Clinical characteristics of pregnancies complicated by both fetal growth restriction and placenta previa or low-lying placenta

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Aim: This study aimed to examine the clinical characteristics of pregnancies complicated by both fetal growth restriction (FGR) and placenta previa or low-lying placenta (PPLLP).

Methods: A retrospective cohort study was performed to compare clinical characteristics of pregnancies complicated by FGR and/or PPLLP in women who do not habitually smoke or consume alcohol and who underwent delivery of singletons at ≥ 22 weeks’ gestation at Japanese Red Cross Katsushika Maternity Hospital between 2002 and 2015. Assessed factors related to patients and perinatal outcomes included maternal age, parity, history of in vitro fertilization, hypertensive disorders, delivery mode, fetal ultrasonographic findings, delivery mode, gestational age at delivery, neonatal asphyxia, and postpartum hemorrhage.

Results: There were 24,118 singleton deliveries assessed for eligibility. Of these, 7 were complicated by both FGR and PPLLP. The development of FGR was not associated with the presence of PPLLP (odds ratio 1.12, 95% confidence interval 0.54–2.4, \( P = 0.69 \)). Multivariate logistic regression analysis revealed that the incidence of preterm cesarean delivery due to massive bleeding in pregnancies complicated by both FGR and PPLLP was higher than that in pregnancies complicated by PPLLP or FGR alone (vs. PPLLP alone: adjusted OR 7.11, \( P = 0.03 \); vs. FGR alone: adjusted OR 195, \( P < 0.01 \)).

Conclusion: Obstetricians should be aware of the increased risk of preterm delivery related to antepartum massive bleeding in pregnancies complicated by both FGR and PPLLP.

Introduction

Fetal growth restriction (FGR) is a serious obstetrical complication associated with placental insufficiency constituting the syndrome of ischemic placental disease and continues to be a leading cause of preventable stillbirth and poor neurodevelopmental outcomes.\(^1,2\) Placental insertion abnormalities such as placenta previa and low-lying placenta (PPLLP) require strict management of labor and delivery and carry the risk of massive maternal bleeding.\(^3,4\)

To date, there is no consensus on whether PPLLP contributes to placental insufficiency leading to FGR. A recent study by Baumfeld et al.\(^5\) demonstrated an increased rate of placental insufficiency-associated complications in women with PPLLP. The authors recommended the careful surveillance of women with PPLLP to minimize maternal, fetal, and neonatal complications.\(^5\) Based on other reports examining the association of PPLLP with preterm delivery and/or FGR,\(^6–8\) the association between low birth weight and PPLLP has been suggested to be mainly attributed to preterm delivery and, to a lesser extent, FGR. Therefore, these latter reports have recommended the management of PPLLP with a main focus on maternal hemodynamic complications such as massive bleeding, rather than fetal conditions.

Against this backdrop, the present study aimed to examine the clinical characteristics of pregnancies complicated by both FGR and PPLLP.
Methods

This retrospective cohort study analyzed data from the total population of women who underwent delivery of singleton at ≥ 22 weeks’ gestation at Japanese Red Cross Katsushika Maternity Hospital between 2002 and 2015. The protocol for this study was approved by the Ethics Committee of the Japanese Red Cross Katsushika Maternity Hospital. Informed consent to analyze data from a retrospective database was obtained from all subjects at the first perinatal visit.

Gestational ages were determined by ultrasonographic examination of the fetal crown-rump length at 9–11 weeks’ gestation in cases of spontaneous conception, and embryo transfer dates when pregnancy was achieved by in vitro fertilization (IVF). The presence of PPLLP was confirmed by transvaginal ultrasonography just prior to delivery according to the Guidelines for Obstetrical Practice in Japan.9,10 PPLLP was defined as complete, partial, and marginal previa and a low-lying placenta (Japan Society of Obstetrics and Gynecology, Glossary of Obstetrics and Gynecology, The fourth edition, 2018). FGR was defined as fetuses with sex- and age-adjusted birth weights < −1.5 SD according to the fetal growth curve for Japanese.9,10 Exclusion criteria were as follows: women who habitually smoked and/or consumed alcohol during pregnancy, cases of fetal abnormalities such as chromosomal aberration, cases with vertical infection leading to congenital abnormalities such as congenital cytomegalovirus infection, and cases of cord abnormalities such as velamentous cord insertion.

