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Original Article

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

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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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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