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Comparison of neonatal outcomes between multiples and singletons among very low birth weight infants: the Korean Neonatal Network cohort study

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ABSTRACT

Objective: To compare neonatal outcomes between multiples and singletons among very low birth weight infants, this was a prospective cohort study that was conducted by collecting data registered in the Korean Neonatal Network database.

Methods: From January 2013 to December 2016, there were 8265 infants in the Korean Neonatal Network database, and 2958 of them were from multiples. Among them, 2636 infants were twins, 308 infants were triplets, and 14 infants were quadruplets. Maternal and neonatal variables including and mortality major morbidity were compared. Finally, the predicted rates of major morbidity between singletons and multiples.

Results: Multiples had higher gestational age, birth weight, Apgar score at 5 min, rates of cesarean section and artificial reproductive technology but lower maternal hypertension, oligohydramnios, chorioamnionitis rates and Clinical Risk Index for Babies scores II without base excess than the singletons. In univariate analysis, multiples had a lower incidence of respiratory distress syndrome, bronchopulmonary dysplasia, and sepsis. The mortality rate was not significantly different for overall gestational ages except for those born at ≤26 weeks of gestation. In multivariate logistic analysis, the incidences of intraventricular hemorrhage (grade ≥3), and retinopathy of prematurity requiring treatment were significantly higher than the singletons.

Conclusions: Mortality was not significantly different between multiples and singletons according to overall gestational age, except for multiples born at ≤26 weeks. A significant higher risk of intraventricular hemorrhage and retinopathy of prematurity requiring treatment was found in multiples. A new strategy to improve the mortality of immature multiples born at ≤26 weeks of gestation should be developed.

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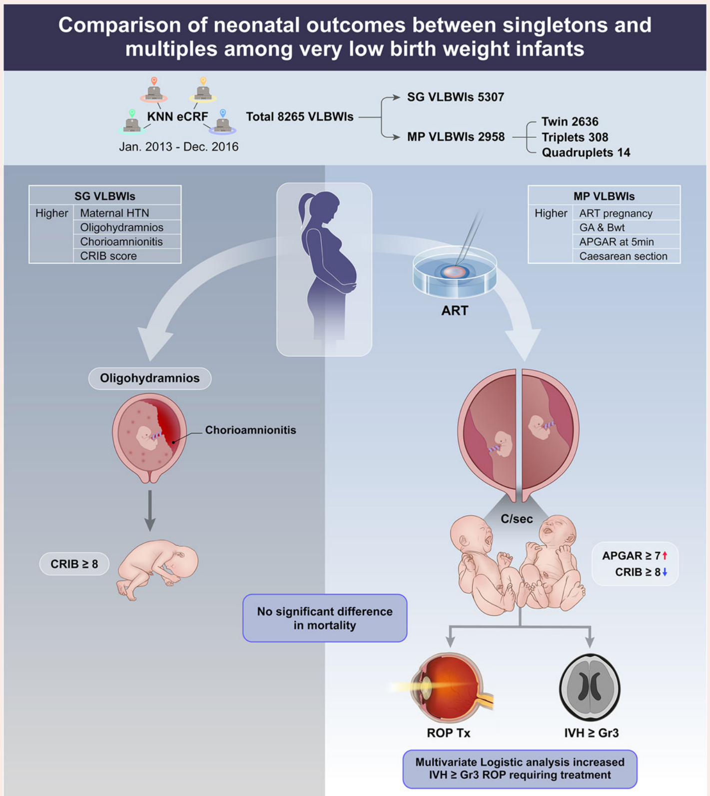
GRAPHICAL ABSTRACT



Introduction

The number of multiple pregnancies has been increasing mainly in developed countries due to the increase in assisted reproductive technology, including *in vitro* fertilization, and the increased reproductive age of mothers [1]. In 2018, 33.5 per 1000 births in the United States were multiple births [2]. In Korea, the multiple birth rate has also increased from 10.0 to 27.5 per 1000 live births between 1991 and 2008 [3], and from 2009 to 2015, the birth rate of twins and triplets increased by 34.5% and 154.3%, respectively [4].