Clinical characteristics of pregnancies complicated by FGR and/or PPLLP were compared in this study. Assessed factors related to patients and perinatal outcomes included maternal age, parity, history of IVF, hypertensive disorders, fetal ultrasonographic findings such as cerebroplacental Doppler ratio and oligohydramnios, delivery mode, gestational age at delivery (preterm delivery due to massive bleeding), neonatal asphyxia, and postpartum hemorrhage requiring transfusion. The first diagnosis of hypertensive disorders was defined as blood pressure ≥ 140/90 mmHg measured at the upper arm by maintaining the arm-cuff position at heart level with the patient in a sitting position in the outpatient examination room. For hospitalized patients, hypertension was confirmed on two or more occasions at least 6 hs apart with the patient under bed rest. The presence of neonatal asphyxia was defined by umbilical artery pH < 7.0. Massive bleeding was clinically diagnosed as hemorrhage that was expected to continue for an amount greater than 200 ml.

During the study period, only neonates requiring hospitalization were pathologically examined. For example, for healthy neonates with a birth weight ≥ 2,300 g delivered at ≥ 36 weeks’ gestation, pathological examination was not performed even for cases with PPLLP. Accordingly, villous damage (chronic villitis) was examined as the sign of placental insufficiency associated with FGR in some cases complicated by FGR with and without PPLLP.9,11,12

Additional potential risk factors for massive bleeding requiring emergency cesarean section in cases of PPLLP were also examined. In addition to FGR, the classification of PPLLP, the presence of placental insufficiency, and the presence of (awareness of) regular uterine contractions were also examined.

Data are expressed as number (percentage). SPSS Statistics software version 20 (IBM Corp., Armonk, NY, USA) was used for statistical analyses. The $X^2$ test with and without Yates correction or Fisher’s exact test was used for categorical variables. A multivariate logistic regression analysis was conducted to compare factors for pregnancies complicated by both FGR and PPLLP vs. pregnancies complicated by FGR or PPLLP alone. Odds ratios (ORs) and 95% confidence intervals (CIs) were calculated. Differences with $P<0.05$ were considered significant.

Results

During the study period, there were 24,118 Japanese women without habitual smoking or alcohol consumption with singleton deliveries at ≥ 22 weeks’ gestation. Of these, 291 (1.2%) and 528 (2.2%) who were diagnosed with PPLLP and FGR, respectively, were assessed for eligibility. Of these, 7 were complicated by both PPLLP and FGR. The OR for FGR in pregnancies with PPLLP was 1.12 (95% CI 0.54–2.4, $P=0.69$).

Table 1 shows the clinical characteristics of the 7 pregnancies complicated by both FGR and PPLLP. There were no cases with serious complications or past histories associated with the development of FGR. The placental position, such as classification and location, in these cases did not differ from those in cases complicated by PPLLP alone ($P=0.25$ and 0.20). Table 2 shows a comparison of clinical characteristics of pregnancies complicated by both FGR and PPLLP and those complicated by FGR or PPLLP alone. Using multivariate logistic regression analysis, the incidence of preterm cesarean delivery due to massive bleeding in pregnancies complicated by both FGR and PPLLP was higher than that in pregnancies complicated by PPLLP or FGR alone ($P=0.25$ and 0.20). Table 2 shows a comparison of clinical characteristics of pregnancies complicated by both FGR and PPLLP and those complicated by FGR or PPLLP alone. Using multivariate logistic regression analysis, the incidence of preterm cesarean delivery due to massive bleeding in pregnancies complicated by both FGR and PPLLP was higher than that in pregnancies complicated by PPLLP or FGR alone ($P=0.25$ and 0.20). Table 2 shows a comparison of clinical characteristics of pregnancies complicated by both FGR and PPLLP and those complicated by FGR or PPLLP alone. Using multivariate logistic regression analysis, the incidence of preterm cesarean delivery due to massive bleeding in pregnancies complicated by both FGR and PPLLP was higher than that in pregnancies complicated by PPLLP or FGR alone ($P=0.25$ and 0.20).
Table 1. Clinical characteristics of 7 pregnancies complicated by fetal growth restriction and placenta previa or low-lying placenta (PPLLP)

