Taiwanese Journal of Obstetrics & Gynecology 54 (2015) 371–375

Contents lists available at ScienceDirect

Taiwanese Journal of Obstetrics & Gynecology

journal homepage: www.tjog-online.com

Original Article

Association of biparietal diameter growth rate with neurodevelopment in infants with fetal growth restriction

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ARTICLE INFO

Article history:
Accepted 7 April 2014

Keywords:
biparietal diameter growth
low birth weight infant
neonatal complication
neurodevelopmental complication
severe fetal growth restriction

ABSTRACT

Objective: To investigate the association between neurodevelopmental complications and biparietal diameter (BPD) growth rate.
Materials and Methods: The patients were pregnant women with severe fetal growth restriction (< 5th percentile) before 30 weeks who delivered after 24 gestational weeks. We defined poor BPD growth as being at least 50% below the mean growth rate for at least 1 week. We analyzed maternal characteristics, neonatal complication morbidities, perinatal mortality rate, and neurodevelopmental complications in the child at age 2 years (corrected).
Results: BPD growth was categorized as normal or poor. Out of 8254 infants, 26 met the above criteria. The poor BPD growth group included 17 infants and the normal BPD growth group included nine infants. The gestational age at delivery was 28.7 (24.7–31.7) weeks in the poor BPD growth group and 28.5 (26.1–32.4) weeks in the normal BPD growth group, showing no significant difference. However, death or neurodevelopmental complications occurred in eight of the 17 infants in the poor BPD growth group, whereas neither death nor neurodevelopmental complications were observed in the normal BPD growth group ($p = 0.009$). Moreover, in those with poor outcomes, BPD growth rates were consistently below 40% and birth weights were < 700 g.
Conclusion: BPD growth was associated with neurodevelopmental outcomes, and growth delay as compared with the mean growth rate is a risk factor for poor neurodevelopment.

Introduction

Consensus is lacking regarding the optimal timing of delivery of the high-risk preterm growth-restricted fetus. There is consensus that the growth-restricted fetus should be delivered if the risk of fetal death, as determined by antepartum monitoring tests, exceeds the risk of neonatal death, which is highly dependent on gestational age [1]. The balance of fetal versus postdelivery risks and the optimal timing of delivery have been key issues in fetal growth restriction (FGR) management for several years [2,3].

The Growth Restriction Intervention Trial randomized patients to either immediate or delayed delivery when obstetricians were unsure about management. Two-year outcomes showed increased prematurity-related developmental morbidity with immediate delivery before 30 gestational weeks [3]. However, at 6–13 years of age, childhood neurodevelopment was identical in both management arms of the trial [4]. Based on this observation, Baschat and Odibo [5] and Baschat [6] reported that fetal neurological outcomes were determined prior to the decision on delivery being made, and that there are four primary determinants of neurodevelopment: (1) fetal head size; (2) overall body size; (3) gestational age at delivery; and (4) the Doppler parameters in the umbilical artery, descending aorta, and cerebral vessels. They also reported that it is unlikely for perinatal

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http://dx.doi.org/10.1016/j.tjog.2014.04.031

management strategies in early onset FGR to affect neurodevelopment.

Slowing of head growth in particular is associated with decreases in perceptual performance, motor ability, cognition, and concentration ability, as well as defects in short-term memory, with consequent poorer school achievement [7,8].

In this study, we retrospectively examined cases with FGR before 30 gestational weeks at our institution, where the only criterion for termination of pregnancy due to FGR is apparent fetal deterioration, to determine how biparietal diameter (BPD) growth rates impact outcomes of infants up to the corrected age of 2 years.

Methods

We retrospectively analyzed medical records of pregnant women showing severe FGR (< 5th percentile) before 30 weeks of gestation who had been managed expectantly for > 1 week at the Perinatal Center for Maternity and Neonate of Yokohama City University Medical Center, Yokohama, Japan during the period from January 2004 to October 2011. Multiple gestations and fetal malformation were the exclusion criteria. The criterion of the fifth percentile for severe FGR was taken from the criteria of the Japan Society of Ultrasonics in Medicine and those reported by Mikolajczyk et al [9] in 2011. Gestational age was confirmed by the last menstrual period and crown-rump length measured with ultrasonography between 8 gestational weeks and 11 gestational weeks.

