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Full length article

Placental mesenchymal dysplasia: An underdiagnosed placental pathology with various clinical outcomes

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ABSTRACT

Background: Placental mesenchymal dysplasia (PMD) is a rare vascular and connective placental anomaly, which is often associated with severe fetal and/or maternal complications. The diversity of presentation of PMD challenges diagnosis and effective pregnancy management.
Objective: We aimed to review cases presenting at 7 tertiary centers worldwide over the last decade and to study the occurrence of obstetric and neonatal complications.
Study design: Pathology databases from 7 tertiary hospitals were screened for cases of PMD (between 2007–2017). Pregnancy history, outcomes and ultrasound images were then reviewed for each case.
Results: Twenty-two cases of PMD were identified. Mean gestational age at diagnosis was 23 weeks (16–39 weeks). Prenatal biochemical screening was abnormal in 8 cases (36%). Of the 12 cases that underwent invasive genetic testing, 4 were abnormal. Six patients (27%) developed maternal complications (preeclampsia/gestational hypertension). Fetal growth restriction was identified in 11 cases (50%) and fetal death in 4 (18%). Four (18%) pregnancies were terminated, 9/14 (64%) delivered preterm and only three (14%) progressed normally. Fourteen babies were born alive; 5 (35%) died in the first sixty-one days after birth, 5 (35%) had transient thrombopenia and 1 (7%) had developmental delay at last follow-up. Our series identified four potential new associations with PMD: placental triploidy mosaicism, CHARGE syndrome, fetal pleuropulmonary blastoma and fetal skeletal dysplasia.
Conclusions: PMD was substantially under-diagnosed before delivery in this cohort. Sonographers, fetal medicine specialists, obstetricians and pathologists should all suspect PMD in cases of an enlarged placenta and should look for fetal abnormalities. Diagnostic genetic testing should be discussed to exclude partial molar pregnancy. Close pregnancy follow-up is indicated due to the high risk of associated fetal or maternal adverse outcomes.

A. Why was this study conducted?

To evaluate obstetrical and neonatal complications associated with placental mesenchymal dysplasia in a multicenter observational study to guide accurate counselling of patients

B. What are the key findings?

PMD was associated with abnormal first trimester biomarkers and genetic testing, fetal growth restriction, malformations and pre/postnatal death. We found a higher incidence of preterm

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Table 1

Case	Maternal age G / P	GA at Dx	1st-trimester screening, HCG, AFP	Prenatal ultrasound	Karyotype	Pregnancy complications	Delivery [type/cause]	Birth outcomes [birthweight, Apgar, pH]	Adverse neonatal outcomes
1	28 2G0P	24	1/5900 HCG 2.67 AFP 2.2	24 WG: - hydramios 27 WG: - anamnios - large hydropic placenta	Newborn: 46,XY Placenta: mos69 XXY/46, XY		28 WG: - EmCS - non reassuring NST	FGR 759g (p5) Apgar 3/5/7/9	RDS treated with CPAP Acute renal failure Thrombocytopenia Hypotension Hypoglycemia NICU during 8 weeks Normal at 2 years old
2	29 1G0P	33	1/280	33 WG: - 4 cm umbilical cord cyst (maternal side) - myocardic hypertrophy	46,XX		33 WG: - SVD	2040g (p45) Apgar 9/9/9 pHa 7.21 pHv 7.27	Wet lung treated with CPAP Anemia & Hyperbilirubinemia Spontaneous resolution of thrombocytopenia Numerous hepatic hamartoma Primary intestinal dysplasia
3	33 1G0P	22	1/6600 HCG 2.5 AFP 1.73	22 WG: - pulmonary hamartoma 27 WG: - massive anasarca	46,XX		27 WG: - EmCs	1420g (>p90)	Neonatal death Solid pleuro-pulmonary blastoma
4	36 4G2P	26	Not done	26 WG: (Twin B) - severe FGR - oligohydramnios - absent end diastolic flow in UV - placentomegaly		26 WG: - Preeclampsia	27 WG: - EmCS - placental abruption - HELLP	Twin B: FGR 660g (p5) Twin A: 990g (p50)	Twin B: - RDS treated with CPAP - gastric perforation operated - anemia & thrombocytopenia - hyperbilirubinemia - prematurity retinopathy Twin A: normal
5	32 7G4P	33	Not done	33 WG: - hydramnios - mild skin edema - increased cardio-thoracic ratio - increased MCA PSV - bulky & swollen placenta	Declined	33 WG: - shortness of breath - due to hydramnios	37 WG: - induction for FGR - SVD	2500g (p10)	NICU for 32 days
6*	32 2G1P	21	1/1470 AFP 3.37	21 WG: - echogenic bowel - left cardiac rotation - mild cerebral ventriculomegaly (10 mm) 34 WG: - FGR (<5th percentile) - enlarged and globular placenta	46,XX		34 WG: - EmCS - non reasuring NST - stop of fetal growth	FGR 1590g (p3)	Hyperbilirubinemia Spontaneous resolution, thrombopenia (52 G/l) Hypoglycemia Discharged home at 15 days of life Neurodevelopmental delay at 2 years old
7	44 3G1P	39	1/81 HCG 2.27 AFP 0.65	Normal	46,XY		39 WG: - EmCS - early labor - suspected macrosomia	4480g (p>90)	Transient RDS Beckwith-Widemann syndrome negative