| Case | Maternal age (y) | Parity (w) | Gestational age at delivery (w) | Classification of placenta previa | Location of the placenta | Main indication for Cesarean delivery | Neonatal birth weight (g) | SD | Apgar score at 1/5 minutes | Umbilical artery pH |
|------|------------------|------------|---------------------------------|----------------------------------|---------------------------|--------------------------------------|--------------------------|----|--------------------------|-------------------|
| 1    | 22               | 0          | 29                              | Low-lying                        | Posterior                 | Massive bleeding                     | 1,096                    | 1.8 | 8/9                      | 7.288             |
| 2    | 25               | 0          | 32                              | Marginal                         | Posterior                 | Massive bleeding                     | 1,421                    | 2.5 | 6/9                      | 7.088             |
| 3    | 30               | 1          | 33                              | Marginal                         | Anterior                  | Arrest of fetal growth               | 1,532                    | 2.0 | 8/8                      | 7.259             |
| 4    | 40               | 4          | 35                              | Low-lying                         | Anterior                  | Arrest of fetal growth               | 1,698                    | 2.3 | 7/8                      | 7.307             |
| 5    | 35               | 1          | 35                              | Low-lying                         | Posterior                 | Massive bleeding                     | 1,952                    | 1.5 | 7/9                      | 7.263             |
| 6    | 37               | 1          | 37                              | Complete                         | Posterior                 | Placenta previa                       | 2,014                    | 2.1 | 8/9                      | 7.328             |
| 7    | 33               | 1          | 37                              | Complete                         | Posterior                 | Placenta previa                       | 2,011                    | 2.2 | 8/9                      | 7.311             |

PPLLP: placenta previa or low-lying placenta.
SD: standard deviation.

Table 2. Results of comparing the clinical characteristics of pregnancies complicated by both fetal growth restriction (FGR) and placenta previa or low-lying placenta (PPLLP) with those complicated by FGR or PPLLP only

|                          | PPLLP only | FGR only | Both | P1  | P2  |
|--------------------------|------------|----------|------|-----|-----|
| Total number             | 284        | 521      | 7    |     |     |
| Maternal age ≥ 35 years  | 94 (33.1)  | 156 (28.9)| 3 (42.9) | 0.69| 0.44|
| Nulliparity              | 122 (43.0) | 251 (48.2)| 2 (29.6) | 0.70| 0.45|
| IVF-use                  | 37 (13.0)  | 43 (8.1)  | 2 (29.6) | 0.23| 0.11|
| Hypertensive disorders   | 2 (0.7)    | 51 (9.8)  | 0 (0)  | 1.00| 1.00|
| Abnormal ultrasonographic findings |      |         |      |     |     |
| Cerebroplacental Doppler ratio < 1.1 | —         | 152 (31.1) | 4 (57.1) | —   | 0.20|
| Oligohydramnios          | 6 (2.1)    | 166 (31.9)| 3 (42.9) | <0.01| 0.69|
| Neonatal birth weight < 2.0 SD | —         | 281 (53.9)| 6 (85.7) | —   | 0.13|
| Cesarean delivery        | 284 (100)  | 270 (52.0)| 7 (100)  | 1.00| 0.02|
| Preterm delivery         | 58 (20.4)  | 155 (29.8)| 5 (71.4) | <0.01| 0.03|
| due to massive bleeding only | 21 (7.4)  | [1 (0.2)] | 3 (42.9) | 0.01| <0.01|
| due to abnormal fetal status | 1 (0.4)   | 145 (27.8)| 2 (29.6) | <0.01| 1.00|
| Neonatal asphyxia        | 1 (0.4)    | 5 (1.0)   | 0 (0)  | 1.00| 1.00|
| Postpartum hemorrhage requiring transfusion | 25 (8.5)  | 10 (1.9)  | 2 (29.6) | 0.13| <0.01|

Data are presented as number (percentage, %).
PPLLP: placenta previa or low-lying placenta.
FGR: fetal growth restriction.
SD: standard deviation.
P1: P-value vs. PPLLP only.
P2: P-value vs. FGR only.
* One case of placental abruption.
** Non-reassuring fetal status on cardiotocography, absent and/or reverse end diastolic flow velocity on umbilical artery, and/or arrest of fetal growth.

Table 3 shows the results of analyzing potential risk factors for massive bleeding requiring preterm emergency cesarean section in cases of PPLLP. Only FGR was a risk factor for massive bleeding. In a multivariate analysis evaluating the 4 potential risk factors, FGR was an independent risk factor for massive bleeding (Table 4).

Discussion
Although the small sample size is a major limitation of this study, our results suggest that the presence of placental insertion abnormalities such as PPLLP is not associated with the development of FGR. Despite the fact that PPLLP reflects abnormal placentation, it was...
Fetal growth restriction with placental insertion abnormality

Table 3. Results of examination concerning potential risk factors for massive bleeding requiring preterm emergency cesarean section in cases of placenta previa or low-lying placenta (PPLLP)

| Potential risk factors | Massive bleeding (+) | Crude OR | 95% CI | P-value |
|------------------------|----------------------|----------|--------|---------|
| FGR                    | Yes                  | 3 (14.3) | 11.3   | 2.6–49  | < 0.01  |
|                        | No                   | 18       |         |         |         |
| Total placenta previa  | Yes                  | 4 (19.0) | 0.945  | 0.32–2.8| 0.92    |
|                        | No                   | 17       |         |         |         |
| Placental insufficiency| Yes                  | 5 (23.9) | 1.08   | 0.34–3.5| 0.98    |
|                        | No                   | 15       |         |         |         |
| Regular uterine contractions | Yes    | 1 (4.7)  | 0.488  | 0.081–3.0| 0.71    |
|                        | No                   | 21       |         |         |         |

Data are presented as number (percentage, %).
OR: odds ratio.
95% CI: 95% confidence interval.

