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Placental abruption associated with cerebral palsy

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Running title: Placental abruption and cerebral palsy
Placental abruption is separation of the placenta from its normal implantation site of the uterine body before delivery of the fetus during pregnancy or labor. It is a major cause of cerebral palsy registered in the Japan Obstetric Compensation System for Cerebral Palsy (JOCS). It is classified into revealed and concealed hemorrhage types by the presence or absence of external bleeding, and the latter is associated with a poorer prognosis for mothers and infants. If the survival of the fetus is confirmed in cases of placental abruption, the fetus should usually be delivered promptly. There is no evidence-based preventive methods for placental abruption. Therefore, an awareness of the early symptoms of placental abruption among pregnant Japanese women is important.

Key words: placenta abruption, cerebral palsy, Japan Obstetric Compensation System for Cerebral Palsy
Introduction

Placental abruption (premature separation of normally implanted placenta, *abruptio placentae*) is separation of the placenta -either partially or totally- from its normal implantation site of the uterine body before delivery of the fetus during pregnancy or labor\(^1,2\). Placental abruption is initiated with necrosis (ischemic changes in the decidua basalis) and rupture (bleeding) of maternal blood vessels in the decidua, followed by hematoma formed along the decidua basalis (retroplacental hematoma or hemorrhage)\(^1-4\). The retroplacental hematoma further causes separation compression of the adjacent placenta, eventually resulting in complete separation of the placenta from uterine wall. Although the cause of placental abruption remains unclear, the phenomenon of impaired trophoblast invasion with subsequent atherosis has been suggested to be associated with the presence of inflammation and infection\(^5-9\).

Placental abruption is a serious and life-threatening obstetric complication for both the mother and fetus. The presence of extensive separation of the placenta will cause fetal asphyxia, leading to cerebral palsy (CP) or fetal demise. The Japan Obstetric Compensation System for Cerebral Palsy (JOCSC) was launched in January 2009 to compensate for the economic burden of
children with severe CP associated with delivery and to conduct an analysis of factors contributing to CP, with the goal of improving the quality of health care\textsuperscript{10}. The JOCSC has systematically organized and accumulated individual case information, and has compiled an annual report every year that proposes recurrence prevention measures based on the findings. To prevent the recurrence of similar cases, the JOCSC has provided the annual report to the public, delivery institutions, related academic societies/organizations, government agencies, etc. In the second annual report of the JOCSC in May 2012\textsuperscript{11}, a history of placental abruption was identified in 20 (25.3\%) of 79 cases of severe CP. On the other hand, maternal disseminated intravascular coagulation (DIC) will occur by the entry of tissue thromboplastin into blood of the maternal circulation, which promotes blood coagulation (microthrombosis) in the whole blood vessels, resulting in marked dysregulated coagulation and fibrinolysis related to widespread clotting with bleeding.

Based on this background, I reviewed the literature on placental abruption associated with adverse fetal/neonatal outcomes.

\textbf{Clinical course of placental abruption}

The typical clinical course of placental abruption varies depending on whether the
ruptured blood vessels are arteries or veins, and their sizes. Since placental findings initiate with hemorrhage in the decidua basalis, the decidua is accompanied by hemorrhagic degeneration and necrosis, and hematoma adheres to the decidua and becomes difficult to peel off manually over time after the formation of a retroplacental hematoma. An indentation of the villous tissue will appear on the surface of the maternal site in the placenta where the hematoma is present. Histopathologically, the presence of blood cells infiltrating the decidua from the hematoma will be revealed. Possible causes of the rupture/collapse of blood vessels in the decidua have been suggested as follows: (1) the absence of physiological transformation of the utero-placental arteries due to abnormal vascular structures deep in the myometrium as the result of trophoblastic invasion, (2) attenuated adhesion of the trophoblast to the uterine wall caused by granulocyte elastase, which is a proteolytic enzyme activated by inflammation in endometrial infection (chorioamnionitis), and (3) weakening of the chorion/decidua with inflammation. Arterial bleeding associated with the first possible cause tends to develop suddenly and progress rapidly, whereas venous bleeding associated with the other 2 possible causes, which are triggered by preterm labor or premature rupture of the membranes (PROM), trends to
progress relatively slowly\textsuperscript{13-15}. In cases with chorioamnionitis associated with preterm labor and PROM, the prematurely delivered placentae have often been observed to be accompanied by a marginal venous hemorrhage that undermines the edge of the placenta and originates from deciduitis\textsuperscript{4}. An acute reduction in the uterine volume and intrauterine surface as a consequence of PROM may ultimately lead to disruption of the site of placental attachment in the decidual spongiosa layer, thereby predisposing to abruption\textsuperscript{16}. Therefore, placental abruption following the presence of inflammation has been suggested to often occur after PROM\textsuperscript{6}. On the other hand, when arterial bleeding develops inside the placenta, the abruption will progress rapidly.