Multiple pregnancies are risk factors for pregnancy complications such as preeclampsia, preterm premature rupture of membranes, premature birth, intrauterine growth restriction and fetal death [4–6]. Multiple Pregnancies are a major risk factor for adverse neonatal outcomes, particularly prematurity and those with very low birth weight infants (VLBWIs). One-third of the VLBWIs admitted to a neonatal intensive care unit (NICU) were multiple pregnancies in Spain [7]. In addition, it has been reported that multiple pregnancies have a high incidence of congenital anomalies and lower efficacy of antenatal steroids [8,9]. Risk factors for multiple pregnancies are the basis for fetal reduction and selective termination during *in vitro* fertilization [10,11].

However, unlike these results, it has also been reported that the neonatal outcomes of multiples are similar to those of singletons [12]. Therefore, the purpose of this study was to analyze the neonatal mortality and morbidity of multiples compared to those of singletons using a recent large cohort of infants from the Korean Neonatal Network (KNN) database.

Material and methods

Study population

This study used data from the KNN obtained from 67 NICUs during the period of January 2013 to December 2016. Data for VLBWIs who were born in the KNN's participating NICUs or transferred within 28 days of birth were prospectively enrolled. The included infants were divided into the singleton (SG) group and the multiple (MP) group. Each of these groups was divided into 5 categories according to gestational age (GA): ≤26 weeks, 27–28 weeks, 29–30 weeks, 31–32 weeks, and ≥33 weeks. All methods were performed in accordance with the relevant guidelines and regulations distributed to participating institutions [13].

Definitions

Multiple pregnancies was defined as the presence of two or more embryos in the uterus by spontaneous pregnancy, ovulation-induction therapy, or the use of artificial reproductive technology methods including *in vitro* fertilization (IVF). Maternal hypertension (HTN) included preeclampsia, eclampsia, and chronic hypertension. Maternal diabetes mellitus (DM) included overt and gestational DM. Premature rupture of membrane (PROM) was defined as rupture of the membrane more than 24 h before the onset of labor.

A clinical risk index for babies II without a base excess score (CRIB II–BE) (≥8 [14],) is calculated based on GA, birth weight (BW), the presence or absence of congenital malformations, and the minimum and maximum appropriate fraction of inspired oxygen during the first 12 h of life [15]. Morbidities were defined as follows: Respiratory distress syndrome (RDS), (based on chest radiographic findings and clinical respiratory difficulty symptoms, only cases were respiratory support therapy such as invasive ventilation or noninvasive ventilation was required is recognized), symptomatic patent ductus arteriosus (PDA) (requiring surgery due to medical treatment failure), moderate or severe bronchopulmonary dysplasia (BPD), sepsis (including both early-onset and late-onset sepsis that is positive result of bacterial or fungal culture in the bloodstream), severe intraventricular hemorrhage (IVH) (worst more than Papile's criteria grade II at any time), necrotizing enterocolitis (NEC) (worst more than Bell's stages II at any time), severe retinopathy of prematurity (ROP) (needs any treatment included surgery) (e.g. cryotherapy, laser photocoagulation and/or vitrectomy) and/or intravitreal injection with antivascular endothelial growth factor (e.g. anti-VEGF) agents) at any time.

Data analysis

We compared maternal variables, including mode of delivery, IVF, maternal HTN, maternal DM, PROM, oligohydramnios and pathological chorioamnionitis between the SG and MP groups. We also compared neonatal variables, including GA, BW, gender, transfer after birth, prenatal steroid use, an Apgar score of ≥7 at 5 min [16], major congenital defects, and a CRIB II-BE, and major morbidities, such as RDS, PDA, BPD, sepsis, IVH, NEC, ROP and mortality between the SG and MP groups.