Table 4. Results of examination with multivariate analysis using the 4 potential risk factors for massive bleeding requiring preterm emergency cesarean section in cases of placenta previa or low-lying placenta (PPLLP)

| Potential risk factors | Adjusted OR | 95% CI | P-value |
|------------------------|-------------|--------|---------|
| FGR                    | 8.44        | 1.7–43 | < 0.01  |
| Total placenta previa  | 0.571       | 0.14–2.3| 0.75    |
| Placental insufficiency| 0.999       | 0.29–3.5| 0.99    |
| Regular uterine contractions | 0.539 | 0.089–3.3| 0.98    |

OR: odds ratio.
95% CI: 95% confidence interval.

not independently associated with an increased risk of FGR, regardless of whether the PPLLP was complete, partial, marginal, or low-lying. These results suggest that PPLLP is not a reason for placental insufficiency, which is consistent with a number of published studies.6–8)

Some perinatal complications such as FGR and preeclampsia have been thought to originate in the placenta, starting with inadequate cytotrophoblast invasion and ending with widespread maternal endothelial dysfunction.13,14) Cytotrophoblast invasion of the spiral arteries is sometimes limited in the superficial decidua and myometrial segments associated with the physiologically hypoxic environment in the intervillous space. The under-perfusion of the placenta results in the villous damage observed in the current cases complicated by FGR with and without PPLLP. Since the blood flow to the lower uterine segment is less affected by the pressure of the myometrium, the blood supply and oxygenation of a placenta implanted in the lower uterine segment is considered to be increased compared with those in a placenta implanted in the upper uterine segment.15–17) In this study, we did not identify any effect on the incidence of hypertensive disorders or FGR. Although we did not pathologically examine most cases complicated by PPLLP alone, the improved blood supply and oxygenation of the placenta may play a maintenance role in pregnancies complicated by PPLLP alone.

In this study, the incidence of massive bleeding requiring preterm emergency cesarean section in pregnancies complicated by both FGR and PPLLP was higher than that in pregnancies complicated by PPLLP alone. This is a new observation which has not been previously reported.5–8) While the mechanism underlying our current results is unclear, a number of potential mechanisms can be considered. At the end of pregnancy, the uterine body usually remodels to form the lower uterine segment. This results in dilation of the internal os and the inevitable separation of some of the implanted placenta.17) If placental circulation that supplies the growth-restricted fetus is limited, the uterine body may be under similar conditions as that observed at the end of pregnancy from the perspective of maternal-placental circulation dysfunction which leads to massive bleeding. After implantation of fertile ovum, small villi enter the endometrium like grass roots, melt around, and float in the maternal circulation to carry oxygen and nutrients to the fetus. Cases complicated by both FGR and PPLLP may have implantation problems, which could also contribute to placental separation associated with massive bleeding. In addition, coagulation defects have been reported to be rare complications of PPLLP.18,19) Placental thromboplastin may readily escape through the cervical
canal rather than be forced into the maternal circulation. This may be associated with the paucity of myometrial blood flow associated with the development of FGR. The incidence of placental insufficiency in cases complicated by both FGR and PPLLP may seem high, but it is important to keep in mind that these hypotheses are based on observations from our small sample population. Unfortunately, we could not analyze this aspect in detail given that most cases complicated by PPLLP alone were not pathologically examined. A further large-scale study will be needed to clarify mechanisms underlying our present results.

To date, the benefits of hospitalization management before labor for women complicated by PPLLP have not been proven. However, those complicated by both FGR and PPLLP may benefit based on the current results.

In conclusion, PPLLP may not be the underlying reason for placental insufficiency leading to the development of FGR. However, an increased risk of massive bleeding requiring emergency cesarean delivery was observed in pregnancies complicated by both FGR and PPLLP. Thus, obstetricians should be aware of the increased risk of preterm delivery related to antepartum massive bleeding in pregnancies complicated by both FGR and PPLLP.

Conflict of interest
None.

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