8	45 1G0P	18	1/51	15 WG: - early FGR 18 WG: - absent end diastolic flow - bulky and swollen placenta 22 WG: - severe FGR - absent end diastolic flow - oligohydramnios - pericardic effusion - swollen placenta - female phenotype	Karyotype: 46,XY shorter Y arm SRY positive CGH array: terminal deletion of 259 kb on chromosome Y	22WG: - severe preeclampsia	22 WG: - TOP - EmCS - placental abruptio	FGR 220g (p<5) Stillbirth	Slight dysmorphism: - high forehead - overcrossing of the 3rd and 5th fingertoes by the 4th toe
9	32 4G1P	18	1/2900 AFP 3,98	18 WG: - omphalocele - macroglossia & visceromegaly - kidneys overgrowth	46,XX UPD in 11p15		21 WG: - TOP	600g (p90) Stillbirth	Beckwith-Wiedemann syndrome
10	35 2G1P	20	Not done	20 WG: - double outlet right ventricule - pulmonary atresia - VSD 30 WG: - left cerebral ventriculomegaly (12 mm) - thin corpus callosum - echogenic kidney MRI: - CHARGE syndrome? **	Declined		31 WG : - EmCS - non reassuring NST	1630g (p50) Apgar 2/5/6 pHa 7.12	Double outlet right ventricule Pulmonary atresia Neonatal death at day 1
11	35 3G1P	19	HCG & AFP increased	19 WG: - enlarged globular placenta 29 WG: - FGR with normal dopplers			29 WG: - EmCS - non reassuring NST - PPROM	970g (p10) Apgar 1/5/10 pHa 7.25 pHv 7.34	RDS treated with CPAP Thrombocytopenia Hypoglycemia Death at 63 days of life
12	40 1G0P	16	Not done	16 WG: - large hydropic placenta	46,XY		38 WG: - SVD	3230g (p50) Apgar 2/8/9 pHa 7.26 pHv 7.41	
13	34 1G0P	18	Not done	18 WG: - severe FGR - abnormal diastolic flow in UV - hypoplastic nasal bone - stenosis of pulmonary artery	Trisomy 21		20 WG: - TOP		
14	29 1G0P	19	AFP increased	19 WG: - normal anatomy and biometry	Karyotype: 46,XX CGH array: normal	37 WG: - gestational hypertension	40 WG: - SVD	2900g (p10) Apgar 8/9	

Table 1 (*Continued*)

Case	Maternal age G / P	GA at Dx	1st-trimester screening, HCG, AFP	Prenatal ultrasound	Karyotype	Pregnancy complications	Delivery [type/cause]	Birth outcomes [birthweight, Apgar, pH]	Adverse neonatal outcomes
15	34 1G0P	18		20 WG: - FGR - single umbilical artery - ASD - placentomegaly 23 WG: - severe FGR - cardiomegaly - absent end diastolic flow in UV	46,XX	22 WG: - gestational hypertension	24 WG: - induction for IUD - SVD	FGR 238 g Stillbirth	
16	28 1G0P	21	Not done	21 WG: (Twin B) - monochorionic diamniotic twins - severe FGR - hyperechoic bowel			34 WG: - EmCS - non reassuring NST	Twin B: 750g Twin A: 2000g Apgar 8/8	Twin B: neonatal death Twin A: normal
17	34 5G2P	21		21 WG: - IUD - placentomegaly			21 WG: - induction for IUD - SVD	FGR 249g Stillbirth	
18	32 2G1P	22		19 WG: - small insula lobe - FGR 22 WG: - severe FGR - small insula lobe - lissencephaly - abnormal ductus venosus	Karyotype: 46,XY CGH array: normal	Post-partum: - HELLP syndrom	27 WG: - induction for IUD - SVD	FGR 670g Stillbirth	
19	35 1G0P	32		32 WG: - microcephaly - bulky and swollen placenta			37 WG: - EmCS - non reassuring NST	FGR 2450g Apgar 7/8	Microcephaly Skeletal dysplasia
20	34 4G2P	21		21 WG: - cardiomegaly - severe FGR - stenosis of pulmonary artery - tricuspidal insufficency - cerebellar hypoplasia - enlarged and globular placenta - oligohydramnios - abnormal diastolic flow in UV			22 WG: - TOP	FGR 221g Stillbirth	
21	34 1G0P	21	Not done	21 WG:(Twin C) - trichorionic pregnancy - severe FGR - VSD		32 WG: Preeclampsia	33 WG: - EmCS - non reassuring NST - preeclampsia	Twin C: FGR 650g Twin A: 1865g Twin B: 1713g	Twin C: neonatal death Twin A+B: - RDS treated with CPAP - NICU

22	32 1G0P	20	HCG & AFP increased	20 WG: - severe FGR - single umbilical artery - cardiomegaly - placentomegaly - absent end diastolic flow in UV	22 WG: Preeclampsia	23 WG: - induction for IUD - SVD	FGR 210g Stillbirth

