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ORIGINAL ARTICLE

Fetal akinesia deformation sequence and massive perivillous fibrin deposition resulting in fetal death in six fetuses from one consanguineous couple, including literature review

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Abstract

Background: Massive perivillous fibrin deposition (MPFD) is associated with adverse pregnancy outcomes and is mainly caused by maternal factors with limited involvement of fetal or genetic causes. We present one consanguineous couple with six fetuses developing Fetal Akinesia Deformation Sequence (FADS) and MPFD, with a possible underlying genetic cause. This prompted a literature review on prevalence of FADS and MPFD.

Methods: Fetal ultrasound examination, motor assessment, genetic testing, postmortem examination, and placenta histology are presented (2009–2019). Literature was reviewed for the association between congenital anomalies and MPFD.

Results: All six fetuses developed normally during the first trimester. Thereafter, growth restriction, persistent flexed position, abnormal motility, and contractures

in 4/6, consistent with FADS occurred. All placentas showed histologically confirmed MPFD. Genetic analyses in the five available cases showed homozygosity for two variants of unknown significance in two genes, *VARS1* (OMIM*192150) and *ABCF1* (OMIM*603429). Both parents are heterozygous for these variants. From 63/1999 manuscripts, 403 fetal outcomes were mobilized. In 14/403 fetuses, congenital abnormalities in association with MPFD were seen of which two fetuses with contractures/FADS facial anomalies.

Conclusion: The low prevalence of fetal contractures/FADS facial anomalies in association with MPFD in the literature review supports the possible fetal or genetic contribution causing FADS and MPFD in our family. This study with literature review supports the finding that fetal, fetoplacental, and/or genetic components may play a role in causing a part of MPFDs.

1 | INTRODUCTION

Fetal Akinesia Deformation Sequence (FADS) is a rare disorder with, in general, autosomal recessive inheritance (Filges & Hall, 2013) with a prevalence of 1 per 13:000 pregnancies (Lowry et al., 2010). The prenatal expression of FADS is visible by, among other things, reduced fetal motility and varies from the presence of multiple contractures, flattening of facial profile (FADS facial anomalies) during early pregnancy to observed growth restriction, polyhydramnios, and suspicion of lung hypoplasia during later gestation. In some cases additional abnormalities are seen such as brain or cardiac anomalies (Skaria et al., 2019). FADS may mimic fetuses exposed to uteroplacental insufficiency as they both show reduced fetal movements and growth restriction. FADS, however, differs from severe uteroplacental insufficiency as FADS is usually accompanied by polyhydramnios and uteroplacental insufficiency has no or limited influence on body posture and joints (Bekedam et al., 1985; Sival et al., 1992a). FADS prognosis is dependent on its cause, namely whether it is genetic and/or neuromuscular (Hall, 2014; Hall & Kiefer, 2016; Hellmund et al., 2016). The outcome of FADS varies with ~30% of fetuses being stillborn and the majority of live-born infants dying of pulmonary hypoplasia (Jones, 2013). To improve the detection of FADS, we demonstrated in a prospective cohort study between 2007 and 2016 that motor assessment is of additional value to structural assessment in diagnosing FADS before 24 weeks of gestation (Tjon et al., 2019). The underlying genetic cause of FADS was demonstrated in about half of the fetuses (Tjon et al., 2019). Presently, more than 400 genes have been found to be associated with FADS (Kiefer & Hall, 2019). In general, when the underlying cause is genetic, parents can be counselled about the prognosis and outcome of the genetic cause, the recurrence risk and their reproductive options including prenatal diagnostics or preimplantation genetic testing. Therefore a joint effort to mobilize knowledge about possible additional genetic abnormalities is paramount (Tjon et al., 2019). Whole exome sequencing (WES) and whole genome sequencing (WGS) have been used with great success to identify novel disease genes for a broad spectrum of monogenic disorders including FADS (Neveling et al., 2013). GeneMatcher can be helpful in collecting multiple cases/families with a similar phenotype and a (candidate) variant in the same gene (Sobreira et al., 2015). However, many cases remain unresolved and a detailed description of such cases could aid in resolving these in the future.

Massive Perivillous Fibrin Deposition (MPFD) of the placenta has a low prevalence of about 1.1% (Devisme et al., 2017). The obstetrical outcome of MPFD varies with recurrent miscarriage, fetal demise, preterm birth, and fetal growth restriction in ongoing pregnancies being described (Faye-Petersen & Ernst, 2013; Katzman & Genest, 2002). Histologically, MPFD is classified as: presence of perivillous fibrinoid material extending from the maternal to fetal surface, transmural, encasing ≥50% of the villi in at least one slide during pathological examination, whereas in borderline MPFD 25%–50% of the villi are encased by fibrinoid material (Katzman & Genest, 2002). A related placental disorder, classical maternal floor infarction (MFI), is classified when basal villi of the entire maternal floor are encased by perivillous fibrinoid with a thickness of ≥3 mm on at least one slide (Katzman & Genest, 2002). Recurrence of MPFD and MFI in following pregnancies varies between 12% and 88.9% (Becroft et al., 2004; Chen & Roberts, 2018; He et al., 2018). This recurrence does not follow

a Mendelian inheritance pattern related to the fetus, but its recurrence rate is suggestive of a genetic or acquired mechanism originating in the mother (Redline, 2020). Such a mechanism is probably not based on a single-disease entity but a reaction triggered by a variety of underlying conditions such as an autoimmune disease, thrombophilia and/or maternal hematogenous infections (Redline, 2020). A few reports emphasize the possibility of a fetal contribution to the causation of MPFD concerning genetic abnormalities Long Chain 3-hydroxyacyl coenzyme A dehydrogenase (LCHAD) mutation and kidney abnormalities (Griffin et al., 2012; Matern et al., 2001; Taweevisit & Thorner, 2010). Moreover, fetoplacental contribution has been reported in association with MPFD (Taweevisit & Thorner, 2010, 2016). Oligohydramnios has been reported as a key feature of MFI/MPFD seen during prenatal ultrasound examination, together with placental thickening and cysts (Mandsager et al., 1994; Viero et al., 2004).

The aim of this article was to describe the phenotype of FADS inducing MPFD or vice versa and the genetic evaluation in six fetuses in one single consanguineous couple between 2009 and 2019 in the Netherlands. We performed a literature review to examine the prevalence of FADS and other congenital anomalies in pregnancies affected by MPFD.

2 | METHODS

A 33-year-old woman of Mediterranean origin with a consanguineous relationship (first cousins) had nine pregnancies in the period 2009–2019. She had five intra-uterine fetal deaths between 20 and 24 weeks gestational age, one neonatal death after immature delivery at 21 weeks, one healthy child and two first-trimester miscarriages. The family tree is depicted in Figure 1.

In all deceased fetuses, the FADS phenotype was identified. All fetuses and the healthy son were born in Amsterdam UMC in the Netherlands. Since no definite underlying genetic cause was found, prenatal genetic diagnostic testing or preimplantation genetic testing could not be performed.

Serial structural and motor assessments were performed in consultation with the parents in the subsequent pregnancies for detection of early signs and deterioration of motility (Donker et al., 2009; Tjon et al., 2019). Motor assessments were performed from the third fetus onwards according to Donker et al. (2009) who described a prospective cohort between 1996 and 2007. The assessment consists of three aspects, see Table 1. Characteristics of abnormal motility in fetuses with FADS have been described previously Donker et al., 2009; Tjon et al., 2019).

Serial fetal growth and Doppler flow velocities were measured to detect early signs of placental insufficiency. Aspirin and low molecular heparin were prescribed to the mother from fetus 4 onwards because of the unexplained recurrent abnormal sonographic and histological findings of the placenta compatible with MPFD, despite the absence of maternal thrombophilia factors.

The placentas were examined for histological abnormalities and MPFD was classified according to Katzman and Genest (2002).

Postmortem examinations were performed in fetuses 4 and 5, in line with the parents wish. Additional tests, including genetic testing were performed with the available techniques over time and were repeated if indicated.

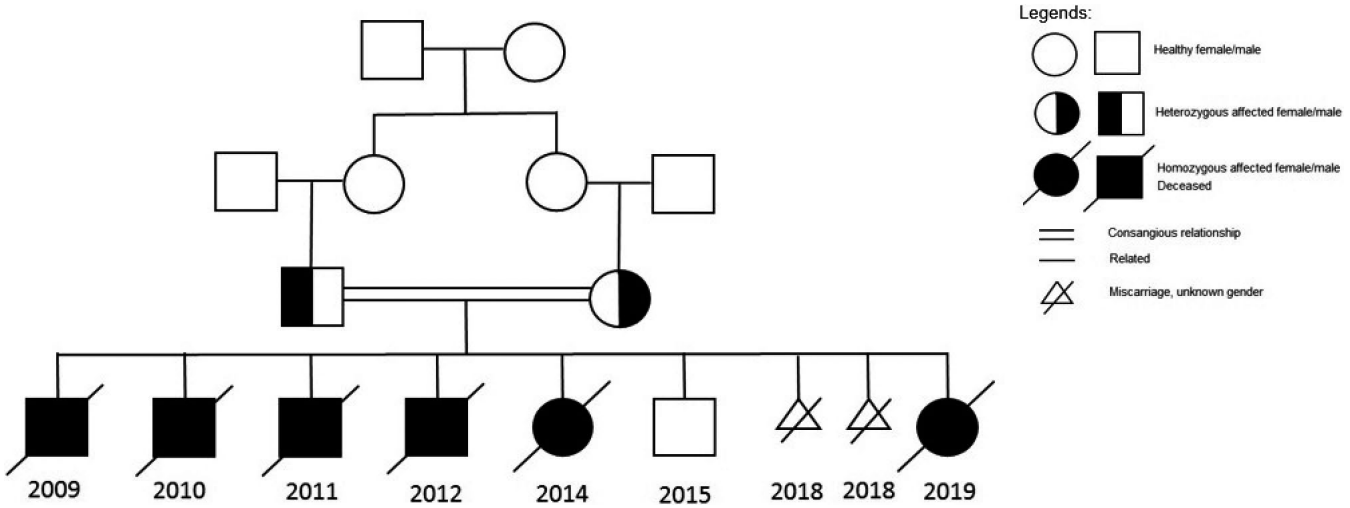

FIGURE 1 Family three showing affected and non-affected family members with VUS *VARS1* and *ABCF1*

