]. NEC was defined as clinical gastrointestinal disturbances associated with pneumatosis intestinalis on abdominal radiography [20]. ROP was defined on the basis of the criteria of the Committee for the Classification of Retinopathy of Prematurity [21]. Sepsis Infection was confirmed by positive blood culture.

In advance, factors associated with cognitive and motor scores ($p < 0.20$) were selected for inclusion in the generalized linear model. For single preterm group, the way of conception, intrauterine growth restriction, and patent ductus arteriosus were factors associated with both cognitive and motor outcomes and therefore selected for inclusion in the generalized linear model. In the twin group, for the cognitive outcome, factors like pre-eclapsia, diavitis, periventricular leukomalacia and retinopathy of prematurity were included in the model. In the twin group, for the motor outcome, factors like pre-eclapsia, diavitis, necrotizing enterocolitis, and retinopathy of prematurity were included in the model.

Neurodevelopmental assessment

A comprehensive 24 months' corrected age evaluation for survivors consisted of the following evaluations: neurologic, hearing, vision, and development. A neurologic examination based on the Hammersmith Infant Neurological Examination was administered [22, 23]. A severe visual deficit was defined as vision < 20/200 in one or both eyes. A severe hearing deficit was defined as the need for amplification or insertion of cochlear implants. A severe motor deficit was defined as the presence of abnormal tone preventing ambulation consistent with cerebral palsy. Severe cognitive deficit was based on a score of less than 2 standard deviations from the mean as determined by the test. One certified individual conducted the Bayley III assessments. One individual conducted the cognitive and motor assessments from Bayley III test. The presence of abnormal tone was determined by the neonatologist in the follow up department.

Analysis

The data were analyzed using the SPSS 17.0 statistical software. Descriptive statistics (means, standard deviations, and proportions) were used to describe the two groups of infants. The relation between categorical variables was investigated using x^2 or Fisher exact tests. One way Anova was used for correlating neonatal factors with outcome. The generalized linear model was used for determining potential risk factors associated with cognitive and motor scores ($p < 0.20$) in twin and singleton groups. A difference in statistical significance was considered if P value was < .05.

Results

From December 1, 2008 to June 30, 2010, 34 sets of twins were admitted to the NICU. Of these, 2 sets were not followed (lost to follow-up). This left a total of 32 sets of twins. A total of 46 twins were followed prospectively to 24 months corrected age. These infants were matched with 46 singleton controls. Regarding chorionicity, 2.3% were monochorionic, 97.7% were dichorionic. Twin-to-twin transfusion syndrome occurred in 2.3% (3 infants) of the twins. In terms of gender, 23 infants were male and 22 were female. The average GA for the twin and singleton groups was 30.6 and 30.7 weeks, respectively.

Obstetrical outcomes

The singleton and twin pregnancies were compared with respect to the more common maternal morbidities as outlined in **Table 1**. In this

Table 1. Maternal morbidities.

	Twins (n = 46) %	Singletons (n = 46) %	p-value
IVF[a], n (%)	35 (76.0)	9 (19.5)	0.0001
PIH[b], n (%)	13 (28.2)	5 (10.8)	0.04
Chorioamnionitis, n (%)	3 (6.5)	2 (4.3)	ns
Tocolysis, n (%)	25 (54.3)	21 (45.6)	ns
PROM[c], n (%)	3 (6.5)	7 (15.2)	ns
IUGR[d], n (%)	18 (39.1)	7 (15.2)	0.025
Steroids, n (%)	39 (84.7)	28 (60.8)	0.028

[a]IVF: In-vitro Fertilization, [b]PIH: Pregnancy-induced Hypertension, [c]PROM: Premature Rupture of Membranes, [d]IUGR: Intrauterine Growth Retardation.

study, there was a statistically significant difference in the administration of antenatal steroids to mothers of twin pregnancies (p = 0.0028). Thirty-five twins (76%) versus 9 (19.5%) singletons were conceived through IVF procedures. Otherwise, twin pregnancies were not seen as having significantly more morbidity.

Neonatal morbidity

Table 2 depicts short term outcomes of major neonatal morbidity between twins and singletons groups. For all morbidities, a significant difference could not be demonstrated. It should be noted that for most of the morbidities, there was a trend towards higher incidence in the twins group as compared to the singletons.

Table 2. Neonatal characteristics.

