Early Human Development 90 (2014) 455–458

Contents lists available at ScienceDirect

Early Human Development

journal homepage: www.elsevier.com/locate/earlhumdev

Acute and massive bleeding from placenta previa and infants' brain damage

Ken Furuta, Shuichi Tokunaga, Seishi Furukawa, Hiroshi Sameshima *

Department of Obstetrics and Gynecology, Center for Perinatal Medicine, University of Miyazaki, Faculty of Medicine, Miyazaki, Japan

ARTICLE INFO

Article history:
Received 14 April 2014
Received in revised form 31 May 2014
Accepted 5 June 2014

Keywords:
Cerebral palsy
Placenta previa
Periventricular leukomalacia
Third trimester bleeding

ABSTRACT

Background: Among the causes of third trimester bleeding, the impact of placenta previa on cerebral palsy is not well known.
Aims: To clarify the effect of maternal bleeding from placenta previa on cerebral palsy, and in particular when and how it occurs.
Study design: A descriptive study.
Subjects: Sixty infants born to mothers with placenta previa in our regional population-based study of 160,000 deliveries from 1998 to 2012. Premature deliveries occurring at<26 weeks of gestation and placenta accreta were excluded.
Outcome measures: Prevalence of cystic periventricular leukomalacia (PVL) and cerebral palsy (CP).
Results: Five infants had PVL and 4 of these infants developed CP (1/40,000 deliveries). Acute and massive bleeding (>500 g within 8 h) occurred at around 30–31 weeks of gestation, and was severe enough to deliver the fetus. None of the 5 infants with PVL underwent antenatal corticosteroid treatment, and 1 infant had mild neonatal hypocapnia with a $PaCO_2$ <25 mm Hg. However, none of the 5 PVL infants showed umbilical arterial acidemia with pH<7.2, an abnormal fetal heart rate monitoring pattern, or neonatal hypotension.
Conclusions: Our descriptive study showed that acute and massive bleeding from placenta previa at around 30 weeks of gestation may be a risk factor for CP, and requires careful neonatal follow-up. The underlying process connecting massive placental bleeding and PVL requires further investigation.

1. Introduction

Third trimester bleeding is a risk factor for cerebral palsy (CP) [1–4]. Among the causes, placental abruption is more frequently associated with a poor neurological outcome. On the other hand, placenta previa may or may not be a significant risk factor for CP [1,2]. For example, a univariate analysis showed a significant increase in the incidence of CP, while this was not the case with a multivariate analysis. It was also shown that maternal bleeding from placenta previa was a significant risk factor only in low-birth-weight infants, suggesting that prematurity or growth restriction is a contributing factor.

Thus, this study describes the neurological outcome of infants born to mothers with placenta previa and attempts to delineate some of the risk factors associated with CP. For this purpose, we used our regional population-based database relating to perinatal outcome.

2. Materials and methods

We performed a retrospective observational study on infants' short-term and long-term neurological outcome born to mothers with placenta previa. For this purpose, we used our database from a regional population-based study relating to perinatal outcome, and approved by the Ethics Committee of the University of Miyazaki.

Perinatal deaths and infants with neurological damage have been registered since 1998 in the Miyazaki district, where the population was 1 million and annual births totaled 10,000. Details have been described elsewhere [5–7]. Among the registered infants with CP, 5 infants were born to mothers with placenta previa. For a comparison, we enrolled another 55 consecutive women with placenta previa who gave birth to a singleton infant at the University of Miyazaki during the study period. Women with placenta accreta, increta or percreta, preterm deliveries at<26 weeks of gestation, and multiple pregnancies were excluded. Antepartum recognition of placenta previa was accomplished with abdominal and vaginal ultrasonography.

