学位論文

Clinical manifestations of placental mesenchymal dysplasia in Japan:

A multicenter case series

（本邦における間葉性異形成胎盤の臨床像：多施設共同ケースシリーズ）

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Clinical manifestations of placental mesenchymal dysplasia in Japan: A multicenter case series

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Abstract

Aim: This study aimed to evaluate the clinical features and pregnancy outcomes of placental mesenchymal dysplasia (PMD) in Japan.

Methods: We requested detailed clinical information and placental tissue of PMD cases in 2000–2018 from Japanese facilities with departments of obstetrics and gynecology and analyzed the pregnancy course and neonatal outcomes.

Results: We collected 49 cases of PMD. Of 18 patients with measured maternal serum alpha-fetoprotein (MSAFP) levels, 15 (83.3%) had elevated levels. Maternal serum human chorionic gonadotropin (MShCG) levels were transiently elevated in five (17.8%) of 28 patients. Forty-seven patients continued their pregnancies. All pregnancies were singleton and 40 (85.1%) were associated with adverse events including fetal growth restriction (FGR), threatened premature delivery, fetal demise, and hypertensive disorder of pregnancy in 34 (72.3%), 14 (29.8%), eight (17.0%), and six (12.8%) patients, respectively. Of 47 infants, there were eight stillbirths. There were 40 (85.1%) female infants, and eight (17.0%) had Beckwith–Wiedemann syndrome. Of 39 live births, 23 (59.0%) were associated with premature induction of labor or cesarean section for obstetric indications related to FGR. Eighteen (46.2%) neonates had complications. PMD-affected placentas were pathologically heterogeneous in both grossly PMD-affected and non-affected areas.

Conclusions: Our study included the largest number of PMD cases with detailed clinical information. PMD is a high-risk condition for both the mother and the child. Elevated MSAFP levels with normal MShCG levels indicate PMD. Conventional perinatal management of FGR in Japan might be effective in reducing the fetal mortality rate.

Key words: fetal demise, fetal growth restriction, hypertensive disorder of pregnancy, maternal serum alpha-fetoprotein levels, placental mesenchymal dysplasia.

Introduction

Placental mesenchymal dysplasia (PMD) is a rare morphological disorder of the human placenta characterized by placentomegaly and multicystic vesicles, accounting for approximately 0.02% of examined placentas.[1] In Japan, it was previously reported as a structural abnormality of the placenta associated with Beckwith-Wiedemann syndrome (BWS) by Takayama et al in 1986.[2] However at that time, it was not

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recognized as a clear clinical manifestation. It was considered a new entity according to Moscoso et al in 1991.[3] As knowledge accumulated, PMD has become recognized as being related with fetal complications including fetal growth restriction (FGR), fetal demise (FD), and BWS, as well as maternal adverse events such as hypertensive disorders of pregnancy (HDP).[4–6] Clinical reports of PMD have been limited to one or several cases from each institution, and the clinical entity of PMD has not been established. Therefore, a nationwide multicenter collaborative research group with uniform medical standards was necessary. This study is the first and largest case series to focus on the clinical features of PMD in Japan.

Methods

We reviewed the literature on PMD published in Japan between 2000 and 2014. We requested detailed clinical information and histopathological specimens of placental tissues from the authors. In 2015, we launched a program to support PMD diagnosis. Cases in which consultation was sought for diagnosis or management of PMD between 2015 and 2018 were also collected, including cases at our institution.

For clinical assessment, we analyzed variables such as age, treatments for infertility, pregnancy complications, gestational age (in weeks) at delivery, delivery method, infant weight, placental weight, and neonatal complications. An infant weight below the 10th percentile for gestational age in Japan indicated FGR and light for date (LFD). A delivery at less than 37 completed weeks was considered preterm delivery and a delivery between gestational weeks 22 to 28 was considered extremely preterm delivery. Furthermore, clinical information included medical imaging with ultrasonography and magnetic resonance imaging (MRI) and biochemical markers such as maternal serum human chorionic gonadotropin (MShCG) and alpha-fetoprotein (MSAFP). Elevated MShCG or MSAFP level was defined as higher than the normal range or 2.0 multiple of the median (MoM) for gestational age.[7] Fisher's exact test or Welch's *t*-test was used for comparisons. Statistical analyzes were performed with SPSS, version 21.0 (IBM Corp., Armonk, NY, USA).

