

## Comparison of Mortality and Morbidity in Multiple versus Singleton Very Low Birth Weight Infants in A Neonatal Intensive Care Unit

Multiple births in Korea have been increased recently as a consequence of increased infertility due to advancing maternal age at first birth, and increased use of assisted reproductive technology. Multiples suffer higher mortality and morbidity than singletons. However, it is not clear whether preterm multiple very low birth weight infants (VLBWI) suffer higher mortality and morbidity than comparable singletons. We evaluated 266 singleton and 113 multiple VLBWI to determine whether mortality and morbidity in multiple VLBWI were higher than those in comparable singletons. The rate of in vitro fertilization and cesarean section were significantly higher in multiples than singletons. The total and the adjusted mortality with gestational age and birth weight were not significantly different between the two groups. Maternal age and the incidence of respiratory distress syndrome, patent ductus arteriosus, bronchopulmonary dysplasia, intracranial hemorrhage (grade  $\geq 3$ ), cystic periventricular leukomalacia, and retinopathy of prematurity (stage  $\geq 3$ ) were not significantly different between the two groups, and the incidence of abnormal brainstem auditory evoked potential was higher among the singletons. These results suggest that multiple VLBWI do not suffer higher mortality or morbidity than comparable singletons.

Key Words : Multiple Birth Offspring; Infant; Very Low Birth Weight; Mortality; Morbidity

Kye Hyang Lee, Soo Jung Hwang,  
Sung Hye Kim, Soo Hyun Lee,  
Dong Kil Yu, Jong Hee Hwang,  
Chang Won Choi, Jae Won Shim\*,  
Yun Sil Chang, Won Soon Park

Department of Pediatrics, Samsung Medical Center,  
Kangbuk Samsung Hospital\*, Sungkyunkwan University  
School of Medicine, Seoul, Korea

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### Address for correspondence

Won Soon Park, M.D.  
Department of Pediatrics, Samsung Medical Center,  
50 Ilwon-dong, Kangnam-gu, Seoul 135-710, Korea  
Tel : +82.2-3410-3523, Fax : +82.2-3410-0043  
E-mail : wspark@smc.samsung.co.kr

### INTRODUCTION

Multiple births have become a focus of perinatal interest, especially because of the dramatic increase in frequency in recent years during the 1980s and 1990s (1), and the situation is similar also in Korea (2). The increased rate of multiple births might be attributable to advancing maternal age at first birth and increased incidence of infertility, and therefore, to the greater use of assisted reproductive technology including ovarian stimulation and in vitro fertilization (3).

Historically, multiples have been considered to be at increased risk for perinatal mortality and morbidity than singletons, mainly because of higher rate of preterm birth and low birth weight (3). Some authors noted multiple very low birth weight infant (VLBWI) had higher mortality and morbidity than singleton (3-10), while others found no differences between two groups (11-15). So, it is not clear whether multiple VLBWI suffer higher mortality and morbidity than comparable singletons. We, therefore, conducted this retrospective study to determine whether mortality and morbidity in multiple VLBWI were higher than those in comparable singletons.

### MATERIALS AND METHODS

In this retrospective study, we reviewed the medical records

of all live born preterm VLBWI with birth weight less than 1,500 g, who were admitted to the neonatal intensive care unit of Samsung Medical Center from October 1995 to December 2001. Live born singletons were included in singleton group, and live born twin, triplets, and survivors whose co-twins were stillborn were included in multiple births group. Four stillborn multiple infants (one anencephaly, one acardia, two twin to twin transfusion), and one selective abortion due to alleged Down syndrome in triplets were excluded from analysis.

Neonatal medical records were reviewed to determine the birth weights, gestational age, mortality and morbidity of the infants. We compared the outcomes from the measurements of mortality and major morbidity, duration of mechanical ventilation, and length of hospitalization between the singletons and the multiples. We also compared perinatal mortality and major morbidity between the first born and the more than second born among multiples.