All patients at ≥ 24 gestational weeks were hospitalized for management, and betamethasone was administered to accelerate fetal lung maturation. For fetal monitoring, nonstress tests (NST) were performed twice daily. When the attending physician determined NST assessment to be insufficient, biophysical profile scores were determined daily. Moreover, ultrasound assessment of fetal growth and amniotic fluid index measurement were performed two to three times per week.

Delivery was performed when the following symptoms were detected during expectant management or at 34 gestational weeks. Maternal indications for delivery were complications such as severe preeclampsia, HELLP syndrome (defined as hemolysis, elevated liver enzymes, and low platelet counts), and premature labor onset with or without rupture of the membranes. Fetal indications for termination of pregnancy included: (1) abnormal fetal heart rate showing repeated late decelerations or severe variable decelerations in the form of traditional NST; (2) biophysical profile score ≤ 4; and (3) reversed end-diastolic flow in the umbilical artery at or after 32 gestational weeks.

We defined the growth rate as millimeters of growth in BPD per day between two sonographic measurements obtained at an interval of > 1 week. BPD measurements were obtained in an axial plane at the level of the thalami, the third ventricle, and the cavum septi pellucidi, from the outer border to the inner border of the skull [10]. The mean BPD growth rate was calculated using the BPD growth curve developed by the Japan Society of Ultrasonics in Medicine. The poor BPD growth group was defined as infants with BPD growth rate < 50% of the mean BPD growth rate, and the normal BPD growth group as those with BPD ≥ 50%. The maternal characteristics and pregnancy outcomes of each group were compared.

The main goals of this study were to compare neonatal and neurological complications of the two groups. The major neonatal complications were fetal death, neonatal death, respiratory distress syndrome, grade III or IV intraventricular hemorrhage (IVH), chronic lung disease (CLD), and necrotizing enterocolitis (NEC). The neonatal composite morbidity rate was defined as the proportion of cases with at least one of the above neonatal complications. Neonatal death was defined as death within 28 days after birth, and infant death as death within 1 year. Respiratory distress syndrome was defined by characteristic findings on chest radiographic examinations and oxygen requirement within 24 hours after birth. Grade III IVH was defined as IVH with ventricular dilatation, and Grade IV IVH as that with parenchymal hemorrhage. CLD was defined as the need for supplemental oxygen within 28 days after birth. NEC was defined based on characteristic clinical signs and symptoms as well as plain abdominal radiographic findings, such as pneumatosis intestinalis, pneumoperitoneum, and portal air. We defined neurological complications as cerebral palsy or mental retardation diagnosed by independent pediatric neurologists at a corrected age of 2 years. We defined intact survival as no major physical or mental deficits.

Next, the associations of BPD growth rates with gestational age at delivery and birth weight were examined. Moreover, the poor outcome group was defined as infants with neurological complications and who died in the 1st year of life, and the favorable outcome group as those without neurological sequelae. Risk factors for each group were examined.

The data are presented as medians (range) or frequencies (%). IBM SPSS statistics 21 program (IBM Corp., Armonk, NY, USA) was used for statistical analyses. We applied the Mann–Whitney *U*-test to continuous variables. Fisher's exact tests were used to detect differences in categorical data by group. The results of statistical tests were considered significant at p-< 0.05 and were two-tailed.

Results

During the study period, 8254 women delivered infants, 26 of whom met the above criteria. The poor BPD growth group included 17 infants, and the normal BPD growth group included nine infants.

Maternal characteristics are shown in Table 1. There were no differences in maternal age or primiparity between the two groups. The most common underlying disease was preeclampsia, identified in ≥ 50% or more of the mothers in both groups. FGR was diagnosed at 25.3 weeks of gestation in both groups. The gestational age at delivery was 28.7 weeks in the poor BPD growth group and 28.5 weeks in the normal BPD growth group. The interval from FGR diagnosis until the pregnancy was considered to be prolonged at 21 days in the poor BPD growth group and 19 days in the normal BPD growth group, showing no statistically significant difference between the two groups. Delivery was due to fetal indications in 76.5% (13/17) of the poor BPD growth group and 33.3% (3/9) of the normal BPD growth group, with significantly more cases requiring delivery for fetal indications in the former ($p = 0.046$). The fetal indications that led to delivery were abnormal fetal heart rate in NST or a biophysical profile score ≤ 4 in all of these cases, and there were no deliveries necessitated by abnormal umbilical cord blood flow alone.