TABLE 1 The seven cases with prenatal findings and outcome of whom six developed the phenotype FADS from one family

Fetus	GA	Advanced ultrasound examination findings	Differentiation[a]	Motor assessment quality[b]	Quantity[d]	Outcome
1 (2009) ♂	19 + 6	Fetus in flexed position Reduced fetal movements Multiple cysts and thickened placenta (53mm) FL <p2,3	Not assessed	Not assessed	Not assessed	21 + 0: immature delivery, PPROM 20 + 4, male, 283 gram
2 (2010) ♂	19 + 6	Fetus in flexed position Reduced fetal movements PI Umbilical artery >p97,7 Multiple cysts placenta FL <2,3	Not assessed	Not assessed	Not assessed	20 + 6: IUFD, male, 217 gram
3 (2011) ♂	15 + 0	NT 2.0 mm, increased risk T21 at combination test Normal growth	Not assessed	Not assessed	Not assessed	22 + 2: IUFD, male, 305 gram
	19 + 5	Fetus in flexed position Reduced fetal movements Reduced filling of bladder Thickened placenta All long bones <p2,3	Not assessed	Not assessed	Not assessed	
	21 + 0	Fetus in flexed position Reduced fetal movements Reduced filling of bladder and stomach CT-ratio >p95, with hydrothorax Thickened placenta HC, AC and FL < p0.1	30 minutes: ↓ (n = 6) BM, IAM, ILM, RFH, JO, SS	[c]	↓	

TABLE 1 (Continued)

Fetus	GA	Advanced ultrasound examination findings	Differentiation[a]	Motor assessment quality[b]	Quantity[d]	Outcome
4 (2012) ♂	13 + 3	NT 2,2 mm Normal growth	Not assessed	Not assessed	Not assessed	24 + 1: IUFD, male, 495 gram
	15 + 0	No abnormalities Normal growth	15 minutes: Normal (n = 10) ST, GM, BM, IAM, ILM, RFH, RH, JO, SW, HFC	Normal	Normal	
	16 + 6	Cyst occipital, 8 × 8.4 × 12 mm Normal growth	15 minutes: Normal (n = 8) ST, GM, BM, IAM, ILM, RFH, JO, SS	Normal	Normal	
	18 + 6	Cyst occipital, right sided 12 × 19 mm most likely arachnoid cyst Fetus in flexed position Multiple cysts placenta Normal growth	30 minutes: Normal (n = 9) ST, GM, BM, IAM, ILM, LFH, Y, HI, MM	Normal	Normal	
	19 + 6	MRI: Arachnoid cyst with compression of the cerebellum, where the cerebellum is moved more posteriorly, together with the vermis, fourth ventricle and brain stem. No signs for Dandy Walker malformation.				
	21 + 0	Arachnoid cyst, 15 × 16 × 18 mm Fetus in flexed position PI Umbilical artery p80 Bilateral notch of uterine artery Multiple cysts placenta <p2,3, AC <p10	30 minutes: ↓ (n = 5) GM, BM, IAM, ILM, JO	[c]	Normal	
	23 + 0	Arachnoid cyst, 19 × 18 × 26 mm Fetus in flexed position PI Umbilical artery >p 97,7 Bilateral notch of uterine artery Multiple cysts placenta Thickened placenta (46 mm) <p2,3, AC <p10	30 minutes: ↓ (n = 5) GM, ST, IAM, ILM, RFH	[c]	↓	

(Continues)

TABLE 1 (Continued)

Fetus	GA	Advanced ultrasound examination findings	Differentiation[a]	Motor assessment quality[b]	Quantity[d]	Outcome
5 (2014) ♀	17 + 2	Fetus mainly with chin flexed on chest PI Umbilical artery normal Retrochorionic cysts Normal growth	Not assessed	Not assessed	Not assessed	21 + 6: IUFD female, 284 gram
	19 + 2	Fetus mainly with chin flexed on chest FL p5, growth following own line	Not assessed	Not assessed	Not assessed	
	19 + 6	No abnormalities	30 minutes: Normal (n = 11) ST, GM, BM, IAM, ILM, RFH, RH, JO, SS, HFC, HI	Normal	Normal	
	20 + 6	Fetus mainly with chin flexed on chest Absent flow of umbilical artery Placental cysts HC, AC and FL <p5	Not assessed	Not assessed	Not assessed	
	21 + 2	Fetus in flexed position Oligohydramnios	30 minutes: Normal (n = 8) GM, BM, IAM, ILM, RH, Y, SS, HFC	[c]	Normal	
6 (2019) ♀	17 + 0	Multiple cysts placenta FL p5	15 minutes: Normal (n = 9) GM, IAM, ILM, RFH, AFH, RH, JO, SS, HFC, NNS	Normal	Normal	20 + 2: IUFD, female, 165 gram
	19 + 0	Fetus in flexed position Oligohydramnios Multiple cysts placenta AC, HC, FL <p2,3	15 minutes: ↓ (n = 5) GM, BM, IAM, ILM, RFH	[c]	Normal	

Abbreviations: AFH, Ante-flexion head; BM, Breathing movements; GM, General movement; HFC, Hand-face contact; HI, Hiccups; IAM, Isolated arm movements; ILM, Isolated leg movements; JO, Jaw opening; LFH, Latero-flexion head; NNS, non-nutritive sucking; RFH, Retro-flexion head; RH, Rotation head; SS, Sucking and swallowing; ST, Startle; Stretch; Y, Yawning.

[a]Differentiation; <8 different specific movement patterns in 15 minutes is considered reduced. Normal ≥8/15 minutes.

[b]Quality: Variation in amplitude, speed, participating body parts and direction should be present in GM, IAM and ILM. Waxing and waning (in- and decreasing activity of movements) and fluency should also be present in GM.

[c]Isolated arm movements reduced variation in amplitude, mainly small, speed, mainly slow, reduced variation in participating joints. Isolated leg movements reduced variation in speed, amplitude and direction, small and slow, reduced variation in participating joints. General Movement reduced variation in; amplitude, mainly small, speed, mainly slow, direction, mainly one direction, participation no participation in head and trunk, no waxing and waning, fluency present/movement too short to evaluate fluency.

[d]Quantity: normal is >3GM's in 15 minutes, motor assessment may be doubled in time to 30 minutes when <3GM's are seen during 15-minute exam. Normal age-related quantitative values are available (Donker et al., 2009).

2.1 | Literature review

A systematic search was performed on January 18, 2021 (by GLB and JT) using the databases PubMed, Embase.com, Clarivate Analytics/Web of Science Core Collection, and the Cumulative Index to Nursing and Allied Health Literature (CINAHL).

Initially, a search was performed with keywords and free text terms for (synonyms of) "Fetal Akinesia Deformation Sequence" or "Arthrogryposis Multiplex Congenita" combined with (synonyms of) "contractures" combined with (synonyms of) "massive perivillous fibrin deposits" or "abnormal placenta." In addition, the synonyms Pena Shokeir syndrome, type 1 OR Pena-Shokeir OR Fetal akinesia OR Fetal akinesia sequence were used. These gave no relevant hits.

A second search was performed with keywords and free text terms for (synonyms of) "massive perivillous fibrin deposits," "maternal floor infarction" or "abnormal placenta." A full overview of the search terms per database can be found in Appendix S1(A–D). No limitations on date or language were applied.

All search results were screened by JT and JV by assessing the title and abstract for inclusion/exclusion criteria. The application Rayyan aided this process (Ouzzani et al., 2016). If there was a disagreement in an article's inclusion or exclusion, the article's full text was read to reach a consensus.

All articles describing cases with MPFD or MFI in the placenta were included. Articles were excluded in cases where there was either no full text available, when the MPFD/MFI could not be related to the outcome, where no cases were described (overview articles), if fibrin deposition was mentioned without definition of grading and when the article was a reply article.

All included articles were read in full to examine the association between MPFD/borderline MPFD and fetal outcomes. The factors: live born, deceased, fetal growth restriction, congenital anomalies, and maternal underlying disease were assessed per article.

3 | RESULTS

3.1 | Findings on advanced ultrasound examination and outcome

From the seven fetuses, six affected and one healthy, the individual data together with obstetrical outcome are presented in Table 1. All fetuses had a normal growth and position at the first trimester ultrasound examination (circa 12 weeks' gestational age).

3.2 | Histological findings

In the placentas of all the six affected fetuses, MPFD was found. The placental parenchyma showed an accelerated maturation. There were no other signs of maternal vascular malperfusion or inflammation. See Table 2. for placental reports and Figure 2. for macroscopic pictures of the placentas.

3.3 | Postmortem examinations

The external inspection was performed. In all affected fetuses facial anomalies were found, in line with FADS, and contractures were found in four out of six (see Table 2). In addition, a complete postmortem autopsy was performed on fetuses 4 and 5. See Figure 3. for pictures of fetus 1 and 3. An overview on the findings of the postmortem examination is presented in Table 2.