G / P: Gravida / Parity.
GA: gestational age.
Dx: diagnosis.
HCG: Human Chorionic Gonadotrophin (in [MoM]).
AFP: Alpha-FetoProtein (in [MoM]).
UPD: UniParental Disomy.
WG: Weeks Gestation.
FGR: Fetal Growth Restriction.
UV: Umbilical Vein.
ASD: Atrial Septum Defect.
VSD: Ventricular Septum Defect.
EmCS: Emergency Caesarean.
SVD: Spontanous Vaginal Delivery.
TOP: Termination of pregnancy.
NST: Non Stress Test.
PPROM: Preterm Premature Rupture of Membranes.
RDS: Respiratory Distress Syndrome.
NICU: Neonatal Intensif Care Unit.
IUD: Intrauterine Death.
CPAP: Continuous Positive Airway Pressure.
MCA PSV: Peak Velocity of Systolic Blood Flow in the Middle Cerebral Artery.
* During pregnancy: parental screening for cystic fibrosis, serological and amniotic TORCH screening all normal At 2 years of age: developmental delay, pectus excavatum, hypotonia, megalencephaly and facial dysmorphism. Genetic analysis for PTEN (Phosphatase and tensin homolog), myotonic dystrophy and Noonan all normal.
** Suspicion of CHARGE syndrome due to cardiopathy, arhinencephaly, abnormal internal ear, vermis dysplasia short corpus callosum, abnormal cerebral gyration, ventriculomegaly.

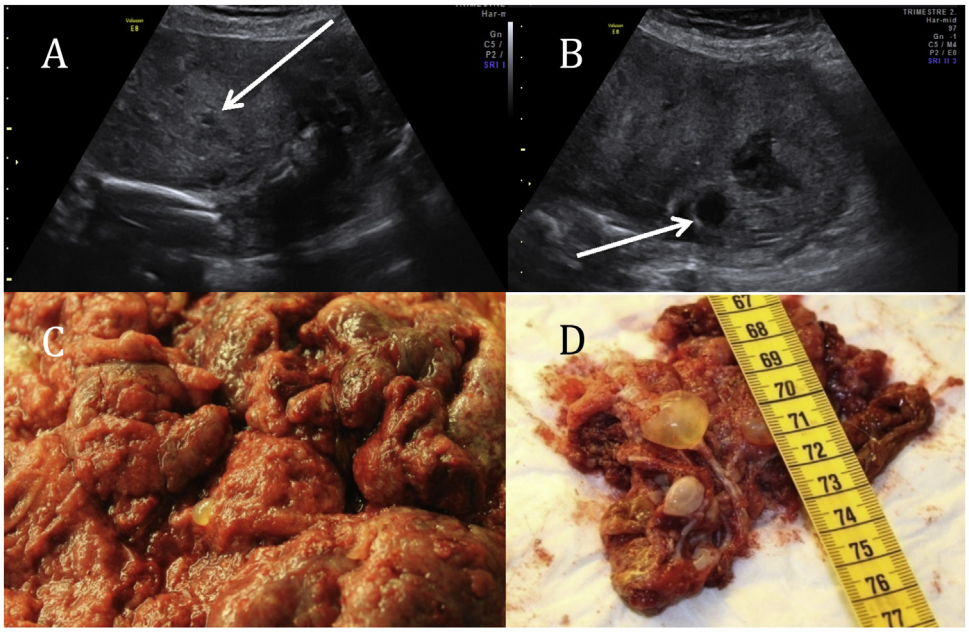

Fig. 1. 1 A. Placental ultrasonographic image at 27 weeks gestation. Large heterogeneous and hydropic placenta, containing small cysts (arrow).
1B. Placental ultrasonographic image at 27 weeks gestation. Dilated superficial placental vessel observed on the fetal side (arrow).
1C. Placental pathology : the maternal side revealed numerous cystically dilated vesicles interspersed between normal appearing parenchyma.
1D. Placenta with one of numerous cyst-like villi seen beneath the maternal surface.

delivery, maternal complications (preeclampsia/gestational hypertension) and neonatal thrombocytopenia.

C. What does this study add to what is already known?

PMD should be suspected in the presence of an enlarged cystic placenta with dilated chorionic vessels and abnormal biomarkers. This international collaborative work also demonstrates new malformations associated with PMD. Pregnancies with suspected PMD are best managed in tertiary centers that have the resources for both perinatal care and perinatal pathology testing.

Introduction

Placental mesenchymal dysplasia (PMD), a rare vascular and connective placental anomaly previously described in 0.02% of