Pregnancy outcomes in the poor and normal BPD growth groups are shown in Table 2. In the poor BPD growth group, birth weight tended to be lower ($p = 0.09$). Regarding infants with an Apgar score < 7 at 5 minutes and umbilical cord arterial pH < 7.10, no difference was observed between the two groups. The neonatal composite morbidity rate was 56.3% (9/16) in the poor BPD growth group and 55.6% (5/9) in the normal BPD growth group, not significantly different. Moreover, there were three deaths in the poor BPD growth group. The intact survival rates were 52.9% (9/16) in the poor BPD growth group and 100% (9/9) in the normal BPD growth group, i.e., significantly lower in the former ($p < 0.009$). Survival and neurological outcomes were poorer in the poor BPD growth group.

The association between BPD growth rate and birth weight is shown in Figure 1, the association between BPD growth rate and gestational age in Figure 2. In the poor outcome group, the

Table 1
Maternal characteristics.

	Poor BPD growth group ($n = 17$)[a]	Normal BPD growth group ($n = 9$)[a]	p
Maternal age (y)	32 (21–45)	33 (23–39)	0.85
Primipara	12 (70.6)	6 (66.7)	> 0.99
Preeclampsia	9 (52.5)	7 (77.8)	0.4
Placental abruption	0	0	
HELLP syndrome	0	1 (11.1)	0.35
Gestational age on admission (wk)[a]	25.3 (21.4–29.9)	25.3 (20.4–28.1)	0.45
Gestational age at delivery (wk)	28.7 (24.7–31.7)	28.5 (26.1–32.4)	0.94
Prolongation (d)[b]	21 (8–57)	19 (8–58)	0.47
Indication for delivery			
Maternal	4 (23.5)	6 (66.7)	0.046
Neonatal	13 (76.5)	3 (33.3)	0.046

Data are presented as median (range) or frequency (%).
BPD = biparietal diameter; FGR = fetal growth restriction; HELLP = hemolysis elevated liver enzymes and low platelet.
[a] Gestational age on admission is the number of weeks at the time FGR diagnosis.
[b] Prolongation means the number of days from FGR diagnosis to delivery.

Table 2
Comparison of pregnancy outcomes between the poor and normal BPD growth groups.

	Poor BPD growth group ($n = 17$)	Normal BPD growth group ($n = 9$)	p
Fetal weight (g)	616 (428–1016)	694 (424–934)	0.09
Apgar score < 7 at 5 min	2 (11.8)	0	
Umbilical artery pH < 7.10	1 (5.9)	0	
NRFS	9/16 (56.3)	5 (55.6)	0.7
RDS	7/16 (0.44)	2 (22.2)	0.23
CLD	5/16 (31.3)	3 (33.3)	> 0.99
IVH	1/16 (6.3)	1 (11.1)	> 0.99
NEC	0	0	
Neonatal composite morbidity	9/16 (56.3)	5/9(55.6)	> 0.99
Fetal death	1 (5.9)	0	> 0.99
Neonatal death	1 (5.9)	0	
Infant death	1 (5.9)	0	
Neurological complication	5/16 (31.3)	0	
Intact survival	9 (52.9)	9 (100)	0.009

Data are presented as median (range) or frequency (%).
BPD = biparietal diameter; CLD = chronic lung disease; FGR = fetal growth restriction; HELLP = hemolysis elevated liver enzymes and low platelet; IVH = Grade III or IV intraventricular hemorrhage; NEC = necrotizing enterocolitis; NRFS = nonreassuring fetal status; RDS = respiratory distress syndrome.

distribution of cases reflected a BPD growth rate ≤ 40% and birth weight ≤ 700 g. No association was observed between gestational age and the BPD growth rate.