3.4 | Additional testing

Since auto-antibodies for acetylcholine and MUSK are associated with FADS, these were examined in 2012 with the results being that both were negative in the mothers' blood. Within the context of the MPFD and the high grade of placental tissue maturity, maternal thrombophilia was tested for and revealed no inheritable or acquired clotting anomalies.

3.5 | Genetic testing

The genetic testing performed over time is depicted in Table 3. Postmortem DNA sampling was performed in all but the first affected fetus. During the first pregnancy, a karyotype was performed after amniocentesis.

In 2014, trio-WES analysis was performed which identified no (likely) pathogenic variants but which found two homozygous variants of unknown significance (VUS) in two candidate genes, *VARS1* (OMIM*192150) and *ABCF1* (OMIM*603429). Both variants and genes were added to GeneMatcher, with no matching response thus far (Sobreira et al., 2015). WES analysis in 2014 was performed at the Genome Laboratory of the VU medical center in Amsterdam and repeated in 2017. WES analysis on another fetus was performed in 2019 at the Genome Laboratory of Radboud UMC in Nijmegen, the Netherlands.

In *VARS1* (NM_006295.2), the variant c.518G>T, p.(Arg173Leu) was identified (Hg19 chr6:31,760,767 C>A), which is a non-conservative missense variant of an in-mammals conserved amino acid. This variant of unknown

TABLE 2 Postmortem investigations of the six affected fetuses

	Eyes	Nose	Mouth and chin	Ears	Extremities	Other
1 (2009) ♂	Hypertelorism, Upward slant eyes	Broad nose bridge	Micro- and retrognathia, Big broad mouth	Low standing ears	Contractures in elbows, left wrist in extension, right elbow in flexion, mild camptodactyly dig II/III/IV, left pes equinovares, contractures of the hip	—
2 (2010) ♂	Hypertelorism	Broad nose bridge	Micro- and retrognathia, No opening from mouth to throat	Low standing ears	Contractures of the hips	Thickened nuchal fold, Pronounced forehead
3 (2011) ♂	—	Deep nose bridge	Micro- and retrognathia	Both ears dysplastic, Left simple helix and low standing, right lobe of ear big	Contractures shoulders, elbows, wrists Overlapping fingers, Camptodactyly dig II-V, Contractures knees, feet pronounced both sides, dig I high implementation and sandal gap, on both sides broad dig I	Prominent nasofacial groove, Narrow thorax
4 (2012) ♂	Hypertelorism	Broad nose bridge	Micro- and retrognathia, Small upper lip	Low standing ears	Both hands broad dig V	X-ray: cervical ribs and slight translucent bones Internal inspection organs: measurement and weight two weeks behind Brain: recent asphyxia signs, multiple point bleeding in the cortex and white matter. No structural brain anomalies and a normal neuromigration pattern was found in the cortex Spinal cord and muscle: normal
5 (2014) ♀	Hypertelorism, Upward slant eyes	Round nose tip	Micro- and retrognathia, No opening from mouth to throat, Flat philtrum	Low standing ears	Heels of feet pronounced, hand in claw position	X-ray: delayed skeletal maturation according to 18–19 weeks Internal inspection organs: measurement and weight according to 19 weeks Brain: normal weight
6 (2019)♀	Upward slant eyes	Deep nose bridge Broad nose bridge	Micro- and retrognathia, Long philtrum	Low standing ears, ear canal placed anterior from ear	No contractures	Hydropic fetus

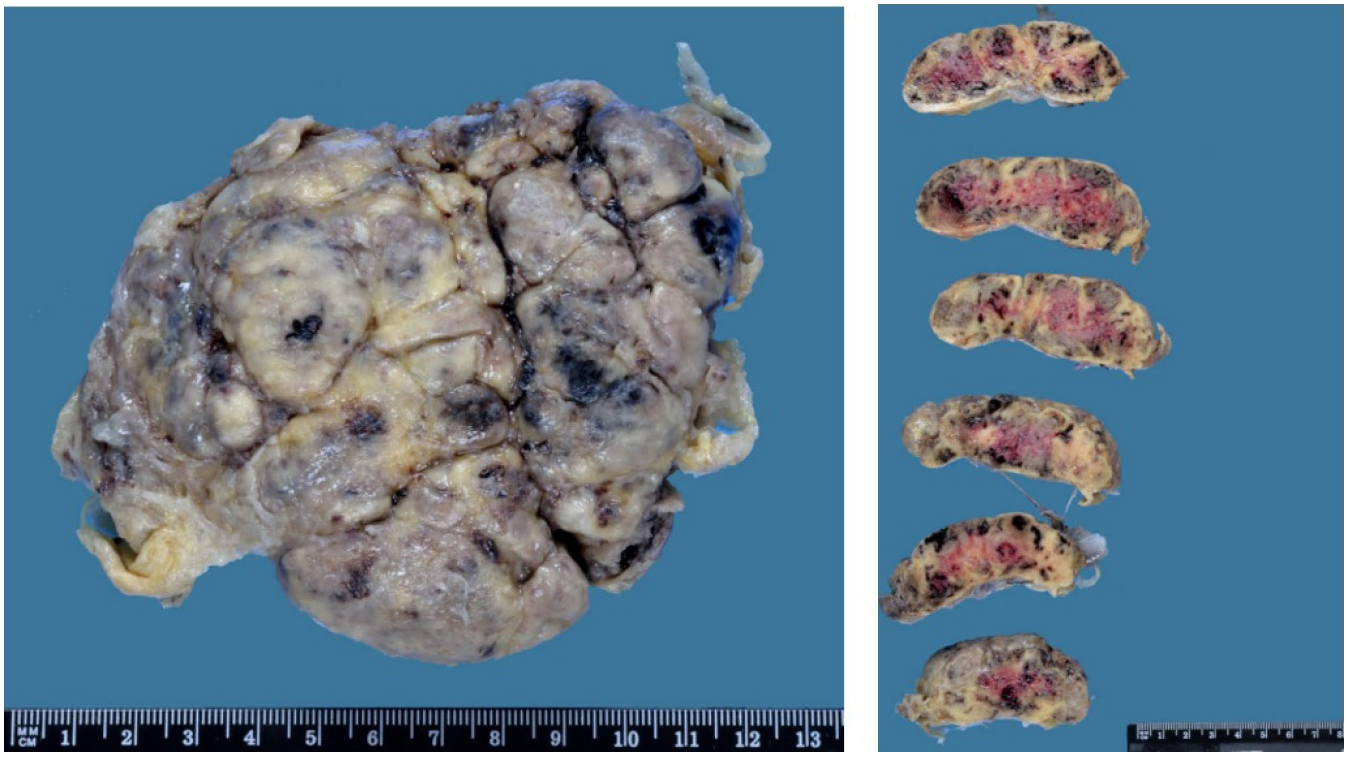

FIGURE 2 Macroscopic pictures of placenta of Fetus 5 showing Massive Perivillous Fibrin Deposition

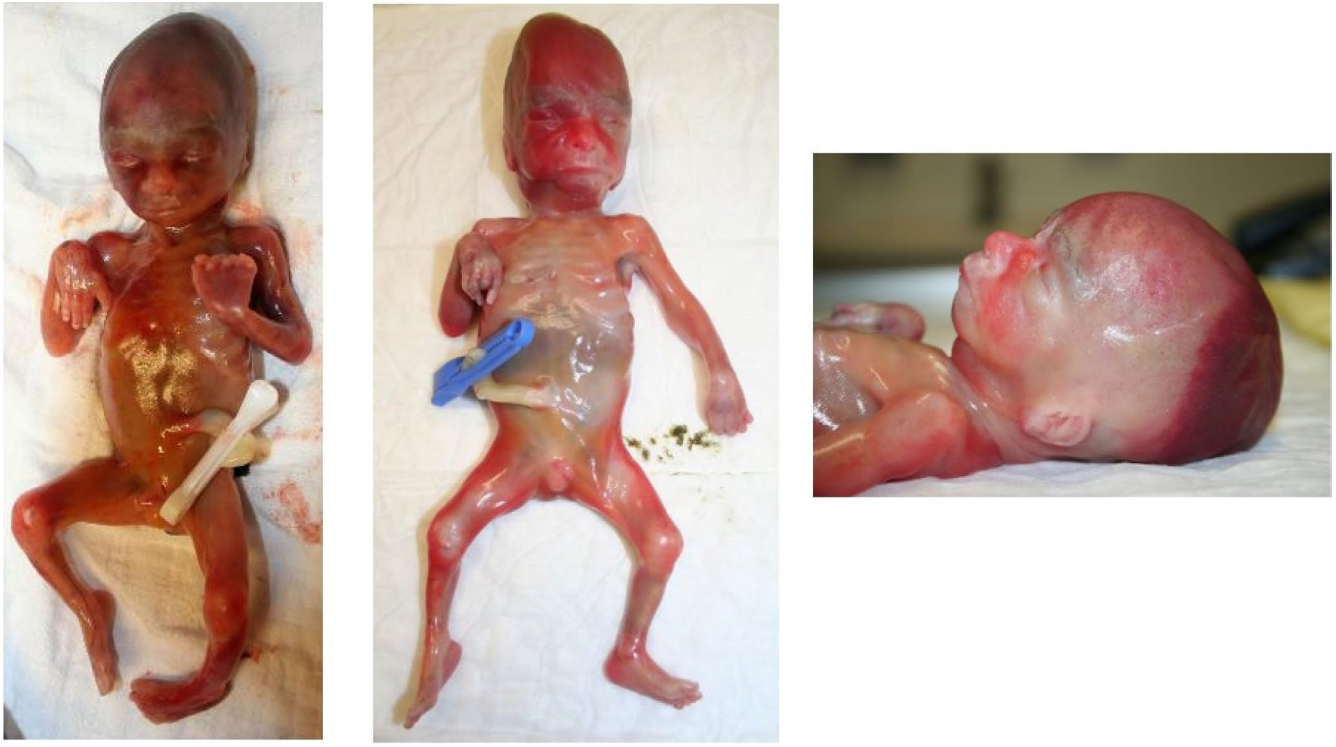

FIGURE 3 Pictures of external inspection of Fetus 1 (Ieft) and 3 (middle and right) showing contractures and micrognathia

significance has a low allele frequency in GnomAD v2.1.1: 2 heterozygous alleles out of a total of 247590. The gene *VARS1* encodes the cytoplasmic aminoacyl-tRNA synthetase for valine (Friedman et al., 2019). In addition, functional analysis of *VARS1* in fibroblast cells of one of the fetuses was performed and showed a decreased

TABLE 3 Performed genetic testing over the years, in six affected with FADS fetuses and one healthy child from one family.