**Placental abruption and neonatal sequelae**

To date, neurological sequelae (abnormalities) have been pointed out in 15-20\% of surviving neonates in cases of placental abruption\textsuperscript{1,17,18}. In addition, about 20\% of the main causes of CP registered in JOCSC involved placental abruption, which was the most common causative perinatal complication for CP identified in Japan\textsuperscript{10}.

According to the Annual Report of placental abruption in the Perinatal Registration System of the Japanese Society of Obstetrics and Gynecology in
2001-2010\textsuperscript{17,19}, the average onset period of placental abruption was 34.2 weeks gestation, and about 36\% of cases developed at less than 34 weeks of gestation. The incidence of fetal/neonatal death and umbilical artery pH less than 7.0 were about 17 and 17\%, respectively. In an earlier examination of neonates delivered prematurely with long-term follow up\textsuperscript{20}, placental abruption was not associated with the risk of increased hospitalization due to neurological symptoms; however, it resulted in an increased incidence of CP and developmental disorders (hazard ratio: 6.71 and 3.36, respectively). Although about 10\% of cases of CP registered in JOCSC have been reported to exhibit no problems with the umbilical artery pH, the umbilical artery pH in cases of CP mainly caused by placental abruption was low, indicating fetal hypoxic acidemia\textsuperscript{21}. Since the fetus is supplied with oxygen and nutrients from the mother through the placenta, if the placenta separates, the oxygen supply to the fetus will be insufficient and fetal hypoxia/acidemia will occur. The prognosis of the fetus/neonate correlates with the placental abruption area, and if the area is large, fetal/neonatal death or CP may occur even if the developed fetus is delivered rapidly after the onset of placental abruption.

In Japan, many textbooks including one formally published by the Japan Society of Obstetrics and Gynecology had employed 'Page's classification'
including the percentage separation of the placenta to express the severity of placental abruption, quoting an article published almost six decades ago\textsuperscript{22,23}. With the classification, there is a possibility of fetal asphyxia/demise even in mild cases. Page stated as follows\textsuperscript{22,23}: the estimates of percentage separation were made in retrospect and could not serve as guides to therapy. The separation percentage may undoubtedly be one of the factors representing disease severity; however, the classification is not useful in clinical practice aiming for improved perinatal outcomes. It can be used only for retrospective examination of the cases\textsuperscript{24}.

**Magnetic resonance imaging findings in cerebral palsy associated with placental abruption**

Since there is no single pathological manifestation of CP, the magnetic resonance imaging (MRI) appearances of the causative condition can vary markedly; however, the main conditions that may manifest as causing CP include hypoxic-ischemic encephalopathy (HIE) in term infants and periventricular leukomalacia (PVL) in preterm infants\textsuperscript{25-31}. The former is subdivided according to the severity and duration of hypoxia/ischemia. If most severe acidemia/ischemia occurs in a short time due to placental abruption with massive arterial bleeding, a
widespread hyperintensity of the supratentorial brain known as the ‘white cerebrum sign’ has been reported to occur in diffusion-weighted images (DWI) (total asphyxia)\(^ {31} \). In cases of acidemia/ischemia caused by severe fetal hypoxia for 20-30 minutes or longer at term, the damage of basal ganglia and thalamus has typically been observed by MRI (profound asphyxia)\(^ {27-29} \). Although the prognosis of term fetuses/neonates correlates with the severity and duration of fetal asphyxia, that of preterm fetuses/neonates may also be associated with the gestational age and intrauterine infection (inflammation)\(^ {31-33} \). These will also be related to the large number of cases managed as preterm labor associated with chorioamnionitis, and they will sometimes be revealed by retroplacental hemorrhage as the separation of the placenta from the uterine wall progresses due preterm RPOM\(^ {10,19} \). During the preterm period, multi-organ disorders such as chronic lung disease and necrotizing enterocolitis may occur associated with fetal inflammatory responses, even if there are no serious complications such as placental abruption.