The results of comparison between the favorable and poor outcome groups are shown in Table 3. The favorable outcome group included 18 infants and the poor outcome group included eight infants. More specifically, the poor outcome group included one fetal death, one neonatal death, one infant death, one case with cerebral palsy, and four cases with mental retardation. While there

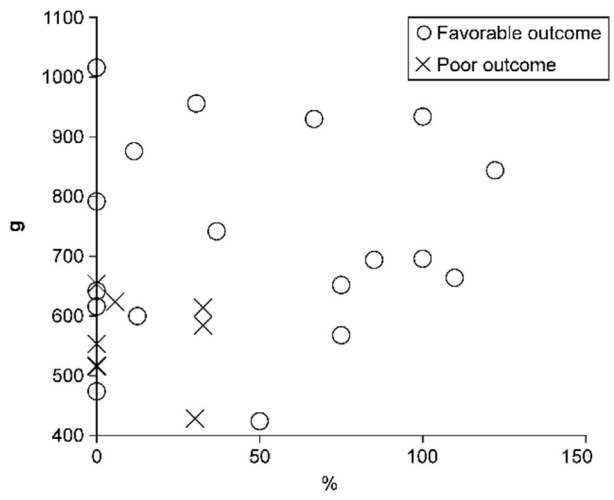

Figure 1. Association between biparietal diameter growth rate and birth weight. In the poor outcome group, the distribution of cases reflected a biparietal diameter growth rate ≤ 40% and birth weight ≤ 700 g.

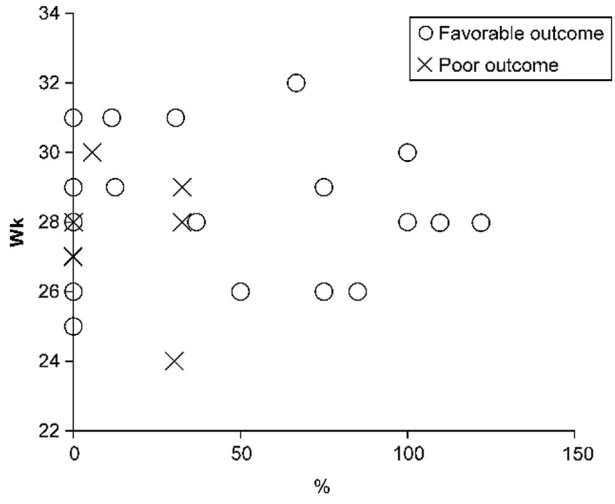

Figure 2. Association between biparietal diameter growth rate and gestational age. No association was observed between gestational age and the biparietal diameter growth rate.

Table 3
Comparison of pregnancy outcomes between the poor and favorable outcome groups.

	Favorable outcome group ($n = 18$)	Poor outcome group ($n = 8$)	p
Maternal age (y)	33 (21–45)	32 (25–40)	0.66
Primipara	12 (66.7)	6 (75)	0.68
Gestational age on admission (wk)	25.3 (21.4–29.9)	24.7 (22.4–26.0)	0.21
Gestational age at delivery (wk)	28.5 (25.3–32.4)	28.3 (24.7–30.4)	0.27
Prolongation (d)	19.5 (8–58)	24.5 (13–40)	0.37
Fetal weight (g)	695 (424–1016)	568 (426–654)	0.011
BPD growth < 50%[a]	9 (50)	8 (100)	0.023
Indication for delivery			
Maternal	9 (50)	1 (12.5)	0.099
Neonatal	9 (50)	7 (87.5)	0.099

Data are presented as median (range) or frequency (%).
BPD = biparietal diameter.
[a] BPD growth < 50% means < 50% of normal BPD growth rate.

was no difference in gestational age at delivery between the two groups, neither was there any significant difference in the interval from FGR diagnosis until delivery. Birth weight was 568 g (428–654 g) in the poor outcome group and 695 g (424–1016 g) in the favorable outcome group, i.e., significantly lower in the former ($p = 0.011$). Moreover, cases with poor BPD growth accounted for 100% (8/8) of the poor outcome group and 50% (9/18) of the favorable outcome group, with significantly more poor BPD growth cases in the former ($p = 0.023$). Although no significant difference was observed in the indications for delivery, there tended to be more pregnancy terminations due to fetal indications in the poor outcome group.