For histopathological assessment of tissue samples, two board-certified pathologists (Y. M. and M. F.) and a gynecologist (H. K.) specializing in gynecologic pathology reviewed glass slides with hematoxylin–eosin (H&E) staining. The number of provided sections varied, ranging from 1 to 12 sections (average, 3.3 sections). In this study, the diagnosis of PMD was based on microscopic findings of large edematous stem villi with occasional cyst formation, thick-walled muscular stem vessels and lack of abnormal trophoblastic hyperplasia.[8]

This clinical study was approved by the ethics committee of our institutional review board.

Results

Attributes of patients with PMD

Forty-nine cases of PMD in Japan were collected, including four cases at our own institution. Table 1 summarizes the maternal characteristics and pregnancy outcomes. Mean maternal age was 30.1 ± 4.6 years (range, 20–42 years), and 26 (53.1%) patients were nulliparous. A total of 39 (79.6%) patients conceived naturally; one (2.0%) patient underwent ovulation induction, two (4.0%) patients underwent intrauterine insemination, and one (2.0%)

TABLE 1 Maternal characteristics and pregnancy outcomes (n = 49)

Age (years)	30.1 ± 4.6
Advanced age (≥35 years)	9 (18.3%)
Parity	
Nullipara	26 (53.1%)
Multipara	21 (42.8%)
N/A	2 (4.1%)
Infertility treatment	
Not received	39 (79.6%)
IUI	2 (4.1%)
IVF-ET	1 (2.0%)
N/A	7 (14.3%)
Artificial abortion	2 (4.1%)
Total number of deliveries	47 (95.9%)
Premature delivery[a]	25 (53.2%)
Extremely preterm delivery	7 (14.9%)
Mode of delivery	
Vaginal	20 (42.6%)
Elective CS	15 (31.9%)
Emergency CS	12 (25.5%)
Fetal complications of pregnancy[b]	
FGR	34 (72.3%)
FD	8 (17.0%)
Threatened premature labor	14 (29.8%)
HDP	6 (12.8%)

Abbreviations: CS, cesarean section; FD, fetal demise; FGR, fetal growth restriction; HDP, hypertensive disorder of pregnancy; IUI, intrauterine insemination; IVF-ET, in vitro fertilization and embryo transfer; N/A, not available. [a]Excludes stillbirth cases and [b]Includes overlapping cases.

underwent in vitro fertilization. All pregnancies were singleton. Two patients opted for artificial abortion.

Prenatal medical imaging and laboratory markers in patients with PMD

All patients underwent ultrasonography, and 34 (69.4%) patients had suspected placental abnormality between gestational weeks 10 and 28. A thickened chorionic plate with a multicystic lesion that resembled partial hydatidiform mole or complete hydatidiform mole with co-twin during the first half of pregnancy was a common ultrasound finding (Figure 1(a)). The course of the cystic lesions was varied; they became gradually apparent in two patients and disappeared in three patients. MRI, which was performed in five patients, showed multiple high-intensity cystic lesions on T2-weighted images, which were often uniformly distributed in a leaf of thickened placenta (Figure 1(b)).

Of 18 patients with measured MSAFP levels, 15 (83.3%) had elevated MSAFP levels during the second and third trimesters (Figure 2(a),(b)). MShCG levels increased transiently in five (17.8%) of 28 patients examined (Figure 2(c)). In 17 patients with both MSAFP and MShCG testing, 14 had elevated MSAFP levels, of whom 11 had normal MShCG levels and three had high MShCG levels. The other three patients had normal MSAFP and normal MShCG levels. None of the patients had normal MSAFP and high MShCG levels.

Complications of pregnancy associated with PMD

Of the 47 continued pregnancies, 14 (29.8%) involved threatened premature delivery. Mean gestational age at delivery was 32.5 ± 5.9 weeks. Twenty-five (53.2%) patients delivered live infants prematurely, and seven (14.2%) of these infants were extremely preterm.