Statistical analysis

Continuous variables are presented as the mean (± standard deviation [SD]) or median [25 percentiles, 75 percentiles]. Categorical variables are presented as percentages in tabulations. Categorical variables were compared between the two groups using either the chi-squared test or Fisher's exact test. Continuous variables were compared using either Student's *t* test or the Kruskal–Wallis rank-sum test. In each GA group (≤26 weeks, 27–28 weeks, 29–30 weeks, 31–32 weeks, and ≥33 weeks), survival and major morbidity were calculated, and multivariate logistic regression was performed to obtain the adjusted odds ratios (ORs) of mortality and morbidity between the MP and SG groups. ORs with 95% confidence intervals (CIs) were used to test morbidity and mortality between the MP and SG groups. Statistical significance was set at $p < .05$. All statistical analyses were performed using R software (Version 4.1.3; R Foundation for Statistical Computing, Vienna, Austria).

Statement of ethics

The KNN data registry was approved by the institutional review board of all hospitals in each participating center, including Ajou University Medical Center (approval no. AJOUIRB-OBS-2013-014) during admission and follow-up, and written informed consent was obtained from the parents of infants at enrollment in the KNN. All methods were performed in accordance with the relevant guidelines and regulations.

Results

According to the national birth weight statistics, 8265 out of 11627 infants [17] born with a birth weight of less than 1500 g were included, and 2958 (35.8%) of them were MP group. Of the 2958 MP VLBWIs, 2636 (89.1%) infants were twins, 308 (10.4%) infants were triplets, and 14 (0.5%) infants were quadruplets.

The mean GA (29^{+2} weeks vs. 28^{+4} weeks; $p < .001$) and mean BW (1150 g vs. 1100 g; $p < .001$) were higher in the MP group than in the SG group. The prevalence of an Apgar score of ≥7 at 5 min, cesarean section, and IVF were significantly higher in the MP group than in the SG group. 1344 (85.9%) were twins, 213 (13.6%) were triplets, and 7 (0.4%) were quadruplets among the 1564 MP infants (52.9%) conceived by

Table 1. Demographic characteristics of singletons versus multiples among VLBWIs.

	Singletons ($n = 5307$)	Multiples ($n = 2958$)	*p*-value
Cesarean section	3892 (73.3)	2499 (84.5)	<.001
IVF	336 (6.3)	1564 (52.9)	<.001
Maternal HTN	1386 (26.1)	308 (10.4)	<.001
Maternal DM	439 (8.3)	260 (8.8)	.442
PROM	1914 (36.1)	1002 (33.9)	.053
Oligohydramnios	815 (15.4)	283 (9.6)	<.001
Chorioamnionitis	1716 (32.3)	648 (21.9)	<.001
Antenatal steroid use	4043 (76.2)	2272 (76.8)	.405
Gestational age (weeks)	28^{+4} [26^{+4}, 30^{+4}]	29^{+2} [26^{+6}, 31^{+1}]	<.001
Birth weight (g)	1100 [850, 1310]	1150 [880, 1354]	<.001
Male sex	2716 (51.2)	1444 (48.8)	.042
Apgar score at 5 min (≥7)	3356 (63.2)	2010 (68.0)	<.001
CRIB II-BE (≥8)	2020 (38.1)	866 (29.3)	<.001
Major congenital defect	199 (3.7)	98 (3.3)	.337
Outborn birth	180 (3.4)	96 (3.2)	.771

Values are expressed as the mean [*minimum value, maximum values*] or as the number (percentage) of patients.
VLBWI: very low birth weight infant; IVF: *in vitro* fertilization; HTN: hypertension; DM: diabetes mellitus; PROM: premature rupture of membranes; CRIB II-BE: Clinical Risk Index for Babies II without base excess.

IVF. In contrast, the incidence of male sex, maternal HTN, oligohydramnios, chorioamnionitis, and a CRIB score of ≥8 was significantly lower in the MP group than in the SG group. There were no significant differences between groups in the incidence of transfers, maternal DM, PROM, antenatal steroid use, or major congenital defects (Table 1).