Discussion

The neurological outcomes of infants with severe FGR occurring before 30 gestational weeks who were followed up to a corrected age of 2 years were examined with a focus on the BPD growth rate. Neurological outcomes were significantly poorer in the poor BPD growth group. Moreover, all deaths and neurological complications occurred in cases with a BPD growth rate < 40% and birth weight < 700 g.

Neurological outcomes were significantly unfavorable in the poor BPD growth group. Sameshima et al [11], who examined pregnancy outcomes in 40 infants delivered at 25–30 gestational weeks with FGR, reported that growth arrest of head circumference (HC) and encephalopathy were significantly associated, and that the HC growth rate may serve as a predictive parameter of poor outcomes in FGR infants. The authors attributed this to the BPD growth disorder being caused by impairment of the brain sparing effect. Moreover, Baschat [6] reported that in cases with FGR due to placental dysfunction, growth arrest of HC is observed before fetal deterioration occurs, and that the fetal neurological outcome has been determined before a decision on delivery is made. Our results are consistent with theirs, revealing a BPD growth rate < 40% for at least 1 week to be a poor prognostic factor for fetal neurological outcome.

In the poor outcome group, all deaths and neurological complications occurred in infants with birth weights < 700 g. Vimercati et al [12] who examined 54 infants with extremely low birth weight, showed birth weight and gestational age to be the principal obstetrical factors correlating with survival in these infants, based on both univariate and multivariate analyses. In multivariate analysis, only extreme prematurity (< 25 weeks) and birth weight < 500 g remained significantly associated with mortality, whereas no factor correlated with neuromotor impairment. Moreover, Lemons et al [13] reported that rates of mortality and major morbidity (CLD, severe IVH, and NEC) remain high for the smallest infants, particularly those weighing < 600 g at birth. In their study, the mortality rate for 195 infants weighing 401–500 g was 89%, with nearly all survivors developing CLD. The mortality rate in infants weighing 501–600 g was 71%; among survivors, 62% had CLD, 35% had severe IVH, and 15% had proven NEC. In our study targeting cases with severe FGR, birth weight in the poor outcome group was 568 g (428–654 g). Because birth weight was < 700 g in all infants, this was confirmed to be an important factor affecting the survival of infants.

Meanwhile, another important result of our study is that neurological outcomes were favorable in all infants in the normal BPD growth group. Johnsen et al [14] describe prolonging the duration of pregnancy by 1 day between 26 gestational weeks and 29 gestational weeks as improving neonatal survival by 1–2%. They recommend expectant management for infants delivered at < 30 gestational weeks in consideration of their immaturity. When our results are also taken into consideration, the presence of BPD growth can potentially serve as an indicator that expectant management can be performed safely for infants with severe FGR occurring at < 30 gestational weeks. In other words, it is suggested that expectant management can be performed even for infants with severe FGR, if BPD growth is favorable.

Our study has limitations. Firstly, the design was retrospective and the number of women was small. Secondly, there may have been technical errors made by the ultrasound operators in BPD measurements. Although gestational age reportedly shows a stronger correlation with HC than BPD [14], this study examined the association between the BPD growth rate and neurological outcomes of offspring. BPD is easier to measure than HC. Moreover, although it has already been recognized that growth arrest of HC is associated with the neurological outcomes of infants [15], there are as yet no reports establishing a standard for this growth rate. The results of our study showing most infants with poor neurological outcomes to have a BPD growth rate < 40% thus appear to have a major clinical significance. Furthermore, our study results suggest that, if the BPD growth is favorable, even infants with severe FGR will have favorable neurological outcomes and can undergo expectant management. This also suggests that our study has major clinical significance.

In summary, neurological outcomes in the poor BPD growth group were significantly decreased as compared with those in the normal BPD growth group, and the BPD growth rate was < 40% in all infants in the poor outcome group. Because birth weight was also < 700 g in all infants in the poor outcome group, birth weight was confirmed to be an important factor predicting the neurological outcomes of these infants. This was a small retrospective cohort study of infants at a corrected age of 2 years. Further large-scale follow-up studies, including surveys of the neurological outcomes of school age and older children, are needed.

Conflicts of interest

We have no conflicts of interest relevant to this article.

Acknowledgments

The work described in this article has been carried out in accordance with the Declaration of Helsinki. The authors have no support or funding to report.

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