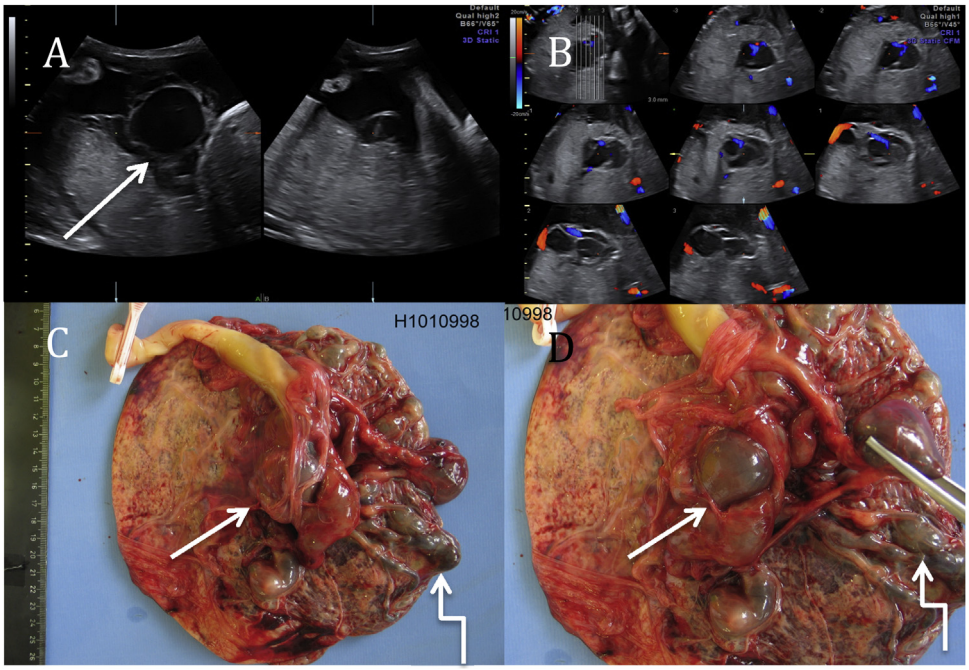

Fig. 2. 2 A. Ultrasound at 33 weeks gestation. 4 cm umbilical cord cyst at the placental insertion (arrow).
2B. 3D reconstruction of the umbilical cyst. No doppler signal seen inside the cyst.
2C & D. Macroscopic aspect of the placenta. The fetal plate of the placenta shows a voluminous arterial aneurysm (arrow) and dilated vessels (arcuated arrow).

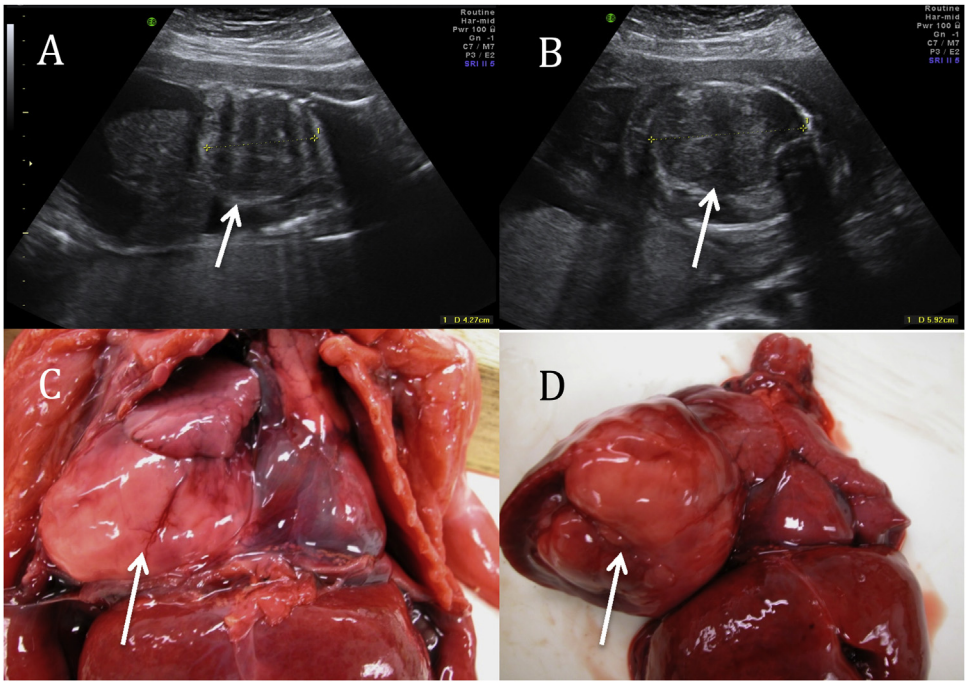

Fig. 3. 3 A & B. Ultrasonongraphy at 26 weeks gestation. Fetal thoracic echogenic lesion of 6 cm (arrow), and ascites.
3C & D : Macroscopic aspect of the pulmonary lesion. Solid right inferior lobar pleuropulmonary blastoma (arrow).

pregnancies [1], was first reported by Moscoso et al. in 1991 [2]. An earlier description was published by Takayama et al. in 1986 [3], but was not recognized as a clear clinical entity at that time. PMD is characterized by varying expressions of: placentomegaly, aneurysmally dilated chorionic plate vessels, thrombosis of dilated vessels and large grapelike vesicles within the placenta. These appearances may mimic molar pregnancy on ultrasound and on initial gross placental examination following delivery. In contrast to molar pregnancy, PMD can be associated with a normal live birth, but also with fetal growth restriction (FGR), macrosomia due to Beckwith-Wiedemann Syndrome, fetal tumors (mostly hamartomas), antepartum fetal death and maternal complications especially preeclampsia [4]. Definitive diagnosis relies on histological features, including mesenchymal hyperplasia, edema of stem-cell villi, dilated stem vessels with thickened vasculature and absence of trophoblastic hyperplasia [5,6]. Fetal karyotype is usually euploid, although cases with aneuploidy (trisomy 13 or mosaic forms of trisomy 13, trisomy 21, Klinefelter, triploidy, mosaic chromosome 7 tetrasomy) have been reported [7–10].

Establishing the diagnosis of PMD's is challenging due to the varied placental and fetal phenotypes. Our aim was to review cases from 7 tertiary centers worldwide over the last decade. Here we report on 22 new cases of PMD with four potential new associations: one placental triploidy mosaicism, one pleuropulmonary blastoma, one CHARGE syndrome and one case of skeletal dysplasia.

CASE reviews

Pathology databases from 7 tertiary hospitals were screened for cases of PMD (between 2007–2017). Pregnancy history, outcomes and ultrasound images were then reviewed for each case (Table 1). Some of the cases with novel associations are described below.