Six (12.8%) presented with HDP. Table 2 lists the features of the patients with HDP. Extremely preterm delivery and very-low-birth-weight infants were significantly more common in the HDP group, but the frequency of LFD was comparable to the frequency of LFD in the non-HDP group. Furthermore, HDP in patients with PMD was significantly associated with male fetal sex (66.7% vs. 7.3% in the non-HDP group, $p < 0.01$) and tended to be associated with fetal BWS (50.0% vs. 12.2% in the non-HDP group, $p = 0.053$).

Twenty-seven (57.4%) patients underwent cesarean section; 12 (44.4%) procedures were urgently performed because of NRFS or maternal deterioration. Of 39 live births, 23 (59.0%) involved premature induction of labor or cesarean section, and 21 (91.3%) of them were related to FGR.

Fetal and neonatal presentations associated with PMD

Thirty-four (72.3%) fetuses had FGR and eight pregnancies (17.0%) resulted in FD. Table 3 summarizes the clinical features of the cases involving FD. FD mostly began during gestational weeks 20–36. FD

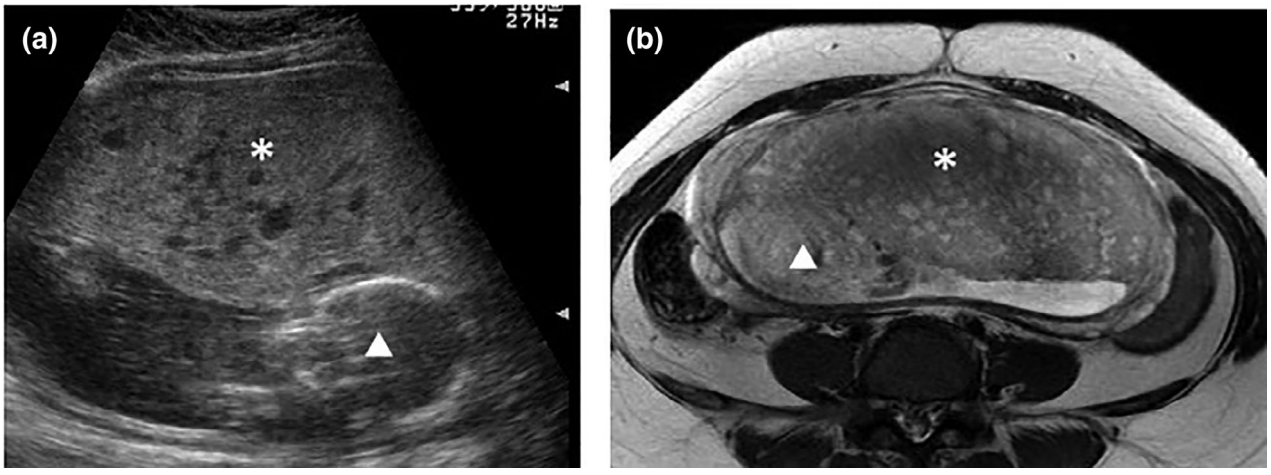

FIGURE 1 Typical prenatal imaging in PMD. (a) Ultrasonography showed a thickened chorionic plate (asterisk) with a multicystic lesion and living fetus (arrowhead) (17 weeks and 5 days of pregnancy, at our institution). (b) T2-weighted magnetic resonance imaging revealed multiple high-intensity cystic lesions in the placenta (asterisk) and fetus (arrowhead) (18 weeks and 0 days of pregnancy, at our institution)