Fetus	Karyotype/CNV analysis (SNP)	Single gene DNA analysis	WES analysis[a]	Segregation of VUS variants	
				VARS1 (OMIM*192150) C.518G>T P.ARG173LEU	*ABCF1* (OMIM*603429) C.1510G>A P.(VAL504ILE)
Parents				Heterozygous	Heterozygous
1 (2009) ♂	46,XY	—	—	—	—
2 (2010) ♂	Normal male pattern (SNP array)	*CHRNG*, *DOK7*, *RAPSN*: no (likely) pathogenic variants	—	Homozygous	Homozygous
3 (2011) ♂	46,XY		—	Homozygous	Homozygous
4 (2012) ♂	—	mtDNA: normal *HADHA*, *HADHB*: no (likely) pathogenic variants (Abdulghani et al., 2017)	2014: VUS in *VARS1* 2017: VUS in *ABCF1*	Homozygous	Homozygous
5 (2014) ♀	Normal female pattern (SNP array)	—	—	Homozygous	Homozygous
Healthy ♂ (2015)	—	—	—	Normal	Normal
6 (2019) ♀	Normal female pattern (CNV analysis in WES data)	—	2019: VUS in *VARS1* and *ABCF1*	Homozygous	Homozygous

Abbreviations: —, test not performed; GA, gestational age; IUFD, intra-uterine fetal death; mtDNA, mitochondrial DNA; VUS, Variant of Unknown Significance; WES, whole exome sequencing; wt, wild type.

[a] Both WES analyses were open exome trio-analyses, with DNA of parents included.

VARS1 activity of 51% compared with normal controls, but a remaining activity that was higher than normally seen in defective *VARS1* cell-lines (which is below 30%). This method has been previously described (Griffin et al., 2012). These results, therefore, did not confirm a causal relationship between the p.(Arg173Leu) variant and the disease phenotype in our family.

The second variant is c.1510G>A p.(Val504Ile) in *ABCF1* (NM_001025091.1) which is a conservative missense variant of a highly conserved amino acid (Hg19 chr6:30,553,369 G>A). The variant has a low allele frequency in GnomAD v2.1.1; 3 heterozygous alleles out of a total of 246638 alleles. *ABCF1* (ATP binding cassette subfamily F member 1) has not been associated with a human disease. Both genes, *VARS1* and *ABCF1* are located in an overlapping region of homozygosity (ROH) on chromosome 6 of ~22 Mb (Hg19 chr6:20,765,548–42,615,698) in which more than 750 genes are located. No additional homozygous (likely) pathogenic variants were identified in the remaining genes in this overlapping ROH. Additional ROH-analysis showed that there were no other overlapping ROH regions larger than 1 MB shared by all five affected fetuses for whom DNA was available as well as for the healthy son. The couple refrained from prenatal genotyping by chorion villus sampling or amniocentesis during subsequent pregnancies after the identification of the VUS in *VARS1* and *ABCF1*.

3.6 | Literature review on MPFD/MFI and congenital anomalies

The search on MPFD with related search terms resulted in a total of 1999 publications with 129 eligible articles. Of these, 12 could not be included because no full text was available. After reading the full text of all of the remaining articles, 63 were included (Abdulghani et al., 2017; Achuthan et al., 2017; Adams-Chapman et al., 2002; Al-Adnani et al., 2008; Al-Sahan et al., 2014; Ananthan et al., 2019; Andres et al., 1990; Bane & Gillan, 2003; Batcup et al., 1985; Bendon & Hommel, 1996; Benirschke et al., 2000; Brown et al., 2002; Chaiworapongsa et al., 2016; Chang et al., 2006; Chisholm et al., 2016; Clewell & Manchester, 1983; da Cunha Castro & Popek, 2007; Devisme et al., 2017; Eom et al., 2008; Faye-Petersen et al., 2018; Feist et al., 2015, 2019, 2020; Gao et al., 2021; Gestrich et al., 2020; Gibbins et al., 2020; Griffin et al., 2012; Gupta et al., 2004; Hannaford et al., 2019; He et al., 2018; Heller et al., 2016; Hung et al., 2006; Jaiman et al., 2020; Katz et al., 1987, 2002; Kim et al., 2019; Leavey et al., 2019; Leong et al., 2013; Linn et al., 2013; Makino et al., 2004; Maloney & Baergen, 2010; Man et al., 2016; Mandsager et al., 1994; Matern et al., 2001; Minamoto et al., 2019; Mongula et al., 2020; Montenegro et al., 1997; Nickel, 1988; Pathak et al., 2011; Qi et al., 2016; Redline et al., 2003; Redline & O'Riordan, 2000; Romero et al., 2013; Sebire et al., 2002; Spinillo et al., 2019; Taweevisit et al., 2020; Taweevisit & Thawornwong, 2020; Taweevisit & Thorner, 2010, 2015, 2016; Weber et al., 2006; Whitten et al., 2013; Yu et al., 2015). The reason for exclusion of the other 54 articles, 22 did not mention MPFD, 10 mentioned only fibrin depositions, 13 were overview articles with no original cases described, 7 contained no numbers of MPFD or did not relate MPFD to outcome and 2 were replies to an article. Based on these 63 articles, an overview of the pregnancy outcomes of MPFD is presented in Table 4. which describes the cases where >50% of the villi was encased by perivillous fibrinoid or the placenta was defined as MFI. Table 5 describes the cases with borderline MPFD where 25%–50% villi was encased by perivillous fibrinoid. Fetuses with congenital abnormalities in association with MPFD were found in 12 out of 63 articles.

4 | DISCUSSION

Here we present a consanguineous couple who lost six fetuses before a gestational age of 24 weeks, but who all developed normally up to the beginning of the second trimester. From a gestational age of around 20 weeks onwards, all deteriorated in growth, posture, and motility, with the development of placental anomalies and oligohydramnios. The couple also conceived one healthy son. In all six cases, the fetal phenotype of the affected fetuses resembled FADS together with severe early onset of placental thickening with cysts on ultrasound examination and histologically confirmed MPFD in the placentas.

We expected to find literature supporting our case with the association of FADS and MPFD since MPFD is known to cause oligohydramnios which can cause anomalies in face and extremities in line with FADS (Mandsager et al., 1994). Our literature review describes the outcome of 403 fetuses of which only fifty percent were live born, a large proportion being delivered preterm. Congenital anomalies were described in only 14/403 cases, of which the majority in deceased fetuses. Despite our expectations, the search only revealed one report of bilateral clubfeet with normal karyotype (Chaiworapongsa et al., 2016) and one case with facial changes in line with FADS (Qi et al., 2016). Other congenital anomalies reported were renal anomalies in seven cases with contractures in four out of seven (Chang et al., 2006; Leong et al., 2013; Linn et al., 2013; Taweevisit & Thorner, 2010), three cases of mutation in LCHAD (Griffin et al., 2012; Matern et al., 2001), one osteochondral junction lesions (da Cunha Castro & Popek, 2007), one aplasia of the left diaphragm, and one

TABLE 4 Fetal outcome associated with histologically classified MPFD/MFI

Author (year)	Number of MPFD/MFI	Number of live-born	GA at birth	Number of FGR	Congenital abnormalities	Number of deceased	GA of IUFD/ stillborn/TOP	Number of FGR	Congenital abnormalities
Adams-Chapman et al. (2002)	44	43	Unknown	43	None	1	Unknown	1	None
Al-Adnani et al. (2008)	1	0	—	—	—	1	34 weeks	0	None
Al-Sahan et al. (2014)	3	2	30, 35 weeks	2	None	1	30 weeks	1	None
Ananthan et al. (2019)	81	34	Unknown	Unknown	Unknown	47	Mean 37.5 weeks	Unknown	Unknown
Andres et al. (1990)	60	36	21 preterm	19	None	24	30–34 weeks (10/24)	Unknown	Unknown
Bane & Gillan (2003)[a]	7	5	30–38 weeks	9	None	2	29, 35 weeks	4	None
Batcup et al. (1985)	1	0	—	—	—	1	35 weeks	0	None
Bendon & Hommel (1996)	2	0	—	—	—	2	19, 24 weeks	1	None
Benirschke et al. (2000)	9	0	—	—	—	9	Unknown	Unknown	Unknown
Brown et al. (2002)	3	3	Unknown	Unknown	Unknown	0	—	—	—
Chaiworapongsa et al. (2016)[a]	2	1	34 weeks	1	No	1	20 weeks	1	Isolated bilateral clubfeet with anhydramnion, 46 XX
Chang et al. (2006)	3	2	33, 37 weeks	0	None	1	17 weeks	0	Bilateral tubular and glomerular microcystic kidneys, bilateral clubfeet, dysplastic tricuspid and mitral cardiac valves, three lobes left lung, pulmonary hypoplasia, 46 XY
Chisholm et al. (2016)[a]	10	10	Unknown	Unknown	Unknown	0	—	—	—
Clewell & Manchester (1983)	2	0	—	—	—	2	31, 35 weeks	0	None
da Cunha Castro & Popek, 2007)	1	0	—	—	—	1	24.5 weeks	1	Osteochondral junction lesions
Devisme et al. (2017)	39	30	Unknown	27	Unknown	9	Unknown	Unknown	Unknown
Eom et al. (2008)	1	0	—	—	—	1	Preterm	1	Unknown