Case 1

A 28-year-old gravida 2 para 0 woman was admitted at 27 weeks gestation due to anhydramnios without evidence of preterm premature rupture of membranes. On ultrasound, the placenta appeared large, heterogeneous in texture and hydropic (Fig. 1A + B). Her first trimester screening showed a low-risk for Down syndrome: 1/5900, although an elevated B-hCG level (2.67 Multiple of Median [MoM]) was noted. Alpha-Fetoprotein (AFP) at 16 weeks gestation was 2.2 MoM and anatomy ultrasound at 20 weeks demonstrated no abnormalities. It should be noted that during a routine follow-up at 24 weeks gestation, borderline polyhydramnios was identified.

At 28 weeks gestation, the patient underwent an emergency C-section for non-reassuring fetal monitoring resulting in a 759 g newborn boy that was meconium stained. APGAR scores were 3/7/9 at one, five and ten minutes respectively. The neonatal period was complicated by respiratory distress syndrome (RDS), hypotension, transient hypoglycaemia, 48 h of renal insufficiency and thrombocytopenia (26 G/l) treated with platelet transfusion. The newborn was discharged home at 8 weeks of life. Growth and development were normal at 2 years of age.

Placental pathology was suggestive of PMD (placental weight 450 g; expected for gestation 270 g) (Fig. 1C + D). Cytogenetic studies demonstrated a 46XY karyotype in the child, but a confined placental triploid mosaicism (mos69,XXY/46,XY).

Case 2

A 29-year-old gravida 1 woman presented at 17 weeks gestation for amniocentesis for a positive first trimester screen for Down syndrome (risk 1/280). The fetal karyotype was 46,XX. The pregnancy was then uneventful until 33 weeks gestation when a 4 cm umbilical cord cyst was identified at the placental cord insertion (Fig. 2A + B). The placenta, amniotic fluid volume, fetal

biometry and detailed anatomy ultrasounds were otherwise normal, except myocardial hypertrophy with normal cardiac function. After onset of labour two days later, the patient delivered a female infant (2040 g), with APGARs of 9/9/9 at one, five and ten minutes respectively, and arterial/venous pH 7.21/7.27, who presented with RDS, hepatomegaly, mild anaemia and thrombocytopenia, which all spontaneously resolved.

Abdominal ultrasound and MRI were performed on the infant due to persistent hepatomegaly, which demonstrated numerous hamartomas in the right lobe of the liver. The placenta was enlarged (475 g) and showed multiple partially occluded vascular dilatations (1 major arterial aneurysm and multiple vein varices). All features were consistent with PMD (Fig. 2C + D). Flow cytometry analysis of paraffin-embedded, fixed placental tissues demonstrated an euploid karyotype.

At 1 month of age, primary intestinal neuronal dysplasia was diagnosed by rectal mucosal biopsy prompted by persistent abdominal discomfort.

Case 3

A fetal thoracic echogenic lesion (right inferior pulmonary lobe) associated with a diaphragmatic eversion was observed in a 33-year-old gravida 1 woman with a low-risk second trimester screen for Down syndrome (risk 1/6600; B-hCG: 2.5 MoM) (Fig. 3 A + B). Fetal MRI was suggestive of a hamartoma. The fetal karyotype on amniocentesis was 46,XX. The pulmonary mass expanded significantly (6 cm) by 26 weeks gestation. Due to fetal hydrops and reversed ductus venosus A waves at 27 weeks gestation, a 1420 g female infant was delivered by C-section. The newborn died due to prematurity within few hours.

Autopsy examination showed a non-dysmorphic neonate with a solid right inferior lobar pleuropulmonary blastoma (Fig. 3C + D). The placenta was enlarged (461 g, expected weight 360 g.) and had extensive foci of PMD.

All cases

We identified 22 new cases with PMD, including the cases described above (Table 2). The median maternal age was 34 years (range 28–45 years). The mean gestational age at diagnosis was 23 weeks (range 16–39 weeks). AFP and B-hCG were elevated in 5 and 3 cases, respectively. Of the 12 cases with fetal genetic investigations available, 4 were abnormal: one had Beckwith-Wiedemann syndrome, one had trisomy 21, one had a terminal deletion on chromosome Y, and one a triploid mosaic 69,XXY/46,XY confined placental mosaicism (case 1).

Four women developed preeclampsia, of whom 3 had a very early onset between 22–26 weeks gestation. Two patients developed gestational hypertension. Eleven cases (50%) presented with FGR (eight of them associated with placentomegaly), including 2 twin pregnancies and one triplet pregnancy with selective IUGR.

After exclusion of four stillbirths and four pregnancy terminations between 20–22 weeks gestation, the mean gestational age at delivery was 33 weeks (27–40 weeks, with 9/14 premature deliveries). Overall, 11 patients (50%) had vaginal deliveries and 11 emergency C-section (50%); after exclusion of stillbirths and pregnancy terminations, 4 patients had vaginal deliveries (29%) and 10 had emergency C-sections (71%).

Among the 14 live born neonates, 5 died between 1–63 days of life (Cases 3, 10, 11, 16 & 21). Five neonates were diagnosed with thrombocytopenia, but platelet transfusion was only necessary in case 1.

Among the nine children discharged home, one had motor and cognitive developmental delay at the age of two years and another was diagnosed with microcephaly associated with skeletal dysplasia, which is still under investigation.

Table 2
Pregnancy characteristics and outcomes of the 22 cases.