**Clinical symptoms of placental abruption associated with cerebral palsy**

The first subjective symptoms of pregnant women who develop placental
abruption include genital bleeding, abdominal pain, labor pains (uterine contractions) that often do not resolve, and abdominal swelling with or without a feeling of decrease/disappearance of fetal movement, suggesting severe fetal asphyxia due to advanced placental abruption. Placental abruption is classified depending on the presence of external bleeding into the hemorrhage/abruption type and concealed hemorrhage/abruption type\textsuperscript{2,34} as shown in Figure. In the former type, the separation progresses from the marginal side of the placenta and external bleeding is observed, while in the latter type the separation progresses primarily from the central side and internal bleeding accumulates between the placenta and uterine wall\textsuperscript{34}. Placental abruption without external bleeding has been reported to be less common and occurs when blood accumulates behind the placenta with no obvious external bleeding. This type accounts for 20-40\% of all placental abruptions\textsuperscript{34}; however, it has been reported that the prognosis of newborns is worse and the number of cases of fetal demise in utero has increased\textsuperscript{34-37}. In the revealed hemorrhage/abruption type, in which bleeding occurs outside of the uterus, it is expected that external bleeding may prevent detachment toward the center of the placenta, but in the concealed hemorrhage/abruption type, the separation progresses from the center of the
placenta and a massive retroplacental hematoma will form. The latter causes an increase in intrauterine pressure, and the thrombin that has entered the uterine muscle layer further induces uterine muscle contraction, which may increase the stress of the fetus. In addition, the absence of external bleeding may delay the diagnosis of placental abruption\textsuperscript{36,37}. The perinatal prognosis may also deteriorate. Furthermore, the poor maternal outcomes are considered to be due to the increased release of thromboplastin into the maternal circulation as the intrauterine pressure increases, thereby inducing maternal DIC\textsuperscript{36}. A delay in visiting a hospital may also occur because both the obstetrician and mother might underestimate the possibility of placental abruption\textsuperscript{37,38}. Unfortunately, a few cases have also been misdiagnosed as preterm labor by medical staff\textsuperscript{10}.

**Diagnosis of placental abruption**

1. **Clinical findings**

The diagnosis of placental abruption is based on the clinical symptoms as follows: genital bleeding (often non-coagulable), abdominal/labor pain (plate-like stiffness, often persistent contractions with unclear intermittent labor), and abnormal fetal heart rate monitoring (suspected preterm labor, frequent or irregular ripple-like, and abnormal fetal heart rate patterns).
2. Ultrasonographic findings

Ultrasound is almost always the first (and usually the only) imaging modality used to evaluate placental abruption; however, ultrasound is relatively insensitive for the diagnosis of placental abruption. In typical and advanced cases, ultrasonography shows placental thickening and/or the presence of a hematoma between the placenta and uterine wall. However, retroplacental hematoma has been reported to be identified in only 2-25% of all abruptions by ultrasound. The sensitivity of the typical findings has been reported to be low (24%) despite high specificity of 96%. In addition, the negative predictive value of ultrasonographic findings for placental abruption has been reported to be low (53%) despite a high predictive value (88%). Therefore, if retroplacental hematoma is found by ultrasonography, it leads to a definitive diagnosis of placental abruption. In other words, the possibility of placental abruption cannot be ruled out even in the absence of abnormal findings on ultrasonography. In addition, if the placenta is on the anterior wall of the uterus, abdominal pain is noticed immediately after the onset of abruption and the diagnosis is straightforward with palpation (plate-like hardness) and/or ultrasonography; however, if the placenta is on the posterior wall, the onset of subjective symptoms and/or
objective findings will be delayed, and it is difficult to obtain typical ultrasonographic findings.

3. Fetal heart rate monitoring

The fetal heart rate pattern reflects the severity of placental abruption\textsuperscript{1,41}. Undetectable variability and bradycardia occur significantly more frequently in cases of severe placental abruption, and so may reflect the severity of placental abruption. According to a previous retrospective study of low-risk pregnant women in Miyazaki Prefecture, Japan\textsuperscript{42}, if fetal heart rate abnormalities (repeated late deceleration or fetal bradycardia) was already been observed at the time of hospital visit for labor, placental abruption is more common (46\%). In addition, 73\% of cases resulted in CP or stillbirth. Therefore, if fetal heart rate abnormalities are observed at the time of hospital visit for (preterm) labor, strict management considering the possibility of placental abruption should be performed. Again, it is important not to rule out the possibility of placental abruption in any situation with fetal heart rate abnormality.

**Treatment in cases of placental abruption**

If placental abruption is considered minimal and fetal heart rate monitoring is normal, close monitoring in preparation for vaginal delivery might be possible;
however, in other situations the fetus should be delivered promptly if fetal survival can be confirmed. Emergency cesarean section is commonly selected, especially in cases with a fetal prognosis of intact survival and prompt vaginal delivery is not possible\textsuperscript{1,10,19}. The golden time for intact survival of the fetus is within 1 hour from the onset of placental abruption\textsuperscript{10,19}. Two-three hours after the onset, the risks of both perinatal mortality and maternal critical obstetrical bleeding with DIC will increase. Because placental abruption is often a medical emergency with no time to prepare, preoperative examination should be omitted as much as possible to shorten the preoperative time. In addition, in cases of severe fetal bradycardia or fetal demise, the cardiotocogram sometimes erroneously records the maternal heart rate as the fetal heart rate, and confirmation of the presence and number of fetal heart beats by ultrasonography will be required\textsuperscript{1,41}. 