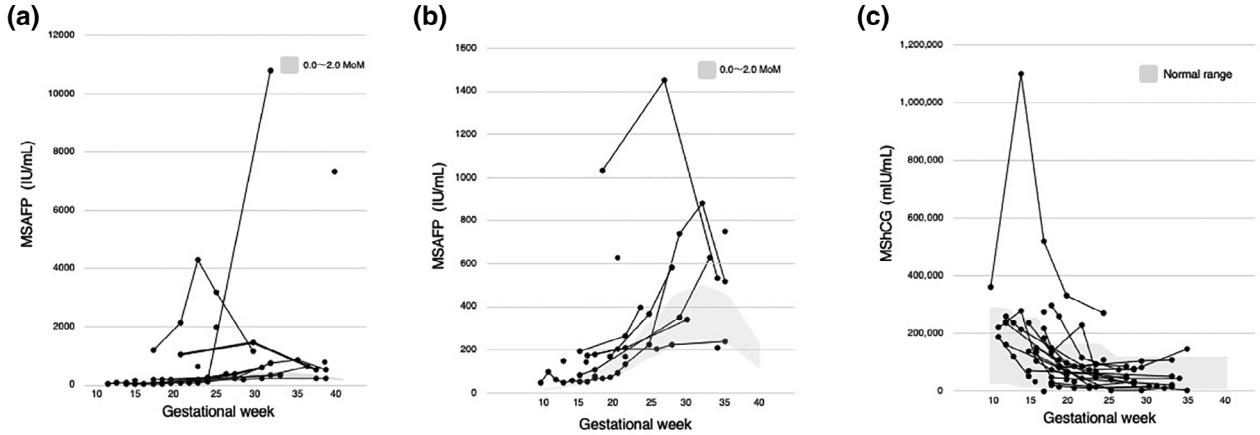

FIGURE 2 Maternal serum levels of biomarkers in PMD. (a, b) Maternal serum alpha-fetoprotein (MSAFP) concentrations over time. Four patients had an extreme rise (a), with MSAFP values greater than 2000 IU/mL. (b) indicates cases with MSAFP levels not exceeding 2000 IU/mL. In 15 (83.3%) of 18 patients examined during the second and third trimesters, MSAFP levels were high during at least one time point (b). (c) Trends in maternal serum hCG (MShCG). In five (17.8%) of 28 patients, MShCG levels increased transiently and decreased gradually as the pregnancy progressed

TABLE 2 Clinical features of patients with HDP

	All (n = 47)	HDP (n = 6)	No HDP (n = 41)	p-value
Maternal characteristics				
Age (years)	30.0 ± 4.5	33.5 ± 3.3	29.9 ± 4.4	
Advanced age (≥35 years)	9 (18.3%)	3 (50.0%)	6 (14.6%)	0.075
Nullipara	25 (53.1%)	2 (33.3%)	23 (56.1%)	0.398
Gestational age at delivery (weeks)	32.5 ± 5.9	28.3 ± 3.4	33.1 ± 6.0	
Premature delivery	25 (53.2%)	6 (100%)	19 (46.3%)	0.023
Extremely preterm	7 (14.2%)	4 (66.7%)	3 (7.3%)	<0.01
Fetal characteristics				
Female	40 (85.1%)	2 (33.3%)	38 (92.7%)	<0.01
Birth weight (g)				
<2500 g	38 (80.9%)	6 (100%)	32 (78.0%)	0.579
<1500 g	17 (36.2%)	5 (83.3%)	12 (29.3%)	0.018
LFD infant	17 (36.2%)	2 (33.3%)	15 (36.6%)	1.000
HFD infant	1 (2.1%)	0 (0%)	1 (2.4%)	1.000
Complication of BWS	8(17.0%)	3 (50.0%)	5 (12.2%)	0.053

Abbreviations: BWS, Beckwith–Wiedemann syndrome; HFD, heavy-for-date; LFD, light-for-date.

only occurred in fetuses without BWS. Two cases of FD were complicated with FGR, of which one exhibited non-reassuring fetal status (NRFS). One case involved fetal malformation, and the other five had no abnormalities preceding FD.

Of 47 infants, which included eight stillbirths, 40 (85.1%) infants were female and seven were male, including a fetus with the 46, XX/XY karyotype. The male-to-female ratio was 1:5.7 (Table 4). Furthermore, eight (17.0%) infants had BWS, which consisted of one male and seven females.

Of 39 live neonates, 10 (25.6%) were LFD. Of the eight children with BWS, three (37.5%) had complications of hypoglycemia and none had anemia, platelet depression, or disseminated intravascular coagulation (DIC), while five (12.8%) of the 31 children without BWS had anemia, five (12.8%) had platelet depression, and four (10.3%) had DIC. Of note, six (15.4%) neonates without BWS had structural anomalies.

Gross appearance and histopathological findings of placentas affected by PMD

Placental weight was measured in 46 cases. The average fixed placental weight was 933 ± 401 g (range, 210–2330 g). Placentomegaly was observed in

TABLE 3 Clinical features of cases involving fetal demise (FD)

	Age	Infertility treatment	Gestational age at FD, weeks	Birth weight (g)		P/I weight ratio	Fetal sex (karyotype)	Abnormal findings preceding FD
				Placenta (P)	Infant (I)			
1	30	Not received	20	735	200	3.68	F (46, XX)	[a]
2	30	Not received	24	690	550	1.25	F (46, XX)	n.p.
3	24	Not received	28	1670	940[b]	1.78	F (46, XX)	n.p.
4	28	Not received	31	1063	1354	0.79	F (N/A)	FGR, NRFS
5	34	Not received	33	663	1586[b]	0.42	F (N/A)	Low-lying placenta, FGR
6	26	N/A	34	1050	1516[b]	0.69	F (46, XX)	N/A
7	31	Not received	36	570	1960[b]	0.29	F (N/A)	n.p.
8	32	Not received	36	720	2336	0.31	F (46, XX)	n.p.

Note: Cases are presented in the order of gestational age at FD. Abbreviations: F, female; FGR, fetal growth restriction; N/A, not available; n.p., nothing particular; NRFS, non-reassuring fetal status; P/I, placental weight to infant birth weight ratio.; [a]Complicated with retroperitoneal tumor, fetal hydrops, and threatened abortion and [b]Light-for-date infant.

TABLE 4 Neonatal outcomes

	All (n = 47)	No BWS (n = 39)	BWS (n = 8)	p-value
Male/female ratio	1:5.7	1:5.5	1:7	
Premature infant	25 (53.2%)	17 (43.6%)	8 (100%)	0.018
Extremely preterm	7 (14.2%)	4 (66.7%)	3 (23.3%)	<0.01
Birth weight (g)	1824 ± 838	1889 ± 725	2096 ± 1136	
<2500 g	30 (63.8%)	24 (61.5%)	6 (0.75%)	0.470
<1500 g	13 (27.7%)	10 (25.6%)	3 (37.5%)	0.495
LFD infant	10 (25.6%)	10 (32.6%)	0 (0.0%)	0.106
HFD infant	1 (2.1%)	0 (0.0%)	1 (12.5%)	0.026
Complications	18 (38.3%)	14 (35.9%)	4 (50.0%)	0.455
Anemia	5 (10.6%)	5 (12.8%)	0 (0.0%)	0.284
Thrombocytopenia	5 (10.6%)	5 (12.8%)	0 (0.0%)	0.284
DIC	4 (85.1%)	4 (10.3%)	0 (0.0%)	0.344
Hypoglycemia	3 (6.4%)	0 (0.0%)	3 (37.5%)	<0.01
Other	6 (12.8%)	6 (15.4%)[a]	1 (12.5%)[b]	0.835

Abbreviations: BWS, Beckwith-Wiedemann syndrome; DIC, disseminated intravascular coagulation; FD, fetal demise; HFD, heavy-for-date; LFD, light-for-date. [a]Includes one case each of lymphangioma, retroperitoneal tumor, liver hamartoma, and clubfoot and [b]Hirschsprung's disease with the characteristic symptoms of BWS.

41 (89.1%) placentas, with a weight above the 95th percentile for gestational age (Figure 3(a)). The ratio of placental weight to birth weight was 0.63 ± 0.57 (range, 0.23–3.68). In the typical enlarged placenta affected by PMD, large, tortuous vessels were found on the fetal surface (Figure 3(b)). The incised planes had heterogeneous areas with cysts that contained gelatinous liquid and normal red-brown or spongy villous tissue. Cystic areas were focally distributed and abundant on the fetal surface (Figure 3(c)).

Specimens for histopathological examination were provided for 27 cases. Specimens from multiple locations included PMD-affected and non-affected areas. Almost all of the placental specimens obtained from grossly PMD-affected areas consisted of histopathologically normal and abnormal areas in varying proportions. Of eight specimens obtained from a grossly normal portion of a placenta affected by PMD, three were diagnosed as normal by at least one diagnostician, while five contained pathological lesions.

Discussion

More than 100 case reports and several literature reviews have provided insights on the pathology of PMD. Consistent with previous reviews, our study revealed that PMD is associated with a higher prevalence of BWS, disproportionate proportion of female fetuses, and increased incidence of HDP, threatened premature labor, FGR, and FD.

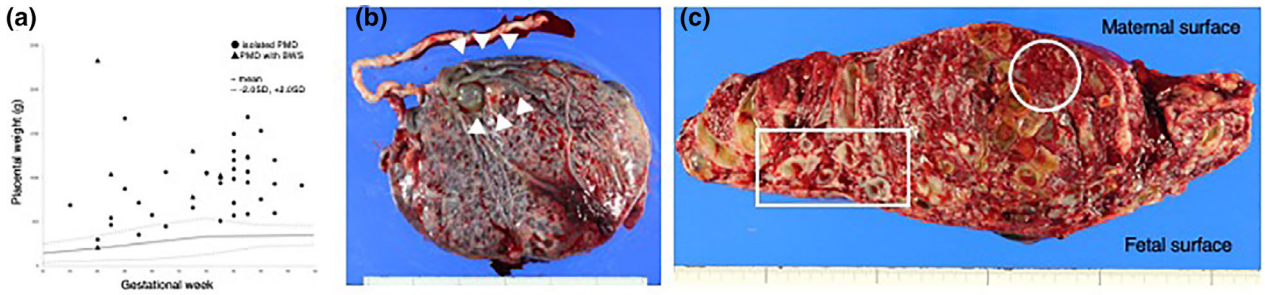

FIGURE 3 Typical placental features of PMD. (a) Weight of the affected placenta by gestational week. The average fixed placental weight was 933 ± 401 g (range, 210–2330 g). Of 46 placentas, 41 (89.1%) had relative placentomegaly based on gestational age. (b) Typical macroscopic view of the fetal surface of a placenta affected by PMD delivered at 38 weeks and 0 days of pregnancy by cesarean section. The birth weight was 2755 g and the placental weight was 1530 g. Large, tortuous vessels (arrowheads) were observed on the fetal surface of the enlarged placenta. (c) Macroscopic view of the incised plane from the same patient. There were heterogeneous areas with numerous cysts containing gelatinous liquid (square) and normal red-brown or spongy villous tissue (circle). The cystic areas were predominantly on the fetal placental surface

Elevated MSAFP or MShCG levels among patients with PMD have been extensively reported.[6,9–11] Alpha-fetoprotein is thought to be transported extraordinarily from the fetus to the maternal circulation because the abnormal placental vessels in PMD are highly permeable.[3,12] In our study, MSAFP increased during the second and third trimesters in 83.3% of examined cases, while MShCG transiently increased in only 17.8%. Thus, elevated MSAFP levels with normal MShCG levels is a potentially useful biomarker for differentiating PMD from molar pregnancies. All three patients with normal MSAFP levels had only one measurement. Multiple MSAFP measurements may be necessary for diagnosing PMD because the levels may rise transiently.

Elevation of both MSAFP and MShCG levels was detected in three patients with PMD. A higher ratio of placental to infant weight was more commonly associated with PMD involving elevated MShCG levels, but this finding was not statistically significant. The reason for higher MShCG levels in patients with PMD remains unclear. The reason might not be related to placental anomaly, considering that high MShCG levels are known to be associated with Down's syndrome[13] and possibly associated with HDP.[14]

Moreover, MSAFP levels might reflect the degree of placental vasodilation and fetal adverse outcomes; in PMD, fetal erythropoiesis might not adapt to the acute enlargement of the vascular bed, resulting in fetal anemia or FD.[15] In our study, nine patients in whom MSAFP was measured within a week before delivery. Three infants with anemia had tended to be higher MSAFP levels than the other six infants who were not anemic (28.6 ± 22.1 ng/mL vs. 2.5 ± 1.5 ng/mL, $p = 0.08$). The role of MSAFP as a biomarker in PMD requires more consideration.

Placental dysfunction is presumed to occur in PMD, which may be related to the mechanism of maternal HDP development. In our study, the incidence of HDP was 12.2%, which was consistent with the reported range of 5.6% to 18.8%.[4–6] All cases of HDP resulted in preterm birth, accounting for 24.0% of preterm cases associated with PMD. These results suggested that HDP contributes to the high incidence of preterm birth in PMD.

Furthermore, our results revealed that HDP in patients with PMD is associated with male fetal sex and BWS. Surprisingly, no mothers with HDP had female infants without BWS. This is the first report to suggest causal factors in the development of HDP in PMD.

Two major reviews found similar trends.[4,5] It was reported that when a fetus has complications of BWS, regardless of the presence of PMD, the incidence of HDP was high (gestational hypertension, 17.7%; preeclampsia, 8.7%).[16] Approximately 50% of patients with BWS have decreased expression of CDKN1c encoded by the imprinted *CDKN1C* gene.[17] Meanwhile, CDKN1c is reportedly involved in the pathophysiology of preeclampsia, according to an analysis of children born to women with preeclampsia or HELLP syndrome and a mouse model of preeclampsia.[18,19] The pathogenesis of PMD remains unclear. However, the association between BWS and sex

distribution suggests a genetic relationship that involves imprinting genes. How fetal BWS and male sex in PMD are related to the development of maternal HDP requires further investigation.

In the earliest reliable review by Pham *et al*. in 2006, FD occurred in 35.6% of fetuses during gestational weeks 16–36.[5] Similarly, our study found that FD onset occurred during gestational weeks 20–36. The mortality rate decreased to 17.0%, similar to results from a recent European multicenter study (18.0%, four of 22 patients).[20] Of 39 live births, 23 (59.0%) were associated with premature induction of labor or cesarean section after gestational week 24; these cases were strongly related to FGR. Although there is currently no PMD-specific perinatal care protocol, these results suggest that conventional perinatal management of FGR in Japan and probably in other developed countries could reduce the mortality rate of fetuses with PMD.

Meanwhile, among the eight cases of FD in this study, four (50.0%) were LFD at delivery, but only one had FGR. No other findings suggesting impending FD were observed. In our study, FD only occurred among fetuses without BWS. However, in a previous case series, eight of 15 fetuses with both BWS and PMD were terminated because of fetal malformations, and four died during the perinatal period.[21] Considering that our study was based on reported or consulted cases, the number of cases with BWS and PMD that end in termination might be underestimated. Factors associated with FD in fetuses with PMD should be clarified in future studies.

Previous case reports have shown that placentas with PMD are not histopathologically homogeneous. This study confirmed this finding and also showed that even grossly normal areas contained histopathological lesions. Normal tissue was observed only in some specimens. Therefore, heterogeneity cannot be ignored in future studies informing the establishment of diagnostic criteria for PMD and the relationship between clinical and histopathological findings. It is necessary to consider multiple specimens according to certain rules.

In conclusion, PMD is a high-risk condition for both the mother and the child. It is a possible risk factor for HDP in a pregnancy with a male fetus or fetus with BWS. For prenatal diagnosis, in addition to ultrasonography, elevated MSAFP levels with normal MShCG levels in the second and third trimesters may be indicative of PMD. Although perinatal management for PMD has not been established, conventional perinatal management of FGR in Japan might reduce the fetal mortality rate.

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Disclosure

The authors declare no competing financial interests.

Author Contributions

T.O. designed the research and C.K., S.A. and K.H. acquired of data. C.K. and T.O. analyzed and interpretated of data, and C.K. drafted the manuscript. Y. M., M.F., H.S. and H.K. were involved in technical support or critical revision of the manuscript for important intellectual content. T.O., H.S. and H.K.

were involved in obtaining funding. All authors reviewed and approved the final paper.

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