TABLE 4 (Continued)

Author (year)	Number of MPFD/MFI	Number of live-born	GA at birth	Number of FGR	Congenital abnormalities	Number of deceased	GA of IUFD/ stillborn/TOP	Number of FGR	Congenital abnormalities
Faye-Petersen et al. (2018)	1 of discordant twin	0	—	—	—	1	22 weeks	1	None
Feist et al. (2019)[a]	1	0	—	—	—	1	29 weeks	1	None
Feist et al. (2020)[a]	4	1	36 weeks	1	Hypercoiling umbilical cord	3	21–24 weeks	3	Hypercoiling umbilical cord ($n = 3$)
Gao et al. (2021)	1	1	Unknown	0	2 × 2 cm defect on head	0	—	—	—
Gestrich et al. (2020)[a]	1	1	34 weeks	1	Normal karyotype, hypercoiling umbilical cord	0	—	—	—
Gibbins et al. (2020)	20	0	—	—	—	20	Unknown	Unknown	Unknown
Griffin et al. (2012)	3	2	25.4, 31 weeks	1	1. Abnormal limbs (bowed femurs), small thoracic circumference, large pericardial effusion, right heart enlarged 2. Bilateral pulmonary hypoplasia Mutations in LCHAD, ($n = 2$)	1	32.4 weeks	1	Large head relative to body, very wide sutures and fontanels, midfacial hypoplasia, hypertelorism, micrognathia, low-set and posteriorly rotated ears, eyelash hypoplasia, small fingernails and toenails, aberrant right subclavian artery, absent right umbilical artery, broad sacral dimple with thin skin at the base, short attachment of small bowel mesentery with free-floating cecum and appendix, accessory spleen, bridged left palmar crease, vertical creases of soles, and delayed ossification of the sternum, Mutation in LCHAD

(Continues)

TABLE 4 (Continued)

Author (year)	Number of MPFD/MFI	Number of live-born	GA at birth	Number of FGR	Congenital abnormalities	Number of deceased	GA of IUFD/ stillborn/TOP	Number of FGR	Congenital abnormalities
Gupta et al. (2004)	1 of discordant twin	1	33 weeks	1	None	0	—	—	—
He et al. (2018)[a]	1	1	31 weeks	1	None	0	—	—	—
Heller et al. (2016)	1	0	—	—	—	1	28 weeks	0	None
Hung et al. (2006)	1	0	—	—	—	1	38 weeks	Unknown	None
Jaiman et al. (2020)[a]	6	2	Unknown	Unknown	Unknown	4	Unknown	Unknown	Unknown
Katz et al. (1987)	2	1	34 weeks	1	None	1	32 weeks	Unknown	None
Katz et al. (2002)	1	0	—	—	—	1	16 weeks	Unknown	None
Kim et al. (2019)[a]	10	0	—	—	—	10	6–9 weeks	Unknown	Unknown
Leong et al. (2013)[a]	1	0	—	—	—	1	21 weeks	0	Renal tubular dysgenesis Mild external features secondary to reduced amniotic fluid, as well as hypertelorism and widely patent sutures and fontanelles. 46 XX
Linn et al. (2013)[a]	3	0	—	—	—	3	14–18 weeks	3	Renal tubular dysgenesis ($n = 3$) 1:18 weeks, external examination revealed bilateral flexion deformities of wrists and eversion deformations of the ankles with apparent dislocation of tibiotalar joints on radiographic examination 2: 18 weeks, no abnormalities, 46 XX 3: 14 weeks, anhydramnios

TABLE 4 (Continued)

Author (year)	Number of MPFD/MFI	Number of live-born	GA at birth	Number of FGR	Congenital abnormalities	Number of deceased	GA of IUFD/ stillborn/TOP	Number of FGR	Congenital abnormalities
Makino et al. (2004)[a]	1	1	28 weeks	1	None, 46 XY	0	—	—	—
Maloney & Baergen (2010)[a]	1	1	35 weeks	1	None	0	—	—	—
Man et al. (2016)	6	0	—	—	—	6	17–41 weeks	Unknown	Unknown
Mandsager et al. (1994)	9	1	34.2 weeks	1	None	8	34.2 weeks	8	None
Matern et al. (2001)	1	1	35 weeks	1	LCHAD Deficiency	0	—	—	—
Minamoto et al. (2019)	1	1	35 weeks	1	None	0	—	—	—
Montenegro et al. (1997)	6	1	—	—	—	5	28–30 weeks	4	1: Aplasia of the left diaphragm, pulmonary hypoplasia, ventricle wall defect, pulmonal valve dysplasia
Nickel (1988)	1	1	36 weeks	1	Hypospadias, bilateral cryptorchidism, inguinal hernias, bilateral bridged palmer creases	0	—	—	—
Pathak et al. (2011)	5	5	34–41 weeks	2	Unknown	0	—	—	—
Qi et al. (2016)[a]	7	5	30–36 weeks	3	None	2	23 weeks	1	Abnormalities consistent with Potter Sequence
Redline et al. (2003)[a]	1 of discordant twin	1	30.3 weeks	1	None	0	—	—	—
Romero et al. (2013)[a]	10	2	30, 38 weeks	1	None	8	15.6–28 weeks	4	None
Spinillo et al. (2019)[a]	11	10	Mean 36.1 weeks	10	None	1	Unknown	1	None

(Continues)

TABLE 4 (Continued)

Author (year)	Number of MPFD/MFI	Number of live-born	GA at birth	Number of FGR	Congenital abnormalities	Number of deceased	GA of IUFD/ stillborn/TOP	Number of FGR	Congenital abnormalities
Taweevisit & Thorner (2010)[a]	2	0	—	—	—	2	31, 39 weeks	2	1: Cystic renal dysplasia, oligohydramnios, prune belly, fixed flexion contractures, lax abdominal wall skin, bilateral multicystic renal dysplasia, bilateral hydroureter, thick-walled bladder, urethra longer and dilated, hypoplastic lungs 2: Flexion contractures, bilateral multicystic renal dysplasia, hypoplastic lungs, oligohydramnios and cystic renal dysplasia
Taweevisit & Thorner (2016)[a]	1	0	—	—	—	1	34 weeks	1	Hypercoiling umbilical cord, single umbilical artery, absent fetal movements
Taweevisit et al. (2020)	1	0	—	—	—	1	28 weeks	1	None
Weber et al. (2006)[a]	1	0	—	—	—	1	37 weeks	1	None
Whitten et al. (2013)[a]	10	2	30, 38 weeks	1	None	8	15.6–28.2 weeks	3	None
Yu et al. (2015)[a]	1	0	—	—	—	1	36 weeks	0	Congenital abnormalities
Total *N* (%)	403	208 (51.6)		131		195 (48.4)		46	None

Abbreviations: —, not applicable; FGR, fetal growth restriction; GA, gestational age; IUFD, intra uterine fetal death; LCHAD, Long-Chain 3-Hydroxyacyl Coenzyme A Dehydrogenase; MFI, maternal floor infarction; MPFD, massive perivillous fibrin deposition; TOP, termination of pregnancy.

[a] Definition according to Katzman et al., all without † no definition was given by the author.

TABLE 5 Fetal outcome associated with histologically categorized borderline MPFD according to Katzman and Genest 2002

Author (year)	Number of MPFD/ MFI	Number of live-born	GA at birth	Number of FGR present	Congenital abnormalities	Number of deceased	GA of IUFD/ stillborn/TOP	Number of FGR present	Congenital abnormalities
Abdulghani et al. (2017)	2	0	—	—	—	2	TOP 21 weeks IUFD 16 + 5 weeks	2	None found
Achuthan et al. (2017)	22	22	Unknown	22	None	0	—	—	—
Al-Adnani et al. (2008)	1	1	32 weeks	1	None	0	—	—	—
Bane & Gillan (2003)	6	4	33 (twin)–40 weeks	4	T21	2	33, 41 weeks	2	None
Feist et al. (2015)	1 (of twin)	1	34 weeks	1	None	0	—	—	—
Hannaford et al. (2019)	1	1	36 weeks	1	None	0	—	—	—
Leavey et al. (2019)	1	1	33.4 weeks	1	None, normal karyotype and array	0	—	—	—
Mongula et al. (2020)	1	1	32.1 weeks	0	None	0	—	—	—
Qi et al. (2016)	5	5	25–38 weeks	5	None	0	—	—	—
Redline & O'Riordan (2000)	14	14	Unknown	Unknown	Neurological impairment	0	—	—	—
Sebire et al. (2002)	3	2	29, 32 weeks	2	None	1	38 weeks	1	None
Spinillo et al. (2019)	31	31	Mean 35.7 weeks	5	None	—	—	—	—
Taweevisit & Thawornwong (2020)	1	1	36.4 weeks	1	Skin desquamation	—	—	—	-
Total *N*(%)	89	84 (94.4)		43 (48.3)		5 (5.6)			

Abbreviations: —, NOT applicable; FGR, fetal growth restriction; GA, gestational age; IUFD, intra uterine fetal death; MPFD, massive perivillous fibrin deposition; TOP, termination of pregnancy.

pulmonary valve dysplasia (Montenegro et al., 1997). The combination of MPFD with hypercoiling of the umbilical cord was reported in six cases (Feist et al., 2020; Gestrich et al., 2020; Taweevisit & Thorner, 2016).