Pregnancy characteristic/outcome	Number of cases (%)
Abnormal prenatal biochemical screening	
- Elevated alpha-fetoprotein	5 (23%)
- Elevated human chorionic gonadotrophin	3 (14%)
Pregnancy outcome	
- Termination of pregnancy	4 (18%)
- Fetal growth restriction	11 (50%)
- Intrauterine fetal death	4 (18%)
- Preterm delivery	9/14 (64%)
Maternal complications	6 (27%)
- Preeclampsia	4 (3 at 22-26 weeks)
- Gestational hypertension	2
Neonatal outcome	14 alive newborns
- Beckwith-Wiedemann syndrome	1 (7%)
- Thrombopenia	5 (35%)
- Death in the first 61 days after birth	5 (35%)
- Developmental delay	1 (7%)
Genetic abnormality	4 (18%)
- Beckwith-Wiedemann syndrome	1 (4,5%)
- Terminal deletion on chromosome Y	1 (4,5%)
- Trisomy 21	1 (4,5%)
- Triploid mos69,XXY/46,XY confined placental mosaicism	1 (4,5%)
Fetal malformations	4 (18%)
- Pleuropulmonary blastoma	1 (4,5%)
- Multiple hepatic hamartoma	1 (4,5%)
- Fetal skeletal dysplasia	1 (4,5%)
- CHARGE syndrome	1 (4,5%)
Uncomplicated pregnancy	3 (14%)

Discussion

Our search for pregnancies with a diagnosis of PMD across 7 centers worldwide identified only 22 new cases, for which we describe their various maternal, fetal and neonatal outcomes. Additionally, we report four new potential disease associations not previously described: placental triploid mosaicism; CHARGE syndrome; fetal pleuropulmonary blastoma; fetal skeletal dysplasia. Fetal hepatic mesenchymal tumors are known to be commonly associated with PMD (hamartoma or blastoma) [11–19], however extra-hepatic tumors are rare, with only 1 case of pulmonary hamartoma [19] and 1 case of facial hamartoma [20] described so far. Androgenic biparental mosaicism seems to underlie most cases of PMD and could contribute to associated fetal lesions such as hamartoma [21].

More than 100 cases of PMD have previously been reported in the literature [22]. The increasing number of recent publications in this field, however, likely highlights an increasing

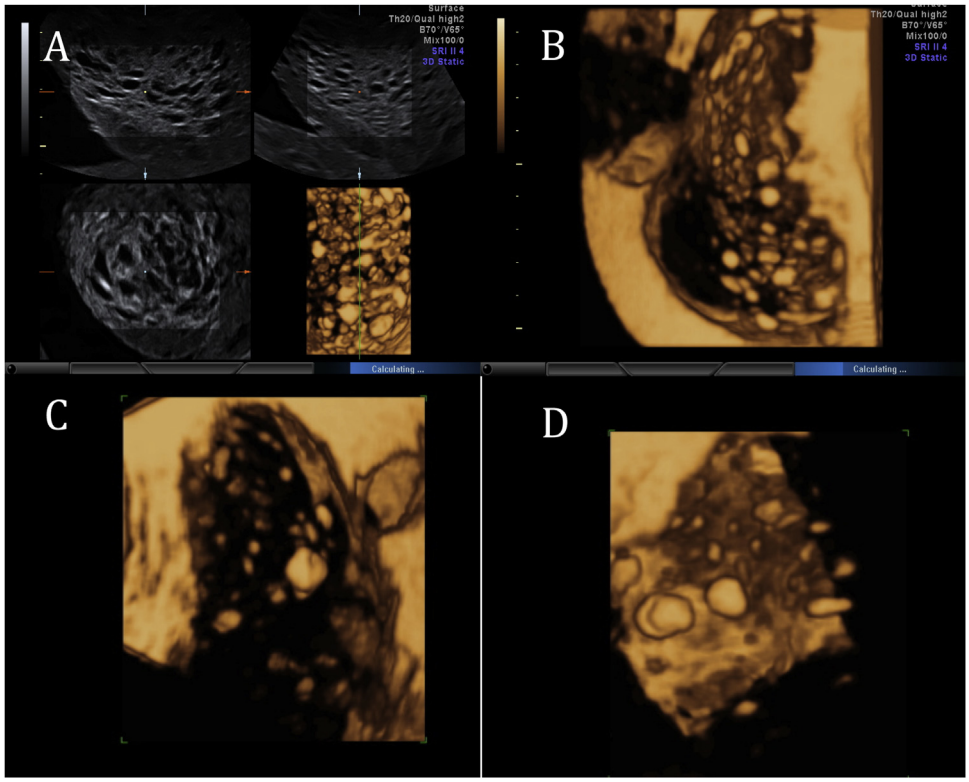

Fig. 4. 4A. 3D sonongraphy of the placenta at 17 weeks gestation. Multicystic placenta arising from the chorionic plate and not from the basal plate.
4B. 3D sonongraphy of the placenta at 17 weeks gestation rendered with the inversion mode.
4C & D. 3D sonongraphy of the placenta at 25 weeks gestation performed with the inversion mode. Gradual reduction of size in placental vesicular lesions compared to 17 weeks gestation.

appreciation of PMD as a specific diagnostic entity. In the present study, two tertiary referral centers reported no PMD cases within the last decade. Since only placentas from complicated pregnancies are typically sent for pathological examination, due to resource constraints, while PMD may be found in clinically uneventful pregnancies (14% of our cases), a reporting bias towards cases of PMD with adverse associated outcomes is likely.