During the study period, women with placenta previa were prophylactically hospitalized by 26 to 32 weeks of gestation depending on the women's choice, or were hospitalized for bed-rest when warning bleeding or preterm labor occurred. Tocolytic agents (magnesium sulfate

* Corresponding author at: Department of Obstetrics and Gynecology, Center for Perinatal Medicine, University of Miyazaki, Faculty of Medicine, 5200, Kihara, Kiyotake, Miyazaki 889-1692, Japan. Tel.: +81 985 85 0988; fax: +81 985 85 6149.
E-mail address: hsameshima@med.miyazaki-u.ac.jp (H. Sameshima).

http://dx.doi.org/10.1016/j.earlhumdev.2014.06.002
0378-3782/

and/or ritodrine hydrochloride) were used if painful uterine contractions occurred, if painless but repetitive uterine contractions occurred at less than 10-min intervals, or if any uterine contractions with significant genital bleeding occurred. Tocolytic agents were continued until the aforementioned clinical signs subsided for greater than 24 h. Antenatal corticosteroid was administered when painful and regular uterine contractions occurred according to the attending physician's decision. These management protocols were standardized in the secondary (n = 7) and tertiary (n = 1) centers.

We performed elective cesarean section (CS) when pregnancies became term, or near-term at >35 weeks following amniocentesis confirmation of fetal lung maturity. Otherwise, emergency CS was performed when acute and massive bleeding occurred, where 'acute' was defined as a relatively short period (several to 8 h) and 'massive bleeding' was defined as>300 g hemorrhage with active bleeding or>500 g hemorrhage at once.

General anesthesia was applied to emergency CS, otherwise, combined spinal and epidural anesthesia was employed. Preterm infants were resuscitated by neonatal specialists and admitted at our neonatal intensive care unit when necessary, and systolic blood pressures were maintained at>50 mm Hg with fluid loading and catecholamine supplementation [8].

Intracranial ultrasonography was performed on admission and at every 2 to 3 week intervals to look for cystic PVL and intracranial hemorrhage. Infants born at<35 weeks of gestation were examined by magnetic resonance imaging at discharge or when the corrected weeks of gestation reached 40 to 44 weeks. These infants were monitored by our pediatric neurologists and CP was diagnosed at 2 years of age or older.

Numerical values were compared using an unpaired student t-test. Chi-square and Fisher's exact tests were used for contingency table analysis. P values<0.05 were considered statistically significant. Data are expressed as mean ± SD.

3. Results

From 1998 to 2012, 158,713 deliveries had occurred in our district. The 60 women enrolled with placenta previa were 33.5 ± 4.6 years old at delivery. Among these, 28 were nulliparous. Tocolytic agents were administered to 41 women; magnesium sulfate (n = 2), ritodrine hydrochloride (n = 12), or both (n = 27). Thirty-five women underwent emergency CS; 8 women progressed into active labor without massive bleeding, 4 women had fetal indication (2 for recurrent late decelerations and 2 for moderate to severe variable decelerations), 9 women had other obstetrical indications, and the remaining 14 women had acute and massive bleeding. All of the latter 14 women showed reassuring fetal heart rate patterns except for one, who showed a non-reactive pattern after 500 mg of bleeding, but gave birth to an intact infant. Although these 14 women had acute and massive bleeding, they showed stable circulatory conditions until emergency CS was initiated.

Of the 60 infants born, 5 had cystic PVL on ultrasonography. All 5 PVL infants were born by emergency CS (Table 1), and 4 of these had developed CP (1/40,000 deliveries). There was a significant difference in the occurrence of CP between the acute and massive bleeding group and the others (4/14 versus 0/46, P < 0.01, Fisher test). Average pH values were also compared between the cystic PVL infants (n = 5) and intact infants (n = 55), and no statistically significant differences were observed (Fig. 1). All 60 infants had umbilical pH values>7.20. Antenatal corticosteroid therapy was given in 5 infants in the 55 intact infants and none in the 5 cystic PVL infants.