It is remarkable that borderline MPFD resulted in live born infants in the majority (84/89) and except for 1 trisomy 21, no other congenital or chromosomal anomalies were reported. The search contradicts the premise that the FADS phenotype in our cases is the result of MPFD only.

Extensive genetic testing in our case was performed through the years. Repetitive WES identified two homozygous missense variants of unknown clinical significance, one in the *VARS1* gene and one in the *ABCF1* gene, both located on chromosome 6 in the only overlapping and shared 22 Mb ROH and within near distance of 1 Mb. Additional genetic analyses revealed no other likely or certain pathogenic cause. At this stage, it remains uncertain whether the homozygous variant in either the *VARS1* gene or the *ABCF1* gene might be associated with the fetal phenotype, or that the cause is still not elucidated but likely present in this homozygous region on chromosome 6. Amongst others lethal congenital contracture syndromes, types 1, 2, and 3 are located on chromosomes other than chromosome 6 (*GLE1* on chromosome 9, *ERBB3* on chromosome 12, and *PIP5K1C* on chromosome 19, respectively). Kiefer and Hall (2019) provide the most recent update of the diversity of genetic anomalies of various forms of AMC and FADS. In none of these genes, (likely) pathogenic variants were identified in our cases.

This is the first article describing a possible association of a fetal genetic anomaly and MPFD other than LCHAD. In 2014, during the first WES analysis, no disease was associated with *VARS1* pathogenic variants. However, at that time, mouse mutants of *GARS*, encoding glycyl-tRNA synthetase had been described to cause embryonic lethality suggesting a possible link between *VARS1* and the phenotype in the foetuses (Seburn et al., 2006). In 2019, biallelic pathogenic (missense) variants in *VARS1* were associated with an autosomal recessive form of progressive neurodevelopmental epileptic encephalopathy with microcephaly and often associated with early-onset epilepsy (OMIM#617802; Friedman et al., 2019; Siekierska et al., 2019). *ABCF1* has been described to function in innate immune response and was studied in 2017 in mice by Wilcox et al (Arora et al., 2019; Wilcox et al., 2017). They used a single gene trap insertion in the *ABCF1* gene in murine embryonic stem cells and demonstrated that knockout mice (*ABCF-/*) were found to be embryonic lethal at 3.5 days post coitum, while *ABCF1*+/− mice appeared developmentally normal. The lethal consequences in *ABCF1* knockout mice possibly resemble with the IUFD cases in the family.

The literature on the phenotype FADS illustrates its variable expression, describing deterioration that starts either with its expression in the fetal motility or in contractures (Hellmund et al., 2016; Hoellen et al., 2011). All fetuses in our case had FADS-like facial abnormalities, flexed posture, contractures in four out of six and abnormal motility in all. The sudden onset of abnormal motility and postural anomalies in these fetuses can, in our experience, not be explained by merely the placental abnormalities. Warrander et al. found placental abnormalities in correlation with reduced fetal movements consisting maternal vascular malperfusion lesions, but MPFD was not found (Warrander et al., 2012). Reports of reduced variation in quality and quantity of general movements have been published in relation to placental insufficiency and fetal growth restriction with, first, reduced variation of the amplitude and thereafter a more flexed posture. Posture has been addressed as being slightly more crouched, with more flexion in cervical spine in fetal growth restriction related to placental insufficiency, however, not as extreme as in our case (Bekedam et al., 1985; Sival et al., 1990, 1992a, 1992b).

Despite the fact that fetal growth restriction is frequently found in fetuses with FADS, in general it has been found during the late second or third trimester of pregnancy, whereas it was already present during early second trimester in this family (Hellmund et al., 2016; Hoellen et al., 2011). Moreover, placental abnormalities like MPFD have not been described in pregnancies with fetuses having the complete spectrum of FADS. Perivillous fibrin depositions show a high recurrence rate with intra-uterine fetal death though the underlying pathogenic cause is still unknown (Becroft et al., 2004; Chen & Roberts, 2018). The clinical presentation, however, is generally later during the third trimester of pregnancy (Becroft et al., 2004). The earlier onset of similar fetal and placental anomalies in all affected fetuses of the family suggests a genetic involvement too.

This study's strength lies in the well-documented ultrasound and postpartum findings in six fetuses who underwent similar deterioration over time which can best be considered to be a form of FADS phenotype together with outspoken placental anomalies including cysts as have been found in MPFD. This was complemented with a literature review which included dedicated examination of the MPFD/MFI classification and fetal outcomes. While the literature review contradicted the expectation that the most severe form MPFD, often associated with oligohydramnios, would induce FADS-like anomalies, several congenital anomalies were described in association with MPFD. This leads to the

conclusion that MPFD is not only associated with maternal factors influencing the vascular system through chronic endothelial damage (obesity, autoimmune disease, diabetes mellitus) or acute damage during viral infections (coxsackie virus A9/A16, cytomegaly virus, SARS-COV-2). Furthermore, from the literature search, the unexpected reports on four discordant twins with one normal placenta and one abnormal supports the theory that it is not simple maternal influence causing the MPFD (Faye-Petersen et al., 2018; Feist et al., 2015; Gupta et al., 2004; Redline et al., 2003). Unfortunately, in the literature search from the 129 eligible articles only 63 could be included to relate MPFD with fetal outcome. This search should increase the awareness that lumping the histological placental data without individual outcomes hinders the examination for possible underlying causes.

5 | CONCLUSION

In one consanguineous couple a strikingly similar phenotype of FADS was encountered in six affected fetuses (male and female) causing intra-uterine fetal deaths between 20 and 24 weeks gestational age. No (likely) pathogenic cause was identified, but two homozygous variants, both of unknown clinical significance in the *VARS1* gene and *ABCF1* gene, both located in the only overlapping homozygous region larger than 1 Mb, on chromosome 6, were identified. These were the only consistent overlapping genetic finding in all five affected fetuses for whom DNA was available. The only healthy child is not a carrier of these variants. The severe fetal growth restriction, reduced variability of motility, flexed posture and oligohydramnios, together with MPFD in all placentas showed an extraordinary presentation of FADS. This study with literature review supports the finding that fetal, fetoplacental, and/or genetic components may play a role in causing some MPFDs.

CONFLICT OF INTEREST

The authors have declared no conflicts of interest.

AUTHOR'S CONTRIBUTION

Jill K. Tjon contributed to writing, analysis, and interpretation of article. Phillis Lakeman, Elisabeth van Leeuwen, Quintin Waisfisz, Marjan M. Weiss, Gita M. B. Tan, Peter G. J. Nikkels, Patrick J. P. van der Voorn, Ingeborg H. Linskens, Bloeme J. van der Knoop, and Johanna I. P. de Vries contributed to writing, analysis, and revising of article. Gajja S. Salomons contributed to research of specific part in article. George L. Burchell contributed to conducting the systematic review.

ETHICAL COMPLIANCE

The patient signed a consent form to publish this article, approval of the ethics committee was not applicable concerning the literature review.

DATA AVAILABILITY STATEMENT

The data are available through the corresponding author.

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REFERENCES

Abdulghani, S., Moretti, F., Gruslin, A., & Grynspan, D. (2017). Recurrent massive perivillous fibrin deposition and chronic intervillositis treated with heparin and intravenous immunoglobulin: A case report. *Journal of Obstetrics and Gynaecology Canada*, *39*(8), 676–681. https://doi.org/10.1016/j.jogc.2017.03.089.

Achuthan, R., Valooran L, J., Velayudhan C, C., & Balachandran, B. (2017). Study of placental histopathology in idiopathic intrauterine growth retardation- a comparative study. *Journal of Evolution of Medical and Dental Sciences*, *6*(32), 2615–2618. https://doi.org/10.14260/Jemds/2017/565

Adams-Chapman, I., Vaucher, Y. E., Bejar, R. F., Benirschke, K., Baergen, R. N., & Moore, T. R. (2002). Maternal floor infarction of the placenta: Association with central nervous system injury and adverse neurodevelopmental outcome. *Journal of Perinatology*, *22*(3), 236–241. https://doi.org/10.1038/sj.jp.7210685

Al-Adnani, M., Kiho, L., & Scheimberg, I. (2008). Recurrent placental massive perivillous fibrin deposition associated with polymyositis: A case report and review of the literature. *Pediatric and Developmental Pathology*, *11*(3), 226–229. https://doi.org/10.2350/07-06-0306.1

Al-Sahan, N., Grynspan, D., von Dadelszen, P., & Gruslin, A. (2014). Maternal floor infarction: Management of an underrecognized pathology. *Journal of Obstetrics and Gynaecology Research*, *40*(1), 293–296. https://doi.org/10.1111/jog.12159

Ananthan, A., Nanavati, R., Sathe, P., & Balasubramanian, H. (2019). Placental findings in singleton stillbirths: A case-control study. *Journal of Tropical Pediatrics*, *65*(1), 21–28. https://doi.org/10.1093/tropej/fmy006

Andres, R. L., Kuyper, W., Resnik, R., Piacquadio, K. M., & Benirschke, K. (1990). The association of maternal floor infarction of the placenta with adverse perinatal outcome. *American Journal of Obstetrics and Gynecology*, *163*(3), 935–938. https://doi.org/10.1016/0002-9378(90)91100-Q