A suspicion of PMD has been identified as early as 8–9 weeks gestation [23,24]. Recently, Ohira et al reported that 70% of all cases described in the literature have been diagnosed between 13–20 weeks [22]. In our series, PMD was diagnosed at a mean gestational age of 23 weeks (16–39) and 41% of our cases were diagnosed between 16–20 weeks.

First and/or second trimester maternal serum analyte levels used in screening for aneuploidy were abnormal in 41% of our cases, as described by others [4,22,25]. Ultrasound findings of the placenta (mostly placentomegaly and large sonographically-visible vesicles) were present in 59% of cases whereas 81% (18/22) of cases had fetal findings, as reported by others [4,6,7,22]. Minekawa-Mehandjiev et al. described a 3D-inversion mode rendering (as used in case 12), which could be useful in the differentiating PMD from partial mole (Fig. 4) [26].

Invasive testing is recommended to exclude an abnormal karyotype [7,8]) and exclude partial molar pregnancy. It is important to differentiate PMD from partial molar pregnancy, as management and outcomes are different. Preterm delivery (64%) and FGR (50%) were the most commonly observed complications of PMD pregnancies in our series, as previously described [4,22]. Placentomegaly and/or the low percentage of functional placental gas-exchanging tissues decreases effective maternal-fetal gas exchange leading to FGR, while the associated preeclampsia (18% of our cases and often severe) may be due to an abnormal circulating placenta-derived angiogenic profile [27]. Amongst live born neonates in our series, 35% presented with transient thrombocytopenia, which is higher than previously described but may be due to associated vascular tumors of the fetus [28]. Hematologic alterations are hypothesized to be related to placental thickness, or to increased vascularity, vasculopathy and consumptive coagulopathy within associated fetal tumors [14,28–33].

In conclusion, the diagnosis of PMD appears to be increasing over the last decade, likely related to increased awareness. Sonographers, fetal medicine specialists, obstetricians and pathologists all should suspect PMD in the presence of an enlarged cystic placenta with dilated chorionic vessels and abnormal circulating levels of hCG and AFP. A detailed and early morphological ultrasound assessment of the fetus and placenta should be performed. The specific fetal abnormalities associated with Beckwith-Wiedmann syndrome or hepatic/thoracic tumors should be sought. Magnetic resonance imaging may aid the diagnosis, as recently reported for discordant fetal growth in a dichorionic twin pregnancy [34]. Invasive genetic testing should be considered, to exclude partial molar pregnancy and plan ongoing care. Although a healthy near-term pregnancy is possible with a concurrent diagnosis of PMD, more often PMD is associated with a variety of adverse fetal, neonatal or maternal outcomes. Therefore pregnancies with suspected PMD are best managed in regional perinatal centers that have the resources for both perinatal care and perinatal pathology testing.

Disclosures

The authors report no conflict of interest.

Funding

None

Condensation

Placental mesenchymal dysplasia, an emerging placental anomaly which could be identified on prenatal ultrasound, remains underdiagnosed despite association with severe adverse fetal and maternal outcomes.