When comparing morbidity and mortality, the incidence of RDS was significantly lower in the MP group than in the SG group according to overall GA. The incidence of RDS was not significantly different between the two groups at ≤32 weeks of gestation but was significantly decreased in the MP group in the ≥33 weeks category. The incidence of PDA requiring surgery was not significantly different between groups at any GA; however, there was a significant increase in the MP group at 29–30 weeks of gestation. BPD and sepsis were significantly decreased in the MP group, but there was no significant difference in the incidence according to the GA category. The incidence of IVH, NEC, and ROP requiring treatment did not differ significantly between these groups across any GA categories. Overall mortality did not differ between groups for GA, except for a significant increase in the MP group at ≤26 weeks of gestation (Table 2). In multivariate logistic regression analysis, IVH was 1.74 times higher (OR, 1.74; 95% CI, 1.23–2.47; $p = .002$) and ROP was 1.41 times higher (OR, 1.41; 95% CI, 1.01–1.97; $p = .041$) in the MP group than in the SG group (Table 3).

Discussion

Recently, assisted reproductive technology (ART) procedures are increasing, and a frequent pregnancy complication through ART is an increase in multiple pregnancies. In one study [18], compared to singletons, twin pregnancies were associated with higher rates of obstetric complications such as gestational diabetes, gestational hypertension or preeclampsia, and also associated with higher perinatal mortality or morbidity such as preterm birth. Therefore, this study aimed to compare the prognosis by comparing morbidity and mortality between singletons and multiples.

In the MP VLBWIs, maternal hypertension was low, cesarean section delivery was more frequent, and as expected, there was an increase in the number of pregnancies conceived through IVF. The rates of chorioamnionitis and oligohydramnios at birth were significantly lower, and the number of infants with CRIB scores ≥8 was lower in MP VLBWIs than SG VLBWIs. This is in contrast to the study by Ballabh et al. [19] As mentioned by Kilby [20], multiple pregnancies increase perinatal morbidity and mortality, so it is possible that the fetus's condition was relatively good because the mother received more attention and care in the MP VLBWIs. Such careful prenatal management may have contributed to the lower rates of RDS, BPD and sepsis in MP VLBWIs compared to SG VLBWIs.

In subgroup GA analysis, there was an increased frequency of PDA surgery in MP VLBWIs compared to SG VLBWIs at gestation weeks 29–30. These results are similar to the report by Lee et al. [21], who reported multiple pregnancies as a risk factor for symptomatic PDA. The subgroup analysis was also similar for gestation age to the findings of Margaryan et al. [22], who presented a mean gestation age of 29.1 weeks, corresponding to the reported age for secondary PDA ligation.

Ward and Caughey [23] compared twins and singletons for the incidence of severe morbidity such as IVH, RDS, NEC and sepsis in late preterm infants between

Table 2. Morbidity and mortality of singletons multiples among VLBWIs.

	≤26 weeks SG ($n=359$) vs. MP ($n=196$)	27–28 Weeks SG ($n=398$) vs. MP ($n=147$)	29–30 Weeks SG ($n=483$) vs. MP ($n=255$)	31–32 Weeks SG ($n=474$) vs. MP ($n=311$)	≥32 Weeks SG ($n=367$) vs. MP ($n=247$)	Total SG ($n=5307$) vs. MP ($n=2958$)
RDS	352 (98.1) vs. 192 (98.0)	378 (95.0) vs. 143 (97.3)	425 (88.0) vs. 220 (86.3)	289 (61.0) vs. 199 (64.0)	113 (30.8) vs. 56 (22.7)*	4239 (79.9) vs. 2218 (75.0)*
PDA surgery	84 (23.4) vs. 44 (22.4)	64 (16.1) vs. 27 (18.4)	28 (5.8) vs. 28 (11.0)*	9 (1.9) vs. 12 (3.9)	8 (2.2) vs. 2 (0.8)	582 (11.0) vs. 298 (10.1)
BPD	160 (44.6) vs. 58 (29.6)	139 (34.9) vs. 54 (36.7)	129 (26.7) vs. 66 (25.9)	67 (14.1) vs. 58 (18.6)	21 (5.7) vs. 18 (7.3)	1447 (27.3) vs. 679 (23.0)*
Sepsis	143 (39.9) vs. 67 (34.2)	110 (27.6) vs. 50 (34.0)	82 (17.0) vs. 36 (14.1)	54 (11.4) vs. 28 (9.0)	28 (7.6) vs. 15 (6.1)	1154 (21.7) vs. 562 (19.0)*
IVH (grade ≥3)	95 (26.5) vs. 61 (31.1)	31 (7.8) vs. 13 (8.8)	21 (4.3) vs. 17 (6.7)	11 (2.3) vs. 7 (2.3)	6 (1.6) vs. 0 (0.0)	476 (9.0) vs. 289 (9.8)
NEC (stage ≥2)	56 (15.6) vs. 30 (15.3)	29 (7.3) vs. 17 (11.6)	20 (4.1) vs. 14 (5.5)	10 (2.1) vs. 8 (2.6)	11 (3.0) vs. 6 (2.4)	369 (7.0) vs. 181 (6.1)
ROP treatment	84 (23.4) vs. 47 (24.0)	34 (8.5) vs. 18 (12.2)	13 (2.7) vs. 8 (3.1)	0 (0.0) vs. 3 (1.0)	0 (0.0) vs. 0 (0.0)	400 (7.5) vs. 240 (8.1)
Mortality	142 (39.6) vs. 100 (51.0)*	66 (16.6) vs. 19 (12.9)	20 (4.1) vs. 14 (5.5)	21 (4.4) vs. 12 (3.9)	8 (2.2) vs. 4 (1.6)	731 (13.8) vs. 404 (13.7)