Gestational age in weeks was based on either the date of the last menstrual period, the known date of conception, fetal ultrasound, or the Ballard scoring system. Small for gestational age (SGA) was defined as a birth weight less than tenth percentile for gestational age plotted on the Lubchenco intrauterine growth charts. Respiratory distress syndrome (RDS) was diagnosed based on the clinical symptoms of respiratory difficulty and compatible chest radiography findings of the diffuse reticulogranular pattern with air bronchograms and decreased

lung volume. Patent ductus arteriosus (PDA) was confirmed in all infants by the echocardiograms demonstrating the left-to-right or the bi-directional blood flow through the ductus arteriosus. Bronchopulmonary dysplasia (BPD) was diagnosed by the presence of chronic respiratory distress, with oxygen required, beyond corrected gestational age of 36 weeks while accompanied by characteristic chest roentgenographic findings. Intraventricular hemorrhage (IVH) was diagnosed with cranial ultrasound examination, and the degree of hemorrhage was graded according to the classification of Papille et al. (16). Cystic periventricular leukomalacia (PVL) was diagnosed by cranial ultrasonographic findings as cystic lesions in the periventricular white matter. The stage of retinopathy of prematurity (ROP) was defined by using the international classification of ROP as a spectrum of finding, including abnormal vasoproliferation and tortuosity, retinal ridge formation, scarring, and retinal detachment. Abnormal brainstem auditory evoked potential (BAEP) was defined as hearing threshold over 45 dB done beyond corrected age of 40 weeks.

### Statistical Analysis

Differences were examined for statistical significance with use of Wilcoxon rank sum test for continuous variables and of the chi-square for discrete variables, and through Fisher's exact test when necessary. *p* value <0.05 were considered significant.

**Table 1.** Demographic findings from the multiple and the singleton very low birth weight infants (VLBWI)

	Singleton (n=266)	Multiple (n=113)
Maternal age (yrs, M±SD)	30±4	31±4
Maternal DM	4 (1.5%)	8 (7.1%)*
Maternal PIH	73 (27.4%)*	8 (7.1%)
Pathologic chorioamnionitis	74 (27.8%)*	13 (11.5%)
Birth weight (g, M±SD)	1,097±250	1,182±226*
Gestational age (weeks, M±SD)	28.9±2.7	29.6±2.4*
Male	135 (50.8%)	60 (53.1%)
IVF	8 (3.0%)	49 (43.4%)*
Cesarean section	164 (61.7%)	95 (84.1%)*
Apgar score (1 min, M±SD)	4.1±2.3	4.3±2.2
Apgar score (5 min, M±SD)	6.3±1.9	6.5±1.6

\**p*-value <0.05. DM, diabetes mellitus; PIH, pregnancy-induced hypertension; IVF, in vitro fertilization.

**Table 2.** Birth weights and mortality according to gestational age

Gestational age (wk)		≤23	24-25	26-27	28-29	≥30	Total
Total (No.)	S	5 (1.9%)	29 (10.9%)	68 (25.6%)	77 (28.9%)	87 (32.7%)	266 (100%)
	M	0 (0.0%)	7 (6.2%)	20 (17.7%)	36 (31.9%)	50 (44.2%)	113 (100%)
Bwt (g, M±SD)	S	650±90	779±156	985±163	1,132±222	1,286±166	1,097±250
	M		840±125	957±137	1,170±200	1,329±138	1,182±226
Mortality (%)	S	3 (60.0%)	12 (41.4%)	13 (19.1%)	9 (11.7%)	4 (4.6%)	41 (15.4%)
	M		3 (42.9%)	4 (20.0%)	1 (2.8%)	2 (4.0%)	10 (8.8%)

Bwt, birth weight; S, singleton very low birth weight infants; M, multiple very low birth weight infants.

## RESULTS

### Demographic Findings

Among the 379 VLBW preterm infants during the study period, 113 (30%) were multiples and 266 (70%) were singletons. Among the multiples, 7 were triplets and 106 were twins.