	Twins (n = 46)	Singletons (n = 46)	p-value
GA[a], (wks[b] ± SD)	30.6 (± 1.73)	30.7 (± 1.81)	ns
BW[c], (gm[d] ± SD)	1313.77 (± 359.08)	1463.21 (± 305.66)	0.004
Sex (male), n (%)	22 (47.8)	23 (50.0)	ns
Mode of delivery (CS), n (%)	43 (93.4)	42 (91.3)	ns
Apgar Score 5 min (± SD)	8.3 (± 1.07)	8.4 (± 0.63)	ns
SGA[e], n (%)	32 (69.5)	25 (54.3)	ns
Use of surfactant, n (%)	31 (67.3)	27 (58.6)	ns
RDS[f], n (%)	35 (76.0)	29 (63.0)	ns
PDA[g], n (%)	4 (8.6)	2 (4.3)	ns
Sepsis, n (%)	9 (19.5)	6 (13.0)	ns
IVH[h], I-II, n (%)	7 (15.2)	6 (13.0)	ns
IVH[h], III-IV, n(%)	5 (10.8)	4 (8.6)	ns
PVL[i], n (%)	5 (10.8)	2 (4.3)	ns
NEC[j], n (%)	3 (6.5)	1 (2.1)	ns
BPD[k], n (%)	4 (8.6)	0 (0)	ns
Days O_2, (± SD)	7.9 (± 20.57)	3.5 (± 8.50)	ns
Days MV[l], (± SD)	3.9 (± 9.83)	1.5 (± 4.91)	ns
Hospital stay, (days ± SD)	40.73 (± 18.5)	37.02 (± 63.75)	ns

[a]GA: Gestational Age, [b]wks: weeks, [c]BW: Birth Weight, [d]gm: grammars, [e]SGA: Small for Gestational Age, [f]RDS: Respiratory Distress Syndrome, [g]PDA: Patent Ductus Arteriosus, [h]IVH: Intraventricular hemorrhage, [i]PVL: Periventricular Leucomalacia, [j]NEC: Necrotizing Enterocolitis, [k]BPD: Bronchopulmonary Dysplasia, [l]MV: Mechanical Ventilation.

Neurodevelopmental outcome

Both groups were essentially very similar in the distribution of severe deficits (**Table 3**). **Table 4** shows the 24 month follow up outcomes of study infants. For the twins and singletons we did not find a link between abnormal results of the Bayley III scores (Fine-Gross Motor and Cognitive scales). Although not found to be significant, there was a trend in the twins group for a higher incidence in early intervention services and mostly on physiotherapy treatment (65.2% in the twins group versus 50.0% in the singleton controls).

The primary outcome for this study was the motor and cognitive assessment at 24 months corrected age. There was no significant difference concerning the composite score in the Fine and Gross motor scales of the Bayley III test for the twins compared to singletons [94.8 (± 12.4) vs 98.1 (± 9.6.), respectively]. It should be noted that there was a trend towards higher motor scores in the twins group.

There was also no significant difference concerning the composite score in the cognitive scale of the Bayley III test for the twins compared to singletons [98.6 (± 10.4) vs 97.8 (± 9.7), respectively].

Furthermore, since there is a substantial difference between the 25 and 34 weeks of gestation, we divided the infants in two groups: group A (25-30 weeks of gestation) and group B (30-34 weeks of gestation) and compared the neurodevelopmental outcome in each group. **Table 5** shows the 24 month

Table 3. Distribution of neurodevelopmental morbidity.

	Twins (n = 46)	Singletons (n = 46)	p-value
Vision impairment, n (%)	1 (2.1)	0 (0)	ns
Hearing impairment, n (%)	0 (0)	0 (0)	ns
Cerebral Palsy, n (%)	3 (6.5)	2 (4.3)	ns
Cognitive impairment, n (%)	1 (2.1)	1 (2.1)	ns

Table 4. Neurodevelopmental outcome in study infants.

Bayley III at 24 months	Twins (n = 46)	Singletons (n = 46)	p-value
Fine Gross Motor, Scale mean (± SD)	94.8 (± 12.4)	98.1 (± 9.6)	ns
Cognitive Scale, mean (± SD)	98.6 (± 10.4)	97.8 (± 9.7)	ns

Table 5. Neurodevelopmental outcome in study groups.

	Group A 25-30 w			Group B 30-34 w		
Bayley III at 24 months	**Twins (n = 18)**	**Singletons (n = 18)**	**p-value**	**Twins (n = 28)**	**Singletons (n = 28)**	**p-value**
Fine Gross Motor, Scale mean (± SD)	93.0 (± 12.3)	98.0 (± 11.9)	ns	95.6 (± 12.7)	99.1 (± 8.9)	ns
Cognitive Scale, mean (± SD)	100.0 (± 5.4)	97.0 (± 10.3)	ns	97.5 (± 12.6)	98.1 (± 9.7)	ns

follow up outcomes of study groups. There was no significant difference concerning the composite score in the Cognitive, Fine and Gross motor scales of the Bayley III test for the twins compared to singletons both in group A and group B.

For the singletons we found a link, but not statistically significant, between abnormal cognitive results of the Bayley III scores and way of conception ($p = 0.067$), and PDA ($p = 0.099$). For the twins, we found a link between abnormal cognitive ($p = 0.012$), and motor ($p = 0.030$) results of the Bayley III scores with pre-eclampsia.

Discussion

The incidence of twin pregnancies has increased substantially [24, 25]. Current literature focuses on short-term outcomes such as perinatal and/or neonatal morbidity. Twin pregnancies have been reported to have increased morbidity, which can threaten the pregnancy and the fetuses. In our study, for all morbidities, a significant difference could not be demonstrated. Similarly, in a case-control study [26] comparing twins with gestation-matched controls was showed no difference in morbidity, length of stay, or cost of care between twins and gestation-matched singletons of < 34 weeks' gestation.

On the other hand, little is currently available to describe long term outcome of major neurodevelopmental parameters unless it is part of a larger scale study where twins are identified as a risk factor. Although there have been studies looking at aspects of outcome of twin pregnancies, long term follow-up specifically looking at twins compared to singletons has been limited [27].

The findings of the present study showed that there was no statistical difference between two groups in cognitive and motor outcomes at 24 months corrected age. Similar results based on neurodevelopmental outcomes have been reported [4]. In our study, there was a trend in the twins group for higher incidence in early intervention services and therefore benefited from the physiotherapy treatment compared to the singleton population. In our department physiotherapy based on Neurodevelopmental Treatment (NDT) is introduced very early (from 40 weeks postmenstrual age to three months corrected age) and this might explain the trend towards high motor scores in the twins group. However, a study by the EPIPAGE study group [28] reported the same results between singletons and children from multiple pregnancies (twins and triplets).

Moreover, it has been reported that 94% of women attending a fertility clinic preferred twins as their treatment outcome. Parents of twins conceived by assisted reproduction may be more involved with their twin children than are parents who conceived their infants naturally and unexpectedly [17]. This could explain the scores in motor and cognitive scales of Bayley III test achieved by the twin group.

Cognitive difficulties are also presenting as an adverse outcome that has long-term impact. Recent studies have presented incidences as high as 25% in their study population [29]. In this study, cognitive outcome did not seem to contribute to the overall combined neurodevelopmental difficulties at 24 months corrected age regardless of grouping. Since the developmental figures do not compare favorably with the literature, there is still a need for concern.

BW has been shown to be one of the most important factors affecting perinatal mortality and is viewed as an important determinant of infant and long-term morbidity [2, 30]. Twins are often reported to be of lower BW as compared to singletons of comparable GA [27]. In this study, the twins group was slightly heavier but the incidence of infants with BWs < 10^{th} percentile was equal between twins and singletons.

Cerebral palsy has been and remains a primary concern of neurodevelopmental difficulty in the preterm population. Studies have frequently associated a higher risk of cerebral palsy in twins and especially in monochorionic twins [12, 31-33]. Our results suggested no significant

difference in CP rates between singletons (4.3%) and twins (6.5%). Similar results based on neurodevelopmental outcomes at 1year corrected age have been reported [27].

The advantages of antenatal corticosteroid treatment for preterm singleton fetuses are well-established, but doubts about the effectiveness in twins have been raised. In our study, although there was a statistically significant difference in the administration of antenatal steroids to twin pregnancies, no significant differences in major neonatal morbidity and mortality were shown.

In the singleton group, none of the potential neonatal factors related adversely to motor and cognitive outcomes. On the contrary, in the twin group, pre-eclampsia was adversely related both to motor and cognitive outcomes. According to a meta-analysis [34], researchers noted that risk for pre-eclampsia was significantly increased in women undergoing assisted reproductive technologies. Our study population consisted of twins conceived mostly by IVF procedures.

This is not a randomized controlled trial; therefore it is open to selection bias. This study took into account only those twins and singletons admitted to the study site.

Conclusion

Although there are some encouraging aspects of this study, there is still need for concern about the future of small, immature twins, which require close developmental monitoring and probably early intervention services.

Declaration of interest

The authors do not have any financial or personal relationships with others that could have inappropriately influenced this work.

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