Values are expressed as the number (percentage) of patients. An asterisk (*) indicates that the value of the multiple (MP) group was significantly different from that of the singleton (SG) group ($p < .05$).
VLBWI: very low birth weight infant; RDS: respiratory distress syndrome; PDA: patent ductus arteriosus; BPD: bronchopulmonary dysplasia; IVH: intraventricular hemorrhage; NEC: necrotizing enterocolitis; ROP: retinopathy of prematurity.

34 and 36 weeks of gestation, and found significant differences in twins born at 34 weeks of gestation. When comparing multiples and singletons in VLBWIs in our study, adjusted multivariate analysis showed increased IVH and ROP in the MP group, but no differences in the prevalence of RDS, NEC, and sepsis. This contrast may be due to our study being conducted in VLBWI and including a patient group born at a younger gestational age.

Compared to singletons, multiples have historically been considered to have an increased risk of perinatal mortality and morbidity, primarily because of higher rates of preterm birth and low BW [24–26]. Although worse neonatal outcomes for multiples have been seen at extremely low gestational ages in several studies [5,27–30], other recent studies have shown comparable outcomes to those for singletons [12,31]. In this study, the mortality rate of the extremely premature MP group born at ≤26 weeks of gestation was higher than that of SG group in univariate analysis. This result is similar to the report of Shinwell [32], but MP was not an independent risk factor for mortality in multivariate analysis.

One of the causes of increased IVH may be differences in blood pressure between singletons and multiples [33] and some qualitative differences in early resuscitation by experienced medical faculty on in neonatal resuscitation program (NRP) teams. It cannot be excluded that the number of NRP team members caring for VLBWIs shortly after birth and the qualitative differences in procedures may differ between MP infants and SG infants. As reported in the paper, the prognosis differs depending on the number and skill level of the medical staff participating in the delivery [34], and NRP teams may require at least 4 or more neonatal medical personnel per VLBWI to participate in the preparation for one newborn at a time. It is considered that there is a difference in the prognosis between VLBWIs born in hospitals where well-trained faculty members can attend every birth and VLBWIs who do not. However, the difference in these conditions was not included in the national data provided in this paper, so it was difficult to analyze, and more research is needed.

The incidence of ROP is generally known to increase with the use of excess oxygen [35,36]. However, as a result of multivariate logistic regression analysis in our study, there was no significant difference in the incidence of RDS, BPD, and sepsis in the MP group, while the increased incidence of ROP requiring treatment was considered meaningful. Friling et al. [37] reported that there was no difference

Table 3. Adjusted odds ratios of mortality and major morbidities of singletons versus multiples among VLBWIs.