Birth weight and gestational age were significantly higher in multiples than in singletons (Table 1). When comparing mean values of birth weight and gestational age that exclude data for the gestation of VLBWI ≤23 weeks, there were no differences in birth weight (1,106±244 g vs. 1,182±226 g, respectively) and gestational age (29.0±2.6 weeks vs. 29.4±2.1 weeks, respectively) between singleton and multiple VLBWI. The birth weight adjusted with gestational age also was not significantly different between the two groups except in ≤23 weeks subgroups (Table 2). The rate of in vitro fertilization and cesarean section, and the incidence of maternal diabetes mellitus (DM) were significantly higher among the multiples (Table 1). The incidence of maternal pregnancy induced hypertension (PIH) and pathologic chorioamnionitis were significantly higher among the singletons. There were no significant differences in maternal age, antenatal use of steroid, antibiotics, and MgSO<sub>4</sub>, duration of premature rupture of membrane (PROM), and 1 and 5 min Apgar scores between the two groups.

### Mortality in VLBW

The mortality in total and the mortality adjusted with the gestational age ≥24 weeks were not significantly different between the two groups (Table 2).

### Morbidity in VLBW

There were no significant differences in the incidence of major morbidities such as SGA, RDS, PDA, BPD, IVH, cystic PVL, and ROP, length of hospitalization, and days of ventilator and total parenteral nutrition (TPN) support between the two groups (Table 3). The rate of abnormal BAEP was significantly higher among the singletons.

**Table 3.** Morbidity among the multiple and the singleton very low birth weight infants (VLBWI)

	Singleton (n=266)	Multiple (n=113)
SGA	48 (18.0%)	19 (16.8%)
RDS	148 (55.6%)	67 (59.3%)
PDA	159 (59.8%)	76 (67.3%)
BPD	81 (30.5%)	28 (24.8%)
Ventilator (days, M±SD)	23.8±33.6	17.9±30.9
TPN (days, M±SD)	21.0±23.9	16.9±15.9
IVH (grade ≥3)	17 (6.4%)	7 (6.2%)
ROP (stage ≥3)	36 (13.5%)	19 (16.8%)
Cystic PVL	13 (4.9%)	8 (7.1%)
Abnormal BAEP	51 (19.1%)*	15 (13.2%)
Hospital stay (days, M±SD)	63.6±40.0	61.1±34.6

\**p*-value <0.05. SGA, small for gestational age; RDS, respiratory distress syndrome; PDA, patent ductus arteriosus; BPD, bronchopulmonary dysplasia; TPN, total parenteral nutrition; IVH, intraventricular hemorrhage; ROP, retinopathy of prematurity; PVL, periventricular leukomalacia; BAEP, brainstem auditory evoked potential.

#### Mortality and Morbidity according to Birth Order within the Multiples

Of the 111 multiples, 54 were the first born and 57 were more than the second born. There were no significant differences in mortality and other major morbidity between the first and more than the second born subgroups within the multiples (Table 4).

## DISCUSSION

The incidence of multiple births has been increased dramatically and also consistently during last two decades from the 1970s to 1990s in all over the world. Twinning rate was increased by 35.8% in the United States, 58.3% in Israel, and 62.5% in Sweden between 1975 and 1995 (1). In Korea, Kang et al. also reported that twinning rate was increased by 36% from 1989 to 1994 (2). The increased incidence of multiple births might occur as a consequence of advancing maternal age at first birth and increased primary infertility, and resultant increased use of assisted reproductive technology (1, 3, 17, 18). Our data of higher in vitro fertilization (IVF) rate in the multiple VLBWI and advancing maternal age comparing with previous study by Kang et al. (2) suggest that these trends are also applicable to the VLBWI groups.

Very high rate of multiples observed in this study suggests that multiple gestation itself might be an important risk factor for preterm VLBW delivery. Although the incidence of maternal DM and the use of assisted reproductive technology were significantly higher in the multiples, the IVF rate between DM and non-DM group was not significantly different. These findings do not support the assumption that higher rate of maternal DM in the multiples might be associated with

**Table 4.** Mortality and morbidity according to birth order within the multiples

	1st born (n=54)	≥2nd born (n=57)
Birth weight (g, M±SD)	1,162±241	1,205±209
Mortality	3 (5.6%)	7 (12.3%)
Hospital stay (days, M±SD)	59.9±27.9	62.9±40.3
Apgar score (1 min, M±SD)	4.7±2.3	3.9±2.1
Apgar score (5 min, M±SD)	6.6±1.5	6.3±1.7
RDS	28 (51.9%)	39 (68.4%)
BPD	9 (16.7%)	19 (33.3%)
Ventilator (days, M±SD)	13.4±16.9	22.1±40.1
Cystic PVL	2 (3.7%)	5 (8.8%)
IVH (grade ≥3)	3 (5.6%)	4 (7.0%)
ROP (stage ≥3)	10 (18.5%)	9 (15.8%)
Abnormal BAEP	8 (14.8%)	7 (12.3%)

SGA, small for gestational age; RDS, respiratory distress syndrome; PDA, patent ductus arteriosus; BPD, bronchopulmonary dysplasia; IVH, intraventricular hemorrhage; ROP, retinopathy of prematurity; PVL, periventricular leukomalacia; BAEP, brainstem auditory evoked potential.

increased infertility with the resultant increased use of assisted reproductive technology in DM patients. Further studies will be necessary to delineate the reasons of higher incidence of maternal DM in the multiples. Higher rate of maternal pathologic chorioamnionitis and PIH among the singletons suggest that these factors could act as the important risk factors for preterm VLBW delivery, especially among the singletons. As multiple gestation is a well known major risk factor for maternal PIH, our data of significantly lower incidence of PIH observed in the multiples are difficult to explain. Further studies will be necessary to clarify this.

Although birth weights of the multiples at full term are smaller than those of the singletons, it is not clear when the divergence of growth in the multiple gestation starts in utero. Some authors noted intrauterine growth for fetuses of the multiple gestation follows that of singletons until 30-34 weeks of gestation when growth curves begin to diverge (4, 19-21). In the study of Alexander et al. (22), divergence of growth for the multiples began much earlier at 22 weeks with marked divergence beginning at 28 weeks. Hoffman et al. (12) and Wolf et al. (13) reported no significant differences in birth weight between the singleton and the twin VLBWI. In this study, no significant differences in gestational age-specific birth weights were observed. These findings suggest that there is no significant divergence of growth of multiple gestation at least until 30-34 weeks of gestation.

The multiples are believed to have higher rate of perinatal mortality and major morbidity than the singletons, mainly because of higher rate of prematurity and VLBW (4-9). However, it is not certain whether perinatal outcomes of the multiples are also worse than the singletons in VLBWI subpopulation. Some authors reported multiple VLBWI had higher rate of mortality and neurodevelopmental morbidity than singleton VLBWI (10, 12). In other studies, no significant

differences in perinatal mortality and major morbidity were observed (11, 13-15, 23). In this study, no significant differences were observed in perinatal mortality and major morbidity between the multiple and the singleton VLBWI. As 5 patients with gestational age less than 23 weeks were included only in the singletons, the total mortality rate in the singletons showed a tendency to be higher than in the multiples without statistical significance. The frequency of abnormal BAEP findings was even higher among the singletons. These findings support the assumption that the multiples is not a significant risk factor for increased perinatal mortality and morbidity in VLBWI.

Birth order of multiples has been considered as a prognostic factor because the second borns are at higher risk for malpresentation, hypoxia, and operative delivery (24-26). With the advent of modern perinatal care, however, most of the complications in the second born twins could be avoided. Ghai et al. (11) and Chen et al. (27) found no differences in perinatal mortality and morbidity between the first and second born twins. In this study, no significant differences in perinatal mortality and morbidity according to birth order were observed in the multiple VLBWI. These findings suggest that the birth order among the multiple VLBWI is not an important prognostic factor.

In summary, there were no significant differences in perinatal mortality and morbidity between the singleton and the multiple VLBWI.

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