Arora, H., Wilcox, S. M., Johnson, L. A., Munro, L., Eyford, B. A., Pfeifer, C. G., Welch, I., & Jefferies, W. A. (2019). The ATP-binding cassette gene ABCF1 functions as an E2 ubiquitin-conjugating enzyme controlling macrophage polarization to dampen lethal septic shock. *Immunity*, *50*(2), 418–31.e6. https://doi.org/10.1016/j.immuni.2019.01.014

Bane, A. L., & Gillan, J. E. (2003). Massive perivillous fibrinoid causing recurrent placental failure. *BJOG*, *110*(3), 292–295. https://doi.org/10.1046/j.1471-0528.2003.00119.x

Batcup, G., Holt, P., Hambling, M. H., Gerlis, L. M., & Glass, M. R. (1985). Placental and fetal pathology in Coxsackie virus A9

infection: A case report. *Histopathology*, *9*(11), 1227–1235. https://doi.org/10.1111/j.1365-2559.1985.tb02802.x

Becroft, D. M., Thompson, J. M., & Mitchell, E. A. (2004). Placental infarcts, intervillous fibrin plaques, and intervillous thrombi: Incidences, cooccurrences, and epidemiological associations. *Pediatric and Developmental Pathology*, *7*(1), 26–34. https://doi.org/10.1007/s10024-003-4032-3

Bekedam, D. J., Visser, G., de Vries, J. J., & Prechtl, H. (1985). Motor behaviour in the growth retarded fetus. *Early Human Development*, *12*(2), 155–165. https://doi.org/10.1016/0378-3782(85)90178-1

Bendon, R. W., & Hommel, A. B. (1996). Maternal floor infarction in autoimmune disease: Two cases. *Pediatric Pathology and Laboratory Medicine*, *16*(2), 293–297.

Benirschke K., Burton G. J., Baergen R. N. Pathology of the Human (2000). *Placenta*, 242.

Brown, D. L., DiSalvo, D. N., Frates, M. C., Davidson, K. M., & Genest, D. R. (2002). Placental surface cysts detected on sonography. *Journal of Ultrasound in Medicine*, *21*(6), 641–646. quiz 7–8. https://doi.org/10.7863/jum.2002.21.6.641

Chaiworapongsa, T., Romero, R., Korzeniewski, S. J., Chaemsaithong, P., Hernandez-Andrade, E., Segars, J. H., DeCherney, A. H., McCoy, M. C., Kim, C. J., Yeo, L., & Hassan, S. S. (2016). Pravastatin to prevent recurrent fetal death in massive perivillous fibrin deposition of the placenta (MPFD). *The Journal of Maternal-Fetal & Neonatal Medicine*, *29*(6), 855–862. https://doi.org/10.3109/14767058.2015.1022864

Chang, P., Millar, D., Tsang, P., Lim, K., Houlihan, E., & Stephenson, M. (2006). Intravenous immunoglobulin in antiphospholipid syndrome and maternal floor infarction when standard treatment fails: A case report. *American Journal of Perinatology*, *23*(2), 125–129. https://doi.org/10.1055/s-2006-931805

Chen, A., & Roberts, D. J. (2018). Placental pathologic lesions with a significant recurrence risk – What not to miss! *APMIS*, *126*(7), 589–601.

Chisholm, K. M., Heerema-McKenney, A., Tian, L., Rajani, A. K., Saria, S., Koller, D., & Penn, A. A. (2016). Correlation of preterm infant illness severity with placental histology. *Placenta*, *39*, 61–69. https://doi.org/10.1016/j.placenta.2016.01.012

Clewell, W. H., & Manchester, D. K. (1983). Recurrent maternal floor infarction: A preventable cause of fetal death. *American Journal of Obstetrics and Gynecology*, *147*(3), 346–347. https://doi.org/10.1016/0002-9378(83)91130-4

da Cunha Castro, E. C., & Popek, E. J. (2007). Osteochondral junction lesions in stillborn fetuses and their relationship to autopsy diagnoses. *Early Human Development*, *83*(9), 593–599. https://doi.org/10.1016/j.earlhumdev.2006.12.007

Devisme, L., Chauvière, C., Franquet-Ansart, H., Chudzinski, A., Stichelbout, M., Houfflin-Debarge, V., & Subtil, D. (2017). Perinatal outcome of placental massive perivillous fibrin deposition: A case-control study. *Prenatal Diagnosis*, *37*(4), 323–328. https://doi.org/10.1002/pd.5013

Donker, M. E., Eijckelhof, B. H., Tan, G. M. B., & de Vries, J. I. P. (2009). Serial postural and motor assessment of Fetal Akinesia Deformation Sequence (FADS). *Early Human Development*, *85*(12), 785–790. https://doi.org/10.1016/j.earlhumdev.2009.10.008

Eom, D. W., Kang, G. H., Cho, C. H., Yi, S. W., Park, H. M., Lee, S. S., & Son, U. S. (2008). Massive perivillous fibrin deposition in placenta. *Korean Journal of Pathology*, *42*(4), 236–239.

Faye-Petersen, O. M., & Ernst, L. M. (2013). Maternal floor infarction and massive perivillous fibrin deposition. *Surgical Pathology Clinics*, *6*(1), 101–114. https://doi.org/10.1016/j.path.2012.10.002

Faye-Petersen, O., Sauder, A., Estrella, Y., & Heller, D. S. (2018). Dichorionic twins discordant for massive perivillous fibrinoid deposition: Report of a case and review of the literature. *International Journal of Surgical Pathology*, *26*(1), 41–46. https://doi.org/10.1177/1066896917720029

Feist, H., Blöcker, T., Rau, G., & Hussein, K. (2015). Discordancy for placental massive perivillous fibrin deposition and fetal growth in dichorionic twins after in vitro fertilization. *Pediatric and Developmental Pathology*, *18*(5), 405–409. https://doi.org/10.2350/15-02-1609-CR.1

Feist, H., Hussein, K., Blöcker, T., & Wohlschlaeger, J. (2020). Pathoanatomical lesions in placentas with excessively hypercoiled umbilical cords: Frequent detection of massive perivillous fibrin deposition. *Pediatric and Developmental Pathology*, *23*(2), 107–114. https://doi.org/10.1177/1093526619865426

Feist, H., Turowski, G., Hussein, K., Blöcker, T., & Heim, A. (2019). Massive perivillous fibrin deposition of an enterovirus a-infected placenta associated with stillbirth: A case report. *Pediatric and Developmental Pathology*, *22*(2), 142–145. https://doi.org/10.1177/1093526618798772

Filges, I., & Hall, J. G. (2013). Failure to identify antenatal multiple congenital contractures and fetal akinesia–proposal of guidelines to improve diagnosis. *Prenatal Diagnosis*, *33*(1), 61–74. https://doi.org/10.1002/pd.4011

Friedman, J., Smith, D. E., Issa, Mahmoud Y., Stanley, Valentina, Wang, Rengang, Mendes, Marisa I., Wright, Meredith S., Wigby, Kristen, Hildreth, Amber, Crawford, John R., Koehler, Alanna E., Chowdhury, Shimul, Nahas, Shareef, Zhai, Liting, Xu, Zhiwen, Lo, Wing-Sze, James, Kiely N., Musaev, Damir, Accogli, Andrea, Guerrero, Kether, Tran, Luan T., Omar, Tarek E. I., Ben-Omran, Tawfeg, Dimmock, David, Kingsmore, Stephen F., Salomons, Gajja S., Zaki, Maha S., Bernard, Geneviève, & Gleeson, Joseph G. (2019). Biallelic mutations in valyl-tRNA synthetase gene VARS are associated with a progressive neurodevelopmental epileptic encephalopathy. *Nature Communications*, *10*(1), 707. https://doi.org/10.1038/s41467-018-07067-3

Gao, L., Ren, J., Xu, L., Ke, Xiaokang, Xiong, Lin, Tian, Xiaoli, Fan, Cuifang, Yan, Honglin, & Yuan, Jingping (2021). Placental pathology of the third trimester pregnant women from COVID-19. *Diagnostic Pathology*, *16*(1), 8. https://doi.org/10.1186/s13000-021-01067-6

Gestrich, C. K., Zhou, Y. Y., & Ravishankar, S. (2020). Massive perivillous fibrin deposition in congenital cytomegalovirus infection: A case report. *Pediatric and Developmental Pathology*, *24*(1), 47–50. https://doi.org/10.1177/1093526620961352

Gibbins, K. J., Pinar, H., Reddy, U. M., Saade, George R., Goldenberg, Robert L., Dudley, Donald J., Drews-Botsch, Carolyn, Freedman, Alexa Ann, Daniels, Lauren M., Parker, Corette B., Thorsten, Vanessa, Bukowski, Radek, & Silver, Robert M. (2020). Findings in Stillbirths Associated with Placental Disease. *American Journal of Perinatology*, *37*(7), 708–715. https://doi.org/10.1055/s-0039-1688472

Griffin, Adrienne Carruth, Strauss, Arnold W., Bennett, Michael J., & Ernst, Linda M. (2012). Mutations in long-chain 3-hydroxyacyl coenzyme a dehydrogenase are associated with placental maternal floor infarction/massive perivillous fibrin deposition. *Pediatric and Developmental Pathology*, *15*(5), 368–374. https://doi.org/10.2350/12-05-1198-OA.1

Gupta, N., Sebire, N. J., Miskry, T., & Rees, Hc (2004). Massive perivillous fibrin deposition associated with discordant fetal growth in a dichorionic twin pregnancy. *Journal of Obstetrics and Gynaecology*, *24*(5), 579–580. https://doi.org/10.1080/01443610410001722752

Hall, J. G. (2014). Arthrogryposis (multiple congenital contractures): Diagnostic approach to etiology, classification, genetics, and general principles. *European Journal of Medical Genetics*, *57*(8), 464–472. https://doi.org/10.1016/j.ejmg.2014.03.008