	Singleton ($n = 5307$)	Multiples ($n = 2958$)	p-value	Odds ratio	95% Confidence interval	p-value
RDS			<.001	0.75	0.54–1.04	.081
No	1069	740				
Yes	4239	2218				
PDA surgery			.206	1.03	0.76–1.40	.852
No	3676	2079				
Yes	582	298				
BPD			<.001	1.06	0.84–1.35	.622
No	3171	1863				
Yes	1447	679				
Sepsis			.003	1.13	0.88–1.46	.343
No	4140	2391				
Yes	1154	562				
IVH (grade ≥3)			.206	1.74	1.23–2.47	.002
No	4658	2553				
Yes	476	289				
NEC (stage ≥2)			.154	1.19	0.78–1.79	.402
No	4907	2763				
Yes	369	181				
ROP treatment			.521	1.41	1.01–1.97	.041
No	2842	1606				
Yes	400	240				
Mortality			.909	1.42	0.55–3.40	.448
No	4576	2554				
Yes	731	404				

VLBWI: very low birth weight infant; RDS: respiratory distress syndrome; PDA: patent ductus arteriosus; BPD: bronchopulmonary dysplasia; IVH: intraventricular hemorrhage; NEC: necrotizing enterocolitis; ROP: retinopathy of prematurity.

in the incidence of ROP when comparing singletons and multiples in 99 VLBWIs. Based on this, they presented the rationale for conducting the ROP screening test in the same way as for singletons. However, Sood et al. [38] reported that multiple gestations may be taken as an independent risk factor for ROP causation. The higher incidence of ROP in the MP group in our study is more meaningful in that it is a study that includes a large number of VLBWIs using a nationwide cohort.

Henceforth, new strategies should be developed to improve the mortality rate of premature infants born at ≤26 weeks of gestation. Therefore, in women with MP pregnancy, who are expected to give birth extremely prematurely, more intensive prenatal management, such as antenatal steroid administration and planned delivery, should be performed. In addition, to reduce the frequency of IVH and ROP requiring treatment for MP VLBWIs, the cause should be identified, and a strategy should be established.

Limitation

A limitation of the study was that it was not possible to analyze the differentiation between units such as in medical resources, decision-making processes, and medical faculties including quality and numbers. Therefore, further studies on these issues should be conducted in the future.

Conclusions

This study aimed to investigate neonatal mortality and morbidity in MP VLBWIs compared with those of SG VLBWIs in Korea. We found that mortality was not significantly different between MP and SG infants according to overall gestational age, except for a significant increase in MP VLBWIs born at ≤26 weeks and a significantly higher risk of IVH and ROP requiring treatment in the MP group. To our knowledge, this study is the first domestic study to evaluate neonatal mortality and morbidity in MP VLBWIs compared with those in SG VLBWIs using a large population-based study in Korea. In addition, close observation and appropriate response to symptomatic PDA is necessary for MP VLBWIs born between 29–30 weeks of gestation.

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Author contributions

J.H.L., J.H.H., H.G.J., and S.C. conceptualized, designed, investigated and conducted research and wrote manuscripts. O.K.N., J.H.L., J.H.H., H.G.J., and S.C. formally analyzed the data. J.H.L. and J.H.H. critically reviewed and supervised the manuscript. All authors approved the final version of the manuscript.

Disclosure statement

The authors report there are no competing interests to declare.

Research data

All the data generated and/or analyzed during the current study are included in this article and are available from the corresponding author upon reasonable request.

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References

[1] Bortolus R, Parazzini F, Chatenoud L, et al. The epidemiology of multiple births. Hum Reprod Update. 1999;5(2):179–187. doi: 10.1093/humupd/5.2.179.

[2] Hamilton BE, Martin JA, Osterman MJ, et al. Births: final data for 2014. Natl Vital Stat Rep. 2015;64:1–64.

[3] Young Sil Park SHC, Shim KS, Chang JY, et al. Multiple births conceived by assisted reproductive technology in Korea. Korean J Pediatr. 2010;53(10):880–885. doi: 10.3345/kjp.2010.53.10.880.

