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Title: Prospective risk of stillbirth in women with placental mesenchymal dysplasia

Satoshi Ishikawa¹, Mamoru Morikawa¹, Takahiro Yamada¹*, Rina Akaishi¹,
Masanori Kaneuchi², Hisanori Minakami¹

1) Department of Obstetrics, Hokkaido University Graduate School of Medicine,
Sapporo, Japan

2) Department of Obstetrics and Gynecology, Nagasaki University Graduate School of Medicine, Nagasaki, Japan

Running head: Prospective risk of stillbirth in PMD

Corresponding author: Takahiro Yamada, MD, PhD,
Department of Obstetrics, Hokkaido University Graduate School of Medicine, N15W7,
Kita-ku, Sapporo, 060-8638, Japan

Tel: +81-11-706-6932; Fax: +81-11-706-6932;
E-mail: taka0197@med.hokudai.ac.jp
Abstract

Aims: To provide better counsel to pregnant women with suspected placental mesenchymal dysplasia (PMD) regarding the risks of preterm birth and intrauterine fetal death (IUFD).

Methods: We reviewed the outcomes of 109 PMD pregnancies with gestational week (GW) ≥ 24 abstracted from 63 reports in the English literature, including two cases that we encountered recently. The prospective risk of stillbirth at GW N was defined as the number of women with stillbirth at GW ≥ N divided by number of women giving birth at GW ≥ N.

Results: A total of 32 (29.4%) women experienced stillbirth at a median GW of 31 (range, 24 – 38). Preterm birth (GW < 37) occurred in 52 (67.5%) of the 77 live-born infants. Only 25 (22.9%) women had full-term (GW ≥ 37) live-born infants. The prospective risks of stillbirth were 29.4% (32/109), 27.5% (25/91), 20.9% (14/67) and 13.0% (6/46) for women who reached GW 24\(^{0/7}\), 28\(^{0/7}\), 32\(^{0/7}\) and 36\(^{0/7}\), respectively.

Conclusion: As women with PMD are at markedly elevated risk of IUFD, early admission to the hospital and intensive monitoring of fetal status should be considered, although whether this policy improves outcome has not been validated.

Key words: antenatal diagnosis, perinatal mortality, placenta, prophylactic treatment, molar pregnancy
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Introduction

As placental mesenchymal dysplasia (PMD) has a distinct placental phenotype, showing cystic areas mimicking hydatidiform mole on ultrasound, PMD can be suspected prenatally. However, as PMD can coexist with a completely normal fetus, it has often been misdiagnosed as a partial hydatidiform mole and has therefore also been referred to as a “pseudo partial mole”\(^1\)\(^-\)\(^3\). PMD is extremely rare, occurring in 0.002% – 0.02% of pregnancies\(^4\),\(^5\), and is seen predominantly in female fetuses\(^5\).

Although PMD is compatible with fetal life, high rates of intrauterine fetal death (IUFD), i.e., 13% and 36%, were reported in two literature reviews\(^6\),\(^7\). However, these reviews\(^6\),\(^7\) did not present “the prospective risk of IUFD” which may be important in the better counselling among women with living fetuses undelivered, since the prospective risk of IUFD changes according to gestational week. Preterm delivery was indicated for severe fetal growth restriction (FGR) and/or non-reassuring fetal status (NRFS) in several cases. In addition, abrupt worsening of fetal condition was documented within one day after confirming fetal well-being in at least two cases\(^8\),\(^9\). These reports together with the high IUFD rate suggest that delay of delivery causes IUFD in a considerable number of fetuses affected by PMD. Therefore, intensive monitoring of women with PMD may improve pregnancy outcome, although this has not yet been verified.

We encountered two women with PMD in whom IUFD occurred at gestational week (GW) 31 in the first case. We performed an extensive literature search focusing on the fetal outcome to determine the prospective risk of stillbirth and to provide better
counselling for the second case. Here, we report the prospective risks of stillbirth according to GW among undelivered infants based on the literature search along with our two cases of PMD. Approval for this presentation was obtained from the patient and the Institutional Review Board of the Ethics Committee of Hokkaido University Hospital.

Materials and Methods

This study was conducted with the approval of the institutional review board of Hokkaido University Hospital and conforms to the provisions of the Declaration of Helsinki (as revised in Tokyo 2004). For this study, informed consent was not needed, because this study is a review of the literatures.

A literature search regarding PMD was conducted using PubMed on June 2014. The search term “placental mesenchymal dysplasia” yielded a list of 88 literature reports. Of these, 50 were included in the present analysis because information was available regarding individual data on PMD pregnancies with GW ≥ 24 in the English language\(^1\)\(^-\)\(^50\). In addition, a further 13 reports\(^51\)\(^-\)\(^63\) that appeared in reference lists of pertinent literature reports were also included in our analysis. As the first PMD pregnancy was described by Moscoso et al\(^60\) in 1991, we included reports published in 1991 and thereafter. We identified a total of 63 literature reports describing a total of 107 PMD pregnancies with GW ≥ 24, consisting of 50 dealing with single cases\(^3\)\(^,\)\(^4\)\(^,\)\(^6\)\(^,\)\(^8\)\(^-\)\(^14\)\(^,\)\(^16\)\(^-\)\(^21\)\(^,\)\(^23\)\(^-\)\(^36\)\(^,\)\(^38\)\(^-\)\(^40\)\(^,\)\(^42\)\(^-\)\(^48\)\(^,\)\(^50\)\(^-\)\(^52\)\(^,\)\(^54\)\(^-\)\(^58\)\(^,\)\(^61\)\(^,\)\(^63\), eight with two cases\(^15\)\(^,\)\(^22\)\(^,\)\(^37\)\(^,\)\(^41\)\(^,\)\(^49\)\(^,\)\(^53\)\(^,\)\(^59\)\(^,\)\(^60\)\(^,\)\(^8\)\(^,\)\(^1\)\(^-\)\(^2\)\(^,\)\(^3\)\(^-\)\(^4\)\(^,\)\(^6\)\(^,\)\(^8\)\(^-\)\(^14\)\(^,\)\(^16\)\(^-\)\(^21\)\(^,\)\(^23\)\(^-\)\(^36\)\(^,\)\(^38\)\(^-\)\(^40\)\(^,\)\(^42\)\(^-\)\(^48\)\(^,\)\(^50\)\(^-\)\(^52\)\(^,\)\(^54\)\(^-\)\(^58\)\(^,\)\(^61\)\(^,\)\(^63\), one with...
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four cases, one with five cases, two with nine cases, and one with 14 cases.

These 107 pregnancies in the 63 English literature reports were considered entirely different populations, without double-counting the same individuals with PMD based on maternal age, gestational age, birth weight, fetal gender and/or clinical courses, although some of the data were unknown in some cases (Table 1). In of the 63 English literature reports, a total of 14 PMD pregnancies that ended at GW 14 – 23, including two with chromosomal aberrations, were presented, but these pregnancies were excluded from the present analyses.

Finally, we analysed the outcomes of a total of 109 PMD pregnancies, including our two cases focusing on GW at delivery, delivery mode and live birth/stillbirth.

Here, we present a brief summary of our two cases. Case 1: a 27-year-old nulliparous Japanese woman with abnormal findings of the placenta suggestive of PMD on ultrasonography at GW 10 was found to have IUFD at a regular antenatal care on GW 31. A dead, normally formed female infant weighing 1354 g was born at GW 31. Although no autopsy was performed in this infant, we suspected that anomalies in the placental vasculature were responsible for the IUFD causing hypoxia in this infant.

Case 2: a 26-year-old multiparous Japanese woman at GW 18 was had abnormal findings of the placenta suggestive of PMD on ultrasonography. She underwent caesarean section at GW 31 following long-term (approximately 9 weeks) intensive monitoring of fetal condition and extensive discussion about the risk of IUFD, giving birth to a premature otherwise healthy but FGR female infant weighing 1116 g. The results of histological examination of both placentas for Cases 1 and 2 were consistent
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with the diagnosis of PMD showing enlarged, oedematous stem villi with focal cistern formation and large, dilated (to varying degrees) and tortuous vessels on the chorionic plate.

Results

Among 109 PMD pregnancies with GW ≥ 24, 84 female infants were born, accounting for 77.1% of all 109 infants (Table 1). Median birth weight was 1870 g (range, 185 – 3650 g) for 95 infants with known birth weight. Delivery mode was caesarean section in 31 (52.5%) of 59 women with known delivery mode and live-born infants. The indication for caesarean deliveries was NRFS in 12 (39%) of the 31 women. Median GW at delivery was 34 (range, 24 – 40) for all 109 women and 36 (24 – 40) for the 77 women with live-born infants. Preterm births at GW < 37 occurred in 74.3% of all 109 pregnancies and 67.5% of 77 pregnancies with a live-born infant.

Among 52 preterm deliveries with live-born infants, the NRFS and/or FGR in the absence of premature rupture of the fetal membranes (PROM) were factors leading to preterm deliveries in 11 (21.2%) pregnancies including our Case 2. Other factors leading to preterm deliveries were PROM in 10 cases and preterm labour pains in 13 cases. Only 25 (22.9%) women had full-term (GW ≥ 37) live-born infants (Fig. 1). Of the 25 infants born to these women, including one with an
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unspecified birth weight $^2$, 15 (60%) were documented to be born with a low birth weight < 2500 g (6 were less than 2000 g) $^5, 7, 15, 22-24, 31, 35, 39, 42, 53, 62$.

Stillbirths occurred in 32 (29.4%) women including our Case 1 at median GW of 31 (24 – 38) (Table 1) $^2, 4, 5, 7-10, 15, 19, 22, 28, 32, 36, 38, 41, 43, 48, 57, 59, 61, 62$. Of 20 infants stillborn at and after GW 30 including our Case 1 (Fig. 1) $^4, 5, 7-9, 15, 19, 22, 28, 32, 38, 43, 48, 59$, at least 10 infants including our Case 1 exhibited no external anomalies on post-mortem examination $^4, 7, 9, 32, 38, 43, 48$ while 7 infants had anomalies including 13 trisomy in one $^{15}$, Beckwith–Wiedemann syndrome in one $^{59}$ and a mass arising from the liver in 5; intra-abdominal large cystic mass attached by a pedicle to the inferior side of the liver $^8$, liver cyst $^{22}$ and liver cavernous haemangioma $^{28}$ in one each, and hepatic mesenchymal hamartoma in two $^7, 19$. Deaths were considered derived from a decreased maternal–fetal gas exchange due to the placental vascular anomalies in five cases without external anomalies including our Case 1 $^4, 9, 43, 48$. Rupture of the cirsoid chorionic vessels was considered responsible for the IUFD in one $^{48}$ of the five cases.

Effects of chromosomal aberration and placental size on IUFD rate were examined (Table 2). Although not all of 109 infants with PMD pregnancies underwent chromosomal analysis, three infants $^{15, 28}$ were identified to have chromosomal aberrations and two of the three were stillborn at GW 30 and GW 36. Both birth weight and placental weight were specified in 82 singleton infants. Median value of the birth weight-to-placental weight ratio (g/g) was 2.10 (range, 0.54 – 5.83) demonstrating that the placenta was large for infant in PMD pregnancies. However, birth weight-to-placental weight ratios (g/g) were not associated with the risks of IUFD.
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Prospective risk of stillbirth according to GW was determined (Fig. 2). Women with PMD reaching GW 24 had a prospective risk of stillbirth of 29.4% (32/109). This risk was very high even in women reaching GW 30, 33 and 36, i.e., 24.4% (20/82), 20.0% (12/60) and 13.0% (6/46), respectively.

Discussion

The present literature review focused on the timing of stillbirth among women with PMD and constructed the prospective risk of stillbirth according to GW to provide better counsel to pregnant women with suspected PMD. The prospective risk of stillbirth showed that women with PMD pregnancies had a markedly higher risk of IUFD at any GW of 24 or later. In addition, the present study emphasized that women with PMD were at markedly higher risk of preterm delivery; less than a quarter of women had a full-term live-born infant and 60% of the 25 full-term newborn infants had a low birth weight < 2500 g.

The risk of stillbirth was 29.4% among PMD women who reached GW 24 in this study, far exceeding that of the general population. Stillbirth is rare, accounting for only approximately 0.4% of all births occurring at GW ≥ 22 over the past 20 years in Japan, and similar figures have been reported in other areas/countries: 0.47% and 0.28% at and after GW 24 for Inuit and non-Aboriginal residents of Quebec in 2000–2009, respectively, and 0.17%, 0.19%, 0.20%, 0.22% and 0.30% at and after GW 32.
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in 2004 for Finland, Austria, USA, Canada and Italy, respectively\(^6\). Therefore, women with PMD had a more than 60-fold greater risk of stillbirth than the general population. The prospective risk of stillbirth remained high (above 10%) even in women who reached term of GW 37 at which time the corresponding figure is less than 0.2% in the general Japanese population\(^6\). Therefore, it is necessary to develop a method to avoid IUFD in women with PMD.

Although causes of IUFD were not known in most cases of PMD pregnancies, dying infants usually show NRFS before death with varying time intervals until death after showing NRFS. Among 52 preterm live-born infants, NRFS and/or FGR were seen in at least 21% of infants, leading to an indicated preterm delivery and the rescue of these infants. Of 20 stillbirths occurring at and after GW 30, 11 of 13 pregnancies with available relevant information\(^4, 8, 9, 15, 19, 22, 28, 32, 38, 43, 48, 59\) including our Case 1 were managed on an outpatient basis and only two stillbirths occurred during hospital stays; a few hours after admission to a hospital for PROM at GW 34, IUFD occurred following abrupt fetal tachycardia and subsequent prolonged bradycardia despite an emergent caesarean section in one case\(^9\), and IUFD occurred one day later in another case with normal fetal heart rate pattern on the day of admission to hospital for preterm labour at GW 31\(^8\). Thus, although the management of PMD pregnancy as an inpatient does not necessarily imply that timely medical intervention can avoid IUFD, we believe that physicians should recommend early hospitalization for women with PMD to allow intensive monitoring of fetal status.

Preterm birth is a major risk factor for increased morbidity and mortality of children.
Prospective risk of stillbirth in PMD

As an induced vaginal delivery is indicated for infants with IUFD and as IUFD occurred in 29% of PMD pregnancies, the preterm birth rate was expected to be high in women with PMD. However, even after excluding women with IUFD, the preterm birth rate was extremely high in PMD pregnancies; preterm births at GW < 32 and < 37 accounted for 31.2% and 67.5% of all 77 live births (Fig. 1), respectively. The corresponding figures were 0.74% (7768/1050806) and 5.7% (60285/1050806) in Japan in 2011. In these 52 preterm deliveries with live-born infants, NRFS and/or FGR, PROM and preterm labour pains occurred frequently. As PMD pregnancy mimics molar pregnancy with living fetus, the PMD pregnancy may be easily suspected on ultrasound study. Blood flow is seen in placental cysts of PMD pregnancies, while blood flow is absent in the cyst of molar pregnancy. This may help to differentiate PMD pregnancies from molar pregnancies. Recommendation for early prophylactic admission to hospital may be justified to prolong the length of gestation and allow intensive monitoring of fetal condition, although whether this policy is actually beneficial has yet to be verified.

The present study had some limitations. First, the data analysed in this study were based on single case reports and small case series in the literature so publication bias is unavoidable. This may have led to accumulation of eventful pregnancies associated with PMD. Although 29% of fetuses with PMD died in utero in this study, there may have been unreported and uneventful pregnancies with PMD. Therefore, it was possible that this study overestimated the risk of IUFD in pregnancy with PMD. Second, the exact time of IUFD was not specified in most cases. IUFD may have preceded the stillbirth by several days to several weeks. Therefore, figures for the
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prospective risk of stillbirth according to GW in this study differed somewhat from
those for actual prospective risk of IUFD according to GW.

In conclusion, although it has been noted that IUFD is frequent in PMD pregnancies,
the prevalence rate of IUFD reported to date was based on retrospective point of view
and was less helpful compared to the prospective risk of stillbirth for clinicians. The
prospective risk of stillbirth constructed in this study suggested that a markedly higher
risk of stillbirth continued to term among women with PMD. Clinicians encounter
PMD women whose fetuses are still alive and have to determine the appropriate
management for improving outcome. Our figures for the prospective risk of stillbirth
may encourage clinicians to recommend early hospitalization for patients with PMD to
allow intensive fetal monitoring. However, whether this policy is beneficial for
improving the outcome remains uncertain. Indeed, a case of sudden IUFD in which
emergent caesarean section failed to rescue the infant has been reported⁹.

Acknowledgement

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Conflict of interest

All authors declare that they have no financial relationships with biotechnology
manufacturers, pharmaceutical companies or other commercial entities with an interest in the subject matter or materials discussed in this manuscript
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Figure legends

Fig. 1 Numbers of live-born and stillborn infants according to gestational age

Among 109 pregnancies, 32 ended in stillbirth. One case with an unspecified GW at delivery, but at term, was assumed to give birth at GW 38.

![Chart showing numbers of live-born and stillborn infants by gestational age](image-url)
Fig. 2 Prospective risk of stillbirth according to gestational week

Prospective risk of stillbirth was calculated based on the numbers in Fig. 1 among women who reached GW $N$ as follows: number of all stillbirths occurring at GW $\geq N$/number of all births occurring at GW $\geq N$.67
Table 1. Demographic characteristics of 109 PMD pregnancies with gestational week ≥24

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Number (Percentage)</th>
</tr>
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<tbody>
<tr>
<td>No. of women</td>
<td>109</td>
</tr>
<tr>
<td>Maternal age (year) for 88 women</td>
<td>28 [18 – 39]</td>
</tr>
<tr>
<td>Unknown maternal age</td>
<td>21 (19.3%)</td>
</tr>
<tr>
<td>Parity</td>
<td></td>
</tr>
<tr>
<td>Nulliparity</td>
<td>31 (28%)</td>
</tr>
<tr>
<td>Multiparity</td>
<td>43 (40%)</td>
</tr>
<tr>
<td>Unknown</td>
<td>35 (32%)</td>
</tr>
<tr>
<td>Twin pregnancy</td>
<td>3 (2.8%)</td>
</tr>
<tr>
<td>Infant sex</td>
<td></td>
</tr>
<tr>
<td>Female</td>
<td>84 (77.1%)</td>
</tr>
<tr>
<td>Male</td>
<td>16 (14.7%)</td>
</tr>
<tr>
<td>Unknown</td>
<td>9 (8.3%)</td>
</tr>
<tr>
<td>Birth weight (g) for 95 infants</td>
<td>1870 [185 – 3650]</td>
</tr>
<tr>
<td>– 1499</td>
<td>29 (26.6%)</td>
</tr>
<tr>
<td>1500 – 1999</td>
<td>27 (24.8%)</td>
</tr>
<tr>
<td>2000 – 2499</td>
<td>24 (22.9%)</td>
</tr>
<tr>
<td>2500 – 2999</td>
<td>8 (7.3%)</td>
</tr>
<tr>
<td>3000 –</td>
<td>7 (6.4%)</td>
</tr>
<tr>
<td>Unknown</td>
<td>14 (12.8%)</td>
</tr>
<tr>
<td>Delivery mode for 77 live-born infants</td>
<td></td>
</tr>
<tr>
<td>Cesarean</td>
<td>31 (40.3%)</td>
</tr>
<tr>
<td>Vaginal</td>
<td>28 (36.4%)</td>
</tr>
<tr>
<td>Unknown</td>
<td>18 (23.4%)</td>
</tr>
<tr>
<td>Gestational week at delivery</td>
<td></td>
</tr>
<tr>
<td>&lt; 30</td>
<td>34 [24 - 40]</td>
</tr>
<tr>
<td>&lt; 34</td>
<td>27 (24.8%)</td>
</tr>
<tr>
<td>&lt; 37</td>
<td>51 (46.8%)</td>
</tr>
<tr>
<td>&lt; 37</td>
<td>81 (74.3%)</td>
</tr>
<tr>
<td>Stillbirth</td>
<td>32 (29.4%)</td>
</tr>
<tr>
<td>Gestational week at stillbirth</td>
<td></td>
</tr>
<tr>
<td>24 – 27</td>
<td>7 (21.9%)</td>
</tr>
<tr>
<td>28 – 31</td>
<td>11 (34.4%)</td>
</tr>
<tr>
<td>32 – 35</td>
<td>8 (25.0%)</td>
</tr>
<tr>
<td>36 -</td>
<td>6 (18.8%)</td>
</tr>
</tbody>
</table>

Data are presented as number of subject (percentage) or median [range].
PMD, placental mesenchymal dysplasia.
†, after excluding 32 cases with stillbirth.
Table 2. Effects of chromosomal aberration and placental size on IUFD rate

<table>
<thead>
<tr>
<th>Confirmed chromosomal aberration</th>
<th>IUFD rate</th>
</tr>
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<tbody>
<tr>
<td>Present</td>
<td>2/3 (67%)</td>
</tr>
<tr>
<td>Absent or undetermined</td>
<td>30/106 (28%)</td>
</tr>
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\[ P=0.206 \]

Birth weight-to-placental weight ratio (g/g) *

<table>
<thead>
<tr>
<th>Range</th>
<th>IUFD rate</th>
</tr>
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<tbody>
<tr>
<td>– 1.49</td>
<td>7/29 (24%)</td>
</tr>
<tr>
<td>1.50 – 2.49</td>
<td>8/30 (27%)</td>
</tr>
<tr>
<td>2.50 –</td>
<td>7/23 (30%)</td>
</tr>
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Not significant

*, Both birth weight and placental weight were specified in 82 singleton infants. The IUFD occurred in 22 (27%) of the 82 infants.