The prognosis associated with placental abruption is better in cases of prompt delivery at the facility where the placental abruption develops than in those of delivery after emergent transportation to a facility. In Japan, about 70\% of placental abruption cases leading to CP involved delivery at the latter\textsuperscript{10}. In Japan, approximately half of all deliveries are managed in private obstetric clinics
that cannot adequately handle severe neonatal asphyxia and/or DIC. Because immediate implementation of emergent cesarean section and preparation for blood transfusion for DIC are often not available in the clinics, early diagnosis and appropriate transfer are of critical issue in Japan. In fact, maternal transport is often carried out if placental abruption is diagnosed at the clinics\textsuperscript{44}. Therefore, in Japan, the development of an emergency transport system in situations where prompt delivery is not possible at such clinics will be needed\textsuperscript{10,44}. Specifically, the following are required for rapid transport: (1) the clarification of transportation judgment criteria according to the function of the obstetric facilities, (2) the smooth provision and grasp of information between the transportation and receiving facilities, and (3) preparing for prompt delivery at the receiving facility. It is also desirable to perform simulations in advance at each facility to make arrangements including the convocation of staff, emergency caesarean section, and preparations for maternal transportation. In addition, since it is often impossible to write a medical record quickly when responding, it will be required to keep a simple record over time and keep a detailed record after the treatment.

It is also important to educate pregnant women so that they can visit the obstetric facility at an early stage of after developing placental abruption\textsuperscript{17,38}. 
Specifically, all pregnant women should be told of the necessity of contacting an obstetric facility as soon as possible if they have unusual symptoms such as atypical abdominal pain or bleeding at 30 weeks of gestation or later.

Risk factors and prevention of placental abruption

From the examination of postpartum placental findings in singleton pregnancies\textsuperscript{45,46}, abnormally shaped placentae such as circumvallate placenta have been reported to be associated with a higher incidence of serious perinatal complications such as placental abruption; however, there is no evidence-based preventative measure against placental abruption. Risk factors for placental abruption have been reported to be a history of placental abruption and young or elderly pregnancies\textsuperscript{47}. In a recent study in Japan\textsuperscript{48}, recurrent placental abruption occurred at an earlier gestational age and followed a more severe course than the first occurrence of placental abruption. In a recent review in Western countries\textsuperscript{47}, there was a marked effect of maternal age on abruption; however, abruption frequencies and other risk factors such as smoking suggested marked variation across countries. Ichizuka et al.\textsuperscript{49} reported that alcohol consumption, smoking during pregnancy, number of deliveries, polyhydramnios, oral administration of ritodrine hydrochloride, and hypertensive disorders in pregnancy were identified
as risk factors for CP following placental abruption in Japan. As a background of pregnant women who developed placental abruption registered in JOCS, the rate of smoking during pregnancy and preeclampsia were reported to be 9.7 and 18.8%, respectively\textsuperscript{10,49}. At the current time, educational activities, including health guidance for pregnant women with all risk factors, may be important to increase their awareness of placental abruption\textsuperscript{10,47-49}.

In an earlier study by Ruiter et al.\textsuperscript{50}, the risk of placental abruption in a subsequent pregnancy was significantly higher in women with a previous placental abruption than in women without such a history (5.8 vs. 0.06%, respectively; adjusted odds ratio, 93). Women with a history of placental abruption that occurred at term in their first pregnancy were more at risk for recurrence than women with preterm or early preterm (< 32 weeks of gestation) placental abruption in their first pregnancy (adjusted odds ratio, 188 vs. 52 or 39, respectively). Therefore, they recommended elective induction from 37 weeks of gestation especially for women with a history of placental abruption at term in a previous pregnancy.

**Conclusion**

Unfortunately, no reliable method has been established to prevent placental
abruption. To prevent poor perinatal outcomes, healthcare providers should diagnose and treat placental abruption based on the severity of the separation and gestational age. Furthermore, it is important to raise awareness among pregnant women.

**Conflict of Interest:** The author declares no conflict of interest.
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Legend for figure

Figure. Revealed hemorrhage/abruption with external bleeding (left) and concealed hemorrhage/abruption without external bleeding (right)
