



## Genetic Diagnosis of Skeletal Dysplasias

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### Introduction

This review is aiming at sharing and detailing our experience and that of others of the abnormal sonographic findings, the macroscopic and microscopic pathologic findings, the role of DNA methylation abnormality leading to androgenic uniparental gene expression, resulting in BWS, and the various pregnancy outcomes associated with PMD. Placental Mesenchymal Dysplasia (PMD) is a rare placental abnormality of yet undetermined etiology. It could be associated with fetal Beckwith-Wiedemann Syndrome (BWS), fetal tumors of various organs, fetal growth restriction as well as intrauterine and neonatal death. It is under-diagnosed as many obstetricians and sonologists, are unfamiliar with the clinical entity.

### Placental Mesenchymal Dysplasia

PMD can be associated with fetal Beckwith Weidman Syndrome (BWS), fetal tumors of various organs, fetal growth restriction as well as intrauterine and neonatal death. It is probably under-diagnosed and under-reported because many healthcare providers, including pathologists and sinologists, are unfamiliar with the clinical entity. Placental Mesenchymal Dysplasia (PMD) is a rare placental abnormality/condition of as yet undetermined etiology with an incidence of about 0.02 per 1000 deliveries. PMD was first recognized by Takayama et al. as a distinct pathologic entity of the placenta. Additional reports of unusual placentas with vascular abnormalities were published in the 1980s and 1990s; finally Moscoso et al. recognized the uniqueness of this disorder and described it as a placental vascular anomaly with diffuse stem villous hyperplasia.

We have diagnosed and cared for 4 cases with confirmed PMD in the last 8 years. Three patients elected to terminate the pregnancy while one case continued the pregnancy and experienced premature delivery at 34 weeks. BWS has been confirmed in the newborn. This review is aiming at sharing and detailing our experience and that of others of the abnormal sonographic findings, the macroscopic and microscopic pathologic findings, the role of DNA methylation abnormality leading to androgenic uniparental gene expression, resulting in BWS, and finally the various pregnancy outcomes associated with PMD. PMD associated with fetal growth restriction in one placenta of a dichorionic diamniotic twin pregnancy have been reported.

### Differential Diagnosis

On ultrasound study, a chorioangioma is a focal lesion and is hypo echoic compared to the rest of the placenta and is typically located on the fetal surface of the placenta. A case of a normal viable fetus with concomitant chorioangioma and PMD, (frequently the two are seen together) has been reported. The differential diagnosis of PMD is broad and includes partial molar pregnancy, complete mole with co-existing normal fetus, hemangioma, sub chorionic hematoma, confined placental mosaicism and hydropic placental changes following extended period of time of spontaneous undiagnosed miscarriage. The observation of intraplacental 'cysts', together with the presence of an embryo or fetus, frequently leads obstetricians to misdiagnose this condition as a partial mole. While the appearance of cysts in molar pregnancy is caused by the presence of edematous villous stroma (hydropic villi), the cysts in PMD are dilated (aneurismal) vessels. The hypo echoic areas also correspond to cistern formation in dysplastic stem villi present in placental parenchyma. In order to help with the sonographic suspicion of PMD, Kuwata et al. have suggested that in the second and third trimesters color Doppler study be used to show blood flow within the placental cysts, leading to what the authors refer to 'stained-glass' appearance, a finding which might be helpful in differentiating PMD from other forms of placental cysts. The placenta of a complete mole with coexisting normal fetus and partial molar pregnancy appears heterogeneous, with partially solid and cystic areas. The case was first identified by prenatal ultrasonography, but the prenatal diagnosis only included chorioangioma. PMD was then confirmed during postnatal evaluation of the placenta, which included gross and microscopic examination of the placenta. Another case of co-occurrence of chorioangioma and PMD has been reported to be associated with maternal pre-eclampsia and fetal growth restriction.

The macroscopic and microscopic findings were consistent with the diagnosis of PMD; however, genetic findings confirmed confined placental chimerism involving a normal bi-parental 46, XY male conceptus Surti et al. have reported of an unusual trizygotic pregnancy that resulted in live-born twins suggesting diverse etiology of PMD cases. The placenta of one twin had Placental Mesenchymal Dysplasia (PMD), which resulted from a chimeric fusion of an androgenetic zygote and a normal bi-parental zygote. One placenta was noted to be diffusely cystic and enlarged.

### PMD and Multiple Gestations

Macroscopically, chorionic vessels on the placental surface of the smaller neonate were prominently enlarged. Pathological histologic findings demonstrated swelling stem villi with enlarged vessels and increased interstitial cells without trophoblast proliferation. Rare cases of PMD including the previously mentioned report by Surti U et al. Have been reported to affect the placenta of one fetus in the setup of dichorionic diamniotic twins as well as monochorionic diamniotic twins. Ultrasound and magnetic resonance imaging showed one placenta of the growth retarded fetus was bulky and had multiple cysts, while the other fetus placenta appeared normal. Immunostaining for p57kip2 was negative in interstitial cells and cytotrophoblasts of the swelling stem villi.

In the case involving monochorionic diamniotic twins pathological examination confirmed a monochorionic diamniotic twin placenta with normal findings in the placental part of twin A. In the part of twin B, the chorionic vessels were much dilated. In the stem villi, This suggested that PMD occurred in one placenta of the dichorionic diamniotic twin, leading to early-onset growth retarded fetus.

In the stem villi, the trophoblastic cells were p57 positive, whereas the stromal fibroblasts were p57 negative, thus confirming discordancy for placental mesenchymal dysplasia in a monochorionic placenta. Stroma was severely hydropic with the formation of central cisterns. Starting from the stem villi and extending into the intermediary and terminal villi, there was also a diffuse capillary proliferation.