[4] Ko HS, Wie JH, Choi SK, et al. Multiple birth rates of Korea and fetal/neonatal/infant mortality in multiple gestation. PLoS One. 2018;13(8):e0202318. doi: 10.1371/journal.pone.0202318.

[5] Garite TJ, Clark RH, Elliott JP, et al. Twins and triplets: the effect of plurality and growth on neonatal outcome compared with singleton infants. Am J Obstet Gynecol. 2004;191(3):700–707. doi: 10.1016/j.ajog.2004.03.040.

[6] Luke B, Brown MB. Maternal morbidity and infant death in twin vs triplet and quadruplet pregnancies. Am J Obstet Gynecol. 2008;198(4):e401-410–401.10. doi: 10.1016/j.ajog.2007.10.785.

[7] Porta R, Capdevila E, Botet F, et al. Morbidity and mortality of very low birth weight multiples compared with singletons. J Matern Fetal Neonatal Med. 2019;32(3):389–397. doi: 10.1080/14767058.2017.1379073.

[8] Shinwell ES, Eventov-Friedman S. Impact of perinatal corticosteroids on neuromotor development and outcome: review of the literature and new meta-analysis. Semin Fetal Neonatal Med. 2009;14(3):164–170. doi: 10.1016/j.siny.2008.12.001.

[9] Dalziel SR, Rea HH, Walker NK, et al. Long-term effects of antenatal betamethasone on lung function: 30 years follow up of a randomised controlled trial. Thorax. 2006;61(8):678–683. doi: 10.1136/thx.2005.051763.

[10] Ogilvie CM. Multiple pregnancy, fetal reduction and selective termination. Reprod Biomed Online. 2013;26(6):522–524. doi: 10.1016/j.rbmo.2013.03.012.

[11] Tse WT, Law LW, Sahota DS, et al. Triplet pregnancy with fetal reduction: experience in Hong Kong. Hong Kong Med J. 2017;23(4):326–332. doi: 10.12809/hkmj176267.

[12] Yeo KT, Lee QY, Quek WS, et al. Trends in morbidity and mortality of extremely preterm multiple gestation newborns. Pediatrics. 2015;136(2):263–271. doi: 10.1542/peds.2014-4075.

[13] Chang YS, Park HY, Park WS. The Korean neonatal network: an overview. J Korean Med Sci. 2015;30 Suppl 1(Suppl 1):S3–S11. doi: 10.3346/jkms.2015.30.S1.S3.

[14] Lee SM, Lee MH, Chang YS. The clinical risk index for babies ii for prediction of time-dependent mortality and short-term morbidities in very low birth weight infants. Neonatology. 2019;116(3):244–251. doi: 10.1159/000500270.

[15] The crib (clinical risk index for babies) score: a tool for assessing initial neonatal risk and comparing performance of neonatal intensive care units. Int Neonatal Net Lancet. 1993;342:193–198. doi: 10.1016/0140-6736(93)92296-6.

[16] American Academy of pediatrics committee On F, Newborn, American College, et al. The apgar score. Pediatrics. 2015;136:819–822.

[17] Korean Statistical Information service. Birth Statistics. Available at http://www/kosis.kr. [accessed 2023 Apr 03]

[18] Prats P, Zarragoitia J, Rodriguez MA, et al. Outcome in a series of 1135 twin pregnancies: does the type of conception play a role? AJOG Glob Rep. 2022;2(4):100129. doi: 10.1016/j.xagr.2022.100129.

[19] Ballabh P, Kumari J, AlKouatly HB, et al. Neonatal outcome of triplet versus twin and singleton pregnancies: a matched case control study. Eur J Obstet Gynecol Reprod Biol. 2003;107(1):28–36. doi: 10.1016/s0301-2115(02)00270-1.

[20] Kilby M. Multiple pregnancy. Semin Fetal Neonatal Med. 2010;15(6):305. doi: 10.1016/j.siny.2010.08.001.

[21] Lee KH, Hwang SJ, Kim SH, et al. Comparison of mortality and morbidity in multiple versus singleton very low birth weight infants in a neonatal intensive care unit. J Korean Med Sci. 2003;18(6):779–782. doi: 10.3346/jkms.2003.18.6.779.