Hall, J. G., & Kiefer, J. (2016). Arthrogryposis as a syndrome: Gene ontology analysis. *Molecular Syndromology*, *7*(3), 101–109. https://doi.org/10.1159/000446617

Hannaford, P., Mittal, N., Sethna, F., & Dahlstrom, J. E. (2019). Recurrent chronic intervillositis: The diagnostic challenge – A case report and review of the literature. *Journal of Obstetrics and Gynaecology Canada*, *41*(3), 344–347. https://doi.org/10.1016/j.jogc.2018.05.007

He, M., Migliori, A., Maari, N. S., & Mehta, N. D. (2018). Follow-up and management of recurrent pregnancy losses due to massive perivillous fibrinoid deposition. *Obstetric Medicine*, *11*(1), 17–22. https://doi.org/10.1177/1753495X17710129

Heller, D. S., Tellier, R., Pabbaraju, K., Wong, S., Faye-Petersen, O. M., Muehlenbachs, A., Goldsmith, C., Denison, A., & Zaki, S. R. (2016). Placental massive perivillous fibrinoid deposition associated with coxsackievirus A16-report of a case, and review of the literature. *Pediatric and Developmental Pathology*, *19*(5), 421–423. https://doi.org/10.2350/15-10-1726-CR.1

Hellmund, A., Berg, C., Geipel, A., Müller, A., & Gembruch, U. (2016). Prenatal diagnosis of fetal akinesia deformation sequence (FADS): A study of 79 consecutive cases. *Archives of Gynecology and Obstetrics*, *294*(4), 697–707. https://doi.org/10.1007/s00404-016-4017-x

Hoellen, Friederike, Schröer, Andreas, Kelling, Katharina, Krapp, Martin, Axt-Fliedner, Roland, Gembruch, Ulrich, & Weichert, Jan (2011). Arthrogryposis multiplex congenita and pena-shokeir phenotype: Challenge of prenatal diagnosis – Report of 21 cases, antenatal findings and review. *Fetal Diagnosis and Therapy*, *30*(4), 289–298. https://doi.org/10.1159/000331401

Hung, N. A., Jackson, C., Nicholson, M., & Highton, John (2006). Pregnancy-related polymyositis and massive perivillous fibrin deposition in the placenta: Are they pathogenetically related? *Arthritis & Rheumatism*, *55*(1), 154–156. https://doi.org/10.1002/art.21710

Jaiman, S., Romero, R., Pacora, P., Jung, Eunjung, Bhatti, Gaurav, Yeo, Lami, Kim, Yeon Mee, Kim, Bomi, Kim, Chong Jai, Kim, Jung-Sun, Qureshi, Faisal, Jacques, Suzanne M., Erez, Offer, Gomez-Lopez, Nardhy, & Hsu, Chaur-Dong (2020). Disorders of placental villous maturation in fetal death. *Journal of Perinatal Medicine*, *48*(4), 345–368. https://doi.org/10.1515/jpm-2020-0030

Jones, K. L. (2013) Smith's Recognizable patterns in human malformation. In: E. Philadelphia, (Ed.). *Smith's Recognizable patterns in human malformation*, 7th ed.

Katz, V. L., Bowes, W. A. Jr, & Sierkh, A. E. (1987). Maternal floor infarction of the placenta associated with elevated second trimester serum alpha-fetoprotein. *American Journal of Perinatology*, *4*(3), 225–228. https://doi.org/10.1055/s-2007-999778

Katz, V. L., DiTomasso, J., Farmer, R., & Carpenter, M. (2002). Activated protein C resistance associated with maternal floor infarction treated with low-molecular-weight heparin. *American Journal of Perinatology*, *19*(5), 273–278. https://doi.org/10.1055/s-2002-33085

Katzman, P. J., & Genest, D. R. (2002). Maternal floor infarction and massive perivillous fibrin deposition: Histological definitions, association with intrauterine fetal growth restriction, and risk of recurrence. *Pediatric and Developmental Pathology*, *5*(2), 0159–164. https://doi.org/10.1007/s10024001-0195-y

Kiefer, J., & Hall, J. G. (2019). Gene ontology analysis of arthrogryposis (multiple congenital contractures). *American Journal of Medical Genetics Part C: Seminars in Medical Genetics*, *181*(3), 310–326. https://doi.org/10.1002/ajmg.c.31733

Kim, E. N., Lee, J. Y., Shim, J. Y., Hwang, Doyeong, Kim, Ki Chul, Kim, So Ra, & Kim, Chong Jai (2019). Clinicopathological characteristics of miscarriages featuring placental massive perivillous fibrin deposition. *Placenta*, *86*, 45–51. https://doi.org/10.1016/j.placenta.2019.07.006

Leavey, K., Cox, B. J., Cargill, Y., & Grynspan, David (2019). Recurrent placental transcriptional profile with a different histological and clinical presentation: A case report. *Pediatric and Developmental Pathology*, *22*(6), 584–589. https://doi.org/10.1177/1093526619852871

Leong, M. Y., Walford, N., Rama Krishna, V. V., Lazda, E. D. (2013). Another case of concomitant fetal renal tubular dysgenesis and placental massive perivillous fibrin deposition. *Pediatric and Developmental Pathology*, *16*(6), 447–449. https://doi.org/10.2350/13-09-1376-LET.1

Linn, R. L., Kiley, J., Minturn, Lucy, Fritsch, Michael K., DeJulio, Todd, Rostlund, Emily, & Ernst, Linda M. (2013). Recurrent massive perivillous fibrin deposition in the placenta associated with fetal renal tubular dysgenesis: Case report and literature review. *Pediatric and Developmental Pathology*, *16*(5), 378–386. https://doi.org/10.2350/13-06-1351-CR.1

Lowry, R. B., Sibbald, B., Bedard, T., Hall, J. G. (2010). Prevalence of multiple congenital contractures including arthrogryposis multiplex congenita in Alberta, Canada, and a strategy for classification and coding. *Birth Defects Research Part A, Clinical and Molecular Teratology*, *88*(12), 1057–1061.

Makino, A., Suzuki, Y., Yamamoto, T., Sato, Takeshi, Kojima, Kazuhisa, & Suzumori, Kaoru (2004). Use of aspirin and low-molecular-weight heparin to prevent recurrence of maternal floor infarction in women without evidence of antiphospholipid antibody syndrome. *Fetal Diagnosis and Therapy*, *19*(3), 261–265. https://doi.org/10.1159/000076708

Maloney, K. F., & Baergen, R. N. (2010). Maternal floor infarction: Massive diffuse perivillous fibrin deposition. *Pathology Case Reviews*, *15*(2), 58–61. https://doi.org/10.1097/PCR.0b013e3181dce239

Man, J., Hutchinson, J. C., Heazell, A. E., Ashworth, M., Jeffrey, I., & Sebire, N. J. (2016). Stillbirth and intrauterine fetal death: Role of routine histopathological placental findings to determine cause of death. *Ultrasound in Obstetrics and Gynecology*, *48*(5), 579–584. https://doi.org/10.1002/uog.16019

Mandsager, N. T., Bendon, R., Mostello, D., Rosenn, B., Miodovnik, M., & Siddiqi, T. A. (1994). Maternal floor infarction of the placenta: Prenatal diagnosis and clinical significance. *Obstetrics and Gynecology*, *83*(5), 750–754.

Matern, D., Schehata, B. M., Shekhawa, P., Strauss, Arnold W., Bennett, Michael J., & Rinaldo, Piero (2001). Placental floor infarction complicating the pregnancy of a fetus with long-chain 3-hydroxyacyl-CoA dehydrogenase (LCHAD) deficiency.

Molecular Genetics and Metabolism, *72*(3), 265–268. https://doi.org/10.1006/mgme.2000.3135

Minamoto, T., Tatsumi, N., Kurose, S., Sawada, Kiyoka, Yoshimura, Yuki, Yamashita, Hitomi, Hara, Tomomi, Ishibashi, Tomoka, Ishikawa, Masako, Oride, Aki, Nakayama, Kentaro, Kanasaki, Haruhiko, Kyo, Satoru, & Ishikawa, Noriyoshi (2019). Maternal floor infarction associated with fetal growth restriction: A case report. *Placenta*, *87*, 71–72. https://doi.org/10.1016/j.placenta.2019.08.059

Mongula, J. E., Frenken, M. W. E., van Lijnschoten, G., Arents, N. L. A., de Wit-Zuurendonk, L. D., Schimmel-de Kok, A. P. A., van Runnard Heimel, P. J., Porath, M. M., & Goossens, S. M. T. A. (2020). COVID-19 during pregnancy: Non-reassuring fetal heart rate, placental pathology and coagulopathy. *Ultrasound in Obstetrics and Gynecology*, *56*(5), 773–776.

Montenegro, N., Laurini, R., Brandäo, O., Nogueira, R. (1997). Placental findings in fetuses with absent or reversed end-diastolic flow in the umbilical artery (ARED flow): A reappraisal. *Journal of Maternal-Fetal Investigation*, *7*(4), 175–179.

Neveling, Kornelia, Feenstra, Ilse, Gilissen, Christian, Hoefsloot, Lies H., Kamsteeg, Erik-Jan, Mensenkamp, Arjen R., Rodenburg, Richard J. T., Yntema, Helger G., Spruijt, Liesbeth, Vermeer, Sascha, Rinne, Tuula, van Gassen, K. L., Bodmer, Danielle, Lugtenberg, Dorien, de Reuver, R., Buijsman, Wendy, Derks, Ronny C., Wieskamp, Nienke, van den Heuvel, Bert, Ligtenberