

# Placental mesenchymal dysplasia

## Displasia mesenquimatosa placentária

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### Abstract

Placental mesenchymal dysplasia is a rare benign abnormality of the placenta. It is characterized by placentomegaly and an ultrasound appearance of "grape-like" vesicles in the placenta, coexisting with a normal fetus. The etiology for these changes is still unknown, although there are some hypotheses. The objective of this article is to review the causes, clinical and pathological features, differential diagnosis and complications of placental mesenchymal dysplasia. It is important that sonographers, obstetricians and pathologists are aware of this entity to be able to make a correct diagnosis and to manage adequately these pregnancies.

**Keywords:** Placental mesenchymal dysplasia; Stem villous hyperplasia; Molar pregnancy; Beckwith-Wiedemann syndrome; Intrauterine growth restriction..

### INTRODUCTION

Placental Mesenchymal Dysplasia (PMD) is a rare placental vascular anomaly, characterized by placentomegaly and grapelike vesicles. It was firstly described in 1991 by Moscoso *et al*<sup>1</sup> and since then it has been increasingly recognized. Some of the authors have preferred to use the term placental mesenchymal hyperplasia, instead of dysplasia<sup>2,3</sup>.

The incidence of PMD was reported as 0,02%<sup>4</sup>, but the true figure is unknown, since this entity has been previously reported under other designations, namely "placentomegaly with massive hydrops of placental stem villi" or "pseudopartial moles". Furthermore, PMD remains unfamiliar to many sonographers and pathologists<sup>5</sup>, and usually only placentas from patients with medical comorbidities or pregnancy complications are sent for pathological examination<sup>6</sup>.

Recently, Zeng *et al.* consecutively studied 34655 deliveries from a single institution performing pathological placental examination and found the incidence of PMD to be 0.002%, much less than the previously reported incidence<sup>7</sup>. PMD is more frequent in female fetuses (male to female ratio 1:8<sup>6</sup>).

### ETIOLOGY

PMD is characterized by overgrowth of placental tissue, but the mechanisms for this overgrowth are not fully understood. Histological examinations of the placentas have demonstrated mesenchymal hyperplasia in stem villi along with other mesenchymal proliferative disorders (such as chorangiomas and chorionic vessel dilatation); hemangiomas and hepatic hamartomas of the fetus are also frequent associated findings<sup>2,8</sup>. These observations led some authors to consider PMD as a congenital mesodermal malformation.

There is also an association between PMD and Beckwith-Wiedemann Syndrome (BWS). Around 23% of PMD cases are associated with BWS<sup>9</sup>. BWS has a highly variable penetrance, and BWS and PMD can be considered as part of the same spectrum of changes with a common etiology: PMD exhibiting changes confined to the placenta and BWS showing additional changes in the fetus (macrossomia, anterior abdominal wall defects, macroglossia, internal visceromegaly and increased susceptibility to childhood tumors<sup>10,11</sup>). The pathogenesis of BWS is related to abnormal expression or disruption of one or more imprinting genes on chromosome 11p15.5<sup>12,13</sup>. It is thought that in PMD this abnormality is confined to the placenta. The genes usually involved are CDKN1C

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(p57), H19, IGF-2 and KVLQT<sup>14-19</sup>.

Hypoxia and hypoperfusion of any etiology can originate the usual placental findings in PMD. During hypoxia, fibroblasts produce a larger amount of connective tissue fibers with subsequent increased production of vascular endothelial growth factor by villous macrophages, leading to angiogenesis<sup>20-21</sup>.

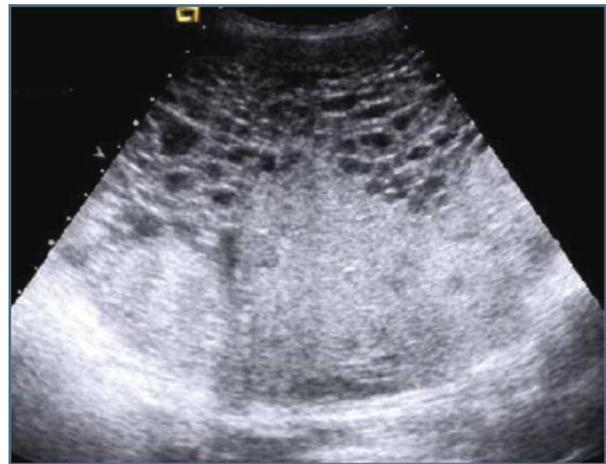
Another theory for the origin of PMD is the presence of androgenetic/biparental mosaicism confined to the placenta; this is supported by the presence of two separate cell lines in placentas with PMD, an androgenetic line and a biparental line. The abnormal androgenetic cells are confined to the chorionic mesoderm membranes and vessels, not affecting the trophoblast cells<sup>21</sup>. This theory may also account for the marked predominance of females in PMD: since the androgenetic line arises from the duplication of the paternal haploid genome, it is likely that this would originate a 46,XX cell line, since a 46,YY cell line is not compatible with life. The presence of PMD in male fetuses cannot be explained by this theory and so it seems that PMD has a heterogeneous etiology<sup>5</sup>.

## CLINICAL FEATURES

Most of PMD cases can be diagnosed by prenatal ultrasound. The classic sonographic feature is a thickened placenta with hypoechoic spaces<sup>5</sup> (Figure 1). Some authors describe this appearance as “swiss cheese” or “moth eaten placenta”<sup>6</sup>. A few small hypoechoic spaces may be present in a placenta without any clinical significance, but whenever they are diffuse, close monitoring of the pregnancy is necessary. Jauniaux *et al.* used ultrasound and Doppler to evaluate PMD cases and found cystic spaces located deep in the placental parenchyma which tended to move towards the chorionic plate as the pregnancy advances. The chorionic plate vessels become progressively dilated/ectatic from midgestation onwards<sup>11</sup>.

Three-dimensional (3D) and color Doppler ultrasound may add information about origin, location, size and blood supply of placental lesions<sup>24-28</sup>. The 3D reconstruction usually demonstrates a multi-cystic placental mass with cysts of various diameters clearly separated but adjacent to a normal appearing placenta. Rendering of the image with inversion mode reveals multiple fluid filled cysts that do not communicate with each other<sup>29</sup>.

The most commonly affected laboratory result is



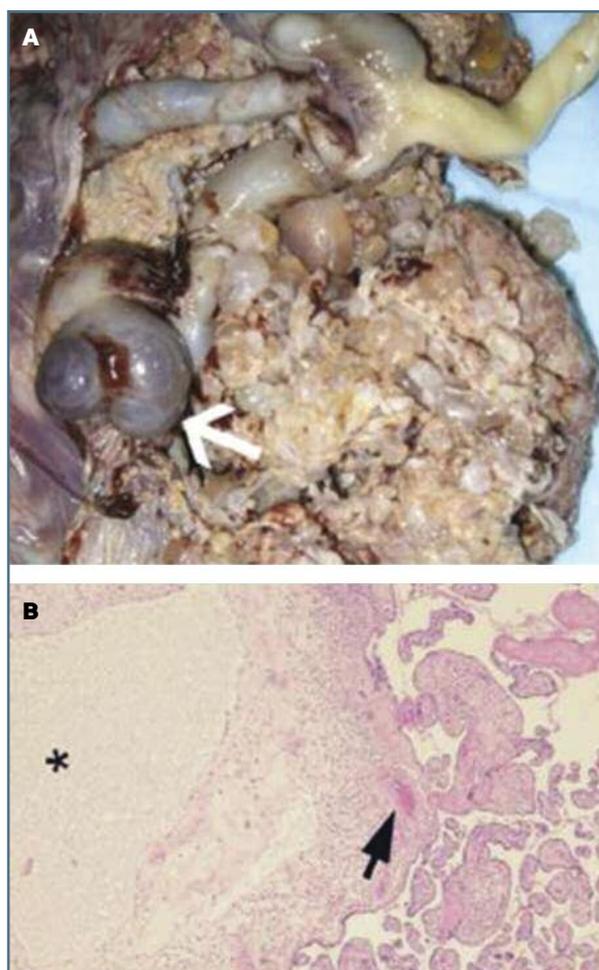
**FIGURE 1.** Ultrasound scan of a 19 weeks pregnancy. A placenta with features of PMD. Adapted from Woo GW, *et al*<sup>40</sup>, with permission

maternal level of alfa-fetoprotein. It is thought that the increase in surface transfer area of the placenta – due to increased volume and increased number of vessels with thinned walls – may originate increased levels of alfa-fetoprotein<sup>1</sup>. The level of beta-hCG is normal to slightly elevated, due to placentomegaly, and returns to normal soon after delivery<sup>1,9,12</sup>. In a recent meta-analysis of 64 cases this hormone was found to be elevated in 38% and alfa-fetoprotein in 70%<sup>6</sup>.

Fetuses with PMD may present later in pregnancy with growth restriction or fetal demise. Polyhydramnios may be present if the fetus has swallowing difficulties as part of BWS. Many cases are asymptomatic and only diagnosed postpartum after delivery of an abnormally large placenta<sup>5</sup>.

Sometimes, prenatal diagnosis is difficult and final diagnosis is only achieved after pathological analysis of the placenta.

Macroscopically, the placenta looks large for gestational age, weighting above the 90<sup>th</sup> centile in more than 90% of the cases<sup>9</sup>. At any gestational age, placental parenchyma may have pale and friable areas, with streaks of prominent stem villi and multiple cysts oriented perpendicular to the chorionic plate<sup>9</sup>. These cysts are grossly similar to those of the molar pregnancy, and range in size from 0.3 to 2.5cm. In rare cases, the vesicle formation is minimal or absent<sup>3</sup>. In the third trimester, chorionic plate vessels are dilated and tortuous, with abnormal branching, reaching up to 2.5cm in diameter<sup>12</sup>. These vessels may have luminal thrombosis or rupture, giving rise to subamniotic hemorrhage,



**FIGURE 2.** A) PMD specimen with markedly dilated chorionic vessels, some of them being aneurysmal (arrow). There are multiple vesicles of various sizes in placental parenchyma. B) microscopic features of PMD, with dilated stem villi exhibiting central cisterns (asterisk) and fibromuscular stem vessels (arrow). The vesicles are interspersed with normal-sized tertiary villi, seen at the bottom of the image. There is no trophoblastic proliferation (hematoxylin-eosin: original magnification x40). Adapted from Woo GW, *et al*<sup>40</sup>, with permission.

which can further compromise fetal growth<sup>3,12</sup>. The vascular malformations are not seen before 20 weeks suggesting that they develop secondarily to circulatory imbalance and poor vascularization of the dysplastic villi<sup>11</sup>. Rarely, amniotic bands have also been described<sup>30</sup>. Abnormalities of the umbilical cords (tortuous and twisted, with furcate insertion, long cords or single umbilical artery) can be found<sup>4</sup>.

The microscopic findings of PMD are rather specific (see Figure 2), irrespective of their association with BWS. In the third trimester, placentas have di-

lated thick walled chorionic plate vessels with fibromuscular hyperplasia and fibroid necrosis; there may be fresh or organized thrombi with varying degrees of luminal obliteration and recanalization, either in arteries or veins<sup>3,32,33</sup>. In both early and late gestation PMD, the stem villi are enlarged, and can reach up to 10 times the normal size. These enlarged villi have central cisterns filled with gelatinous material and fibromuscular vessels at the periphery<sup>32</sup>. The terminal villi also show similar changes, with mesenchymal cell hypercellularity and stromal fibrosis<sup>4,34</sup>. Chorangiomas can also be identified and in rare cases, extramedullary hematopoiesis is identified. This fact is thought to be a consequence of placental hypoxia<sup>12</sup>. An important feature of PMD is the absence of trophoblastic proliferation, stromal trophoblastic inclusions and scalloping of the villous surface, which are characteristics of molar pregnancy<sup>4,32,35</sup>.

In a normal placenta the stromal cells of the villi – mesenchymal cells – acquire vimentin and desmin at the end of the second month of pregnancy, becoming fibroblasts. With further development they acquire alpha smooth muscle actin and therefore they are called myofibroblasts. In PMD the dilated stem villi stromal cells have a staining pattern similar to fibroblasts – positive for vimentin, desmin and negative for alpha smooth muscle actin, and it appears that these cells have ceased to differentiate beyond the fibroblast stage<sup>36</sup>. p57 protein is also a potential marker for PMD; some authors used this marker to differentiate between normal placenta, spontaneous abortion with hydropic changes and partial moles from complete molar pregnancy<sup>37</sup>. So far no studies were performed to evaluate this marker in PMD.

Among the cases of PMD in which karyotype was studied, the majority were diploid<sup>34</sup> and corresponded to normal females. Chromosomal abnormalities were rare and included trisomy 13, Klinefelter syndrome, triploidy and 46,XXp<sup>-1,9,12</sup>. DNA ploidy studies may be important in distinguishing PMD from partial moles, which are mainly triploid, but they are not very helpful to distinguish PMD from complete moles or spontaneous abortions with hydropic changes.

Molecular analysis of microsatellites at various locations in the genome, can also be used to find the presence of an androgenetic cell line. This microsatellite analysis might be useful in cases of suspicion of PMD when prenatal chromosome analysis shows a diploid karyotype. Confined placental mosaicism is a possibility if an androgenetic cell line is identified af-

ter chorionic villous sampling, and therefore amniocentesis should be offered<sup>9</sup>.

## DIFFERENTIAL DIAGNOSIS

The main differential diagnoses of PMD are partial hydatiform mole, twin gestation with complete mole and a normal fetus, spontaneous abortion with hydropic changes and confined placental mosaicism. When ultrasound reveals features of molar pregnancy in the presence of a normal appearing fetus, it is important to make the correct diagnosis, and avoid an unnecessary termination of pregnancy. In cases of PMD, the placenta is almost always diploid and histologically the villi do not show proliferation of trophoblasts or stromal trophoblastic inclusions as in partial moles. Moreover, in these moles the fetus is usually triploid and shows growth restriction with a wide variety of external and internal defects, with a high chance of dying in the first trimester. In cases of twin pregnancies with complete moles there are no abnormal fetal vessels in the stem villi as in PMD and the fetus is usually diploid with a chance of survival. It might be challenging to distinguish PMD from a mole with a normal co-twin, but it carries an important significance due to the risk of persistent gestational trophoblastic disease in the latter case<sup>39,40</sup>. Spontaneous abortion with hydropic changes may have vesicle formation but they are usually small and not diffuse. There are cases of confirmed placental mosaicism for trisomies with cystic villi in the ultrasound, but these cases can be diagnosed by karyotyping<sup>41</sup>.

Immunohistochemical tests using antibodies against p57KIP2 protein (an imprinting gene only expressed in maternal genome) might prove helpful in distinguishing PMD from molar pregnancies<sup>42</sup>. In a complete mole, the villous cytotrophoblastic cells lack maternal genome and are negative for this test, which does not happen in partial moles or hydropic abortions. The immunohistochemical detection of androgenetic/biparental mosaicism in stromal cells suggests PMD since this mosaicism is unusual in molar pregnancies<sup>39</sup>.

## COMPLICATIONS

Because PMD is a rare entity, it is difficult to determine if the complications reported are truly complica-

tions of the disease or just a coincidental finding. According to a recent review, only 9% of cases were fully uncomplicated with respect to maternal or neonatal complications<sup>6</sup>. Approximately one fourth of cases are associated with BWS, and some of the complications seen are secondary to BWS, in cases without a fully phenotypic presentation. For instance, in a neonate with PMD and hyperinsulinemic hypoglycaemia, this can be due to islet cell hyperplasia of the pancreas, which is a frequent finding in BWS<sup>43</sup>.

The usual fetal complications reported in phenotypically normal fetuses with PMD are prematurity, fetal growth restriction and fetal demise<sup>3,32</sup>. Fetal growth restriction can be related to stem villi vessels thrombosis, decreased placental exchange surface, because of a reduced number of normal villi, and diversion of blood within vascular malformations and chorioangiomas; all these factors result in hypoperfusion and hypoxia of the fetus<sup>3,44</sup>. In a review of 45 cases not associated with BWS, 52% of pregnancies had preterm delivery, 33% had fetal growth restriction and 13% had fetal demise<sup>6</sup>. Placentomegaly in PMD is not thought to be a cause of fetal complications, like polyhydramnios, fetal hydrops or preeclampsia<sup>11</sup>. There was not any direct association between placental weight and fetal or maternal complications. Instead, the complications are related to the degree of vascularity and excessive vascular shunting in the chorangiomatic areas<sup>11</sup>. The presence of chorangiomas is related to a higher rate of fetal complications including anemia and thrombocytopenia, which are caused by microangiopathic haemolytic anemia because of abnormal shunting of blood<sup>2,4,30</sup>.

A few number of fetuses have chromosomal abnormalities. There are also reported cases of PMD with fetal congenital adrenal hyperplasia, vascular hamartoma and hepatic mesenchymal hamartoma<sup>45-47</sup>. Although most of them will not show any developmental problem, phenotypically normal fetuses with PMD must be followed up for development of BWS features or other mesenchymal tumors.

Maternal complications occur in around 9% of cases and comprise gestational hypertension, preeclampsia, HELLP syndrome and eclampsia<sup>6</sup>. While these diseases have been reported as maternal complications in PMD, a relationship between them has not been proved yet<sup>48</sup>. All the cases of gestational hypertension reported were also related to BWS<sup>49</sup>.

Around 15% of PMD cases are familiar, and in theory there is a small chance of recurrence in these

families. A follow-up study of 5 years for PMD showed no signs of trophoblastic disease or recurrence of PMD in the next pregnancies<sup>35</sup>.

## CONCLUSION

It is important to make a correct diagnosis of PMD prenatally in order to prevent and reduce the morbidity and mortality associated with it. Sonographers and pathologists must be aware of this entity to be able to deal with the differential diagnoses, particularly in the first trimester of gestation, to prevent unnecessary terminations of pregnancy and to avoid problems related to an undiagnosed gestational trophoblastic disease. Patients should be counselled on the increased risk of preeclampsia, fetal demise, BWS and maternal morbidity. Patients with suspected PMD and normal fetal growth, normal fetal anatomy and uncomplicated maternal history can be reassured that their pregnancies are likely to have a good outcome.

Further studies are still needed to clarify the causes and etiology of PMD, and collaboration among obstetricians, neonatologists and pathologist is fundamental.

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