The 5 PVL infants showed reassuring fetal heart rate patterns immediately prior to birth. These infants were born at 30 or 31 weeks of gestation and weighed appropriate-for-date according to Japanese standard curves. None of the 5 infants underwent antenatal corticosteroid given the occurrence of sudden bleeding (Table 1). All 5 infants required respiratory assistance and surfactant supplementation due to respiratory distress syndrome, and 1 infant (case 3) experienced mild hypocapnia with a $PaCO_2$ of 23.0 mm Hg for several hours. Although none of the infants had intraventricular hemorrhage, 4 had bilateral cystic PVL leading to CP. MRI findings were compatible with PVL, including dilatation of the lateral ventricles. No infant had leukocytosis>30,000/mm^3 or positive C-reactive protein>0.3 mg/dl at birth.

As shown in Fig. 2, we had 10 infants born at 30–31 weeks of gestation in the current study, in which 5 infants developed PVL and the remaining 5 did not. Thus, we performed a case–control study between the 5 PVL and 5 intact infants. A statistical significance was observed in the incidence of acute and massive bleeding (P < 0.05, Fisher exact test), but not antenatal corticosteroid, tocolytic agents, gender, growth restriction, non-reassuring fetal status, or neonatal hypocapnia of a $PaCO_2$ value<25.0 mm Hg (Table 2).

During the neonatal period, systolic blood pressures were almost maintained at>50 mm Hg. The lowest systolic blood pressure recorded was 42.0 ± 4.3 mm Hg (range: 39–47 mm Hg) in the 5 PVL infants and 43.4 ± 4.5 mm Hg (range: 40–51 mm Hg) in controls, which did not reach statistically significant (Table 2).

The hemorrhagic volume during the last bleeding episode was 500 g or more (Fig. 2) that caused PVL. These 5 infants were born in a relatively narrow time window between 30 and 31 weeks of gestation.

4. Discussion

Third trimester bleeding is a risk factor for CP, but previous reports on placenta previa showed controversial results [1–4]. Interestingly, placenta previa is related to CP only in low birth-weight infants suggesting that prematurity is a contributing factor [1,2]. Spinillo et al. studied 22 low-birth-weight infants born to women with placenta previa (31.6 ± 4.3 weeks of gestation and birth weight of 1641 ± 570 g). Although there was no incidence of cystic PVL or CP among these infants, hemorrhagic episodes were not precisely detailed. Matsuda et al. investigated 72 infants with placenta previa (33.4 ± 2.4 weeks of gestation and birth weight of 2117 ± 501 g), and only 2 infants had a poor outcome; 1 infant dead and 1 infant with CP. However, detailed clinical characteristics were not reported. Compared to the previous studies, our regional population-based study showed that maternal massive and acute bleeding from placenta previa is associated with cystic PVL and CP when it occurs at around 30–32 weeks of gestation.

Table 1
Characteristics of the five infants with periventricular leukomalacia.

Case	Admission GA (weeks)	Delivery GA (weeks)	Hospital	BW (kg)	Tocolysis	A/N steroid	1-min Apgar score	RDS	Respirator support	DOA support	IVH	Cystic PVL	Outcome
1	26	31	Tertiary	1.67	Rit + Mg	−	4	+	+	+	−	bil	CP
2	27	31	Tertiary	1.79	Rit + Mg	−	9	+	+	+	−	rt	Normal
3	26	31	Tertiary	1.60	Rit	−	8	+	+	+	−	bil	CP + E
4	26	30	Secondary	1.65	Rit	−	9	+	+	+	−	bil	CP
5	30	30	Secondary	1.44	Rit	−	9	+	+	+	−	bil	CP

GA; gestational age in weeks, BW; birth weight, tocolysis; ritodrine (Rit) and magnesium (Mg), A/N; antenatal, RDS; respiratory distress syndrome, DOA; dopamine, IVH; intraventricular hemorrhage, PVL; periventricular leukomalacia, bil and rt; bilateral and right, and CP and E; cerebral palsy and epilepsy.