References

[1] Arizawa M, Nakayama M. Suspected involvement of the X chromosome in placental mesenchymal dysplasia. Congenit Anom (Kyoto) 2002;42(4):309–17.
[2] Moscoso G, Jauniaux E, Hustin J. Placental vascular anomaly with diffuse mesenchymal stem villous hyperplasia. A new clinico-pathological entity? Pathol Res Pract 1991;187(2-3):324–8.
[3] Takayama M, Soma H, Yagushi S, Funayama H, Fujiwara K, Irie H, et al. Abnormally large placenta associated with Beckwith-Wiedemann syndrome. Gynecol Obstet Invest 1986;22(3):165–8.
[4] Nayeri UA, West AB, Grossetta Nardini HK, Copel JA, Sfakianaki AK. Systematic review of sonographic findings of placental mesenchymal dysplasia and subsequent pregnancy outcome. Ultrasound Obstet Gynecol 2013;41(4):366–74.
[5] Allias F, Lebreton F, Collardeau-Frachon S, Vasiljevic A, Rossignol S, Massardier J, et al. [Placental mesenchymal dysplasia]. Ann Pathol 2008;28(2):85–94.
[6] Woo QW, Rocha FG, Gaspar-Oishi M, Bartholomew ML, Thompson KS. Placental mesenchymal dysplasia. Am J Obstet Gynecol 2011;205(6):e3–5.
[7] Cohen MC, Roper EC, Sebire NJ, Stanek J, Anumba DOC. Placental mesenchymal dysplasia associated with fetal aneuploidy. Prenat Diagn 2005;25(3):187–92.
[8] Mungen E, Dundar O, Muhcu M, Haholu A, Tunca Y. Placental mesenchymal dysplasia associated with trisomy 13: sonographic findings. J Clin Ultrasound 2008;36(7):454–6.
[9] Toru HS, Çobankent Aytekin E, Sanhal CY, Yakut S, Çetin Z, Mendilcioglu II, et al. We can diagnose it if we consider it. Diagnostic pitfall for placenta: placental mesenchymal dysplasia. Turk Patoloji Derg 2017.
[10] Gavanier D, Allias F, Huissoud C, Hajri T, Golfer F, Massardier J. Ultrasound findings and clinical outcomes in 23 cases of placental mesenchymal dysplasia. J Repr Med 2017;62:366–75.
[11] Alwaidh MH, Woodhall CR, Carty HT. Mesenchymal hamartoma of the liver: a case report. Pediatr Radiol 1997;27(3):247–9.
[12] Carta M, Maresi E, Guiffrè M, Catalano G, Piro E, Siracusa F, et al. Congenital hepatic mesenchymal hamartoma associated with mesenchymal stem villous hyperplasia of the placenta: case report. J Pediatr Surg 2005;40(5):e37–9.
[13] Chan YF, Sampson A. Placental mesenchymal dysplasia: a report of four cases with differentiation from partial hydatidiform mole. Aust N Z J Obstet Gynaecol 2003;43(6):475–9.
[14] Francis B, Hallam L, Kecskes Z, Ellwood D, Croaker D, Kent A. Placental mesenchymal dysplasia associated with hepatic mesenchymal hamartoma in the newborn. Pediatr Dev Pathol 2007;10(1):50–4.
[15] Kitano Y, Ruchelli E, Weiner S, Adzick NS. Hepatic mesenchymal hamartoma associated with mesenchymal stem villous hyperplasia of the placenta. Fetal Diagn Ther 2000;15(3):134–8.
[16] Laberge JM, Patenaude Y, Desilets V, Cartier L, Khalife S, Jutras L, et al. Large hepatic mesenchymal hamartoma leading to mid-trimester fetal demise. Fetal Diagn Ther 2005;20(2):141–5.
[17] Mack-Detlefsen B, Boemers TM, Groneck P, Bald R. Multiple hepatic mesenchymal hamartomas in a premature associated with placental mesenchymal dysplasia. J Pediatr Surg 2011;46(8):e23–5.
[18] Tortoledo M, Galindo A, Ibarrola C. Placental mesenchymal dysplasia associated with hepatic and pulmonary hamartoma. Fetal Pediatr Pathol 2010;29(4):261–70.
[19] Wilson M, Peters G, Bennetts B, McGillivray G, Wu ZH, Poon C, et al. The clinical phenotype of mosaicism for genome-wide paternal uniparental disomy: two new reports. Am J Med Genet A 2008;146A(2):137–48.
[20] Gibson BR, Muir-Padilla J, Champeaux A, Suarez ES. Mesenchymal dysplasia of the placenta. Placenta 2004;25(7):671–2.
[21] Ernst LM. Placental mesenchymal dysplasia. J Fetal Med 2015;2:127–33.
[22] Ohira S, Ookubo N, Tanaka K, Takatsu A, Kobara H, Kikuchi N, et al. Placental mesenchymal dysplasia: chronological observation of placental images during gestation and review of the literature. Gynecol Obstet Invest 2013;75(4):217–23.
[23] Starikov R, Goldman R, Dizon D, Kostadinov S, Carr S. Placental mesenchymal dysplasia presenting as a twin gestation with complete molar pregnancy. Obstet Gynecol 2011;118(2 Pt 2):445–9.
[24] Umazume T, Kataoka S, Kamamuta K, Tanuma F, Sumie A, Shirogane T, et al. Placental mesenchymal dysplasia, a case of intrauterine sudden death of fetus with rupture of cirsoid periumbilical chorionic vessels. Diagn Pathol 2011;6:38.
[25] Jalil SS, Mahran MA, Sule M. Placental mesenchymal dysplasia-can it be predicted prenatally? A case report. Prenat Diagn 2009;29(7):713–4.
[26] Minekawa-Mehandjiev R, Masuda K, Yamamoto K, Miura K, Nakayama M, Murata Y. Placental mesenchymal dysplasia differentially diagnosed from molar pregnancy by 3-D inversion mode rendering: a case report. J Obstet Gynaecol Res 2014;40(1):284–7.
[27] Herraiz I, Simon E, Toldos O, Rodriguez Y, Gomez-Arriaga PI, Galindo A. Angiogenesis-related biomarkers (sFlt-1/PlGF) in placental mesenchymal dysplasia. J Matern Fetal Neonatal Med 2017;30(8):958–61.
[28] Koga H, Makimura M, Tanaka H, Sumioki H. Placental mesenchymal dysplasia and fetal hematologic disorder. J Pediatr Hematol Oncol 2014;36(6):e389–91.
[29] Pham T, Steele J, Stayboldt C, Chan L, Benirschke K. Placental mesenchymal dysplasia is associated with high rates of intrauterine growth restriction and fetal demise: a report of 11 new cases and a review of the literature. Am J Clin Pathol 2006;126(1):67–78.
[30] Sander CM. Angiomatous malformation of placental chorionic stem vessels and pseudo-partial molar placentas: report of five cases. Pediatr Pathol 1993;13(5):621–33.
[31] Chen CP, Chern SR, Wang TY, Huang ZD, Huang MC, Chuang CY. Pregnancy with concomitant chorangioma and placental vascular malformation with mesenchymal hyperplasia. Hum Reprod 1997;12(11):2553–6.
[32] Kinoshita T, Fukaya S, Yasuda Y, Itoh M. Placental mesenchymal dysplasia. J Obstet Gynaecol Res 2007;33(1):83–6.
[33] Robinson WP, Lauzon JL, Innes AM, Lim K, Arsovska S, McFadden DE. Origin and outcome of pregnancies affected by androgenetic/biparental chimerism. Hum Reprod 2007;22(4):1114–22.
[34] Jitsumori S, Shiro M, Kojima F, Ota N, Minami S, Ino K. Placental mesenchymal dysplasia with severe fetal growth restriction in one placenta of a dichorionic diamniotic twin pregnancy. J Obstet Gynecol Res 2018;5.