[22] Margaryan R, Arcieri L, Murzi B. Surgical closure of pda in low-weight premature infants. J Matern Fetal Neonatal Med. 2009;22(sup3):81–84. doi: 10.1080/14767050903195484.

[23] Ward C, Caughey AB. Late preterm births: neonatal mortality and morbidity in twins vs. Singletons. J Matern Fetal Neonatal Med. 2022;35(25):7962–7967. doi: 10.1080/14767058.2021.1939303.

[24] Keith LG, Oleszczuk JJ, Keith DM. Multiple gestation: reflections on epidemiology, causes, and consequences. Int J Fertil Womens Med. 2000;45:206–214.

[25] Rand L, Eddleman KA, Stone J. Long-term outcomes in multiple gestations. Clin Perinatol. 2005;32(2):495–513, viii. doi: 10.1016/j.clp.2005.03.002.

[26] Imaizumi Y, Hayakawa K. Infant mortality among singletons and twins in Japan during 1999-2008 on the basis of risk factors. Twin Res Hum Genet. 2013;16(2):639–644. doi: 10.1017/thg.2012.156.

[27] 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(4):1035–1043. doi: 10.1093/humrep/dep430.

[28] Petit N, Cammu H, Martens G, et al. Perinatal outcome of twins compared to singletons of the same gestational age: a case-control study. Twin Res Hum Genet. 2011;14(1):88–93. doi: 10.1375/twin.14.1.88.

[29] Donovan EF, Ehrenkranz RA, Shankaran S, et al. Outcomes of very low birth weight twins cared for in the national institute of child health and human development neonatal research network's intensive care units. Am J Obstet Gynecol. 1998;179(3 Pt 1):742–749. doi: 10.1016/s0002-9378(98)70075-4.

[30] Shinwell ES, Blickstein I, Lusky A, et al. Excess risk of mortality in very low birthweight triplets: a national, population based study. Arch Dis Child Fetal Neonatal Ed. 2003;88(1):F36–40.

[31] Ray B, Platt MP. Mortality of twin and singleton livebirths under 30 weeks' gestation: a population-based study. Arch Dis Child Fetal Neonatal Ed. 2009;94(2):F140–143. doi: 10.1136/adc.2008.143016.

[32] Shinwell ES. Neonatal morbidity of very low birth weight infants from multiple pregnancies. Obstet Gynecol Clin North Am. 2005;32(1):29–38, viii. doi: 10.1016/j.ogc.2004.10.004.

[33] Vesoulis ZA, Flower AA, Zanelli S, et al. Blood pressure extremes and severe ivh in preterm infants. Pediatr Res. 2020;87(1):69–73. doi: 10.1038/s41390-019-0585-3.

[34] de Graaf JP, Ravelli AC, Visser GH, et al. Increased adverse perinatal outcome of hospital delivery at night. BJOG. 2010;117(9):1098–1107. doi: 10.1111/j.1471-0528.2010.02611.x.

[35] Tokuhiro Y, Yoshida T, Nakabayashi Y, et al. Reduced oxygen protocol decreases the incidence of threshold retinopathy of prematurity in infants of <33 weeks gestation. Pediatr Int. 2009;51(6):804–806. doi: 10.1111/j.1442-200X.2009.02856.x.

[36] Hellstrom A, Smith LE, Dammann O. Retinopathy of prematurity. Lancet. 2013;382(9902):1445–1457. doi: 10.1016/S0140-6736(13)60178-6.

[37] Friling R, Rosen SD, Monos T, et al. Retinopathy of prematurity in multiple-gestation, very low birth weight infants. J Pediatr Ophthalmol Strabismus. 1997;34(2):96–100. doi: 10.3928/0191-3913-19970301-08.

[38] Sood V, Chellani H, Arya S, et al. Changing spectrum of retinopathy of prematurity (rop) and variations among siblings of multiple gestation. Indian J Pediatr. 2012;79(7):905–910. doi: 10.1007/s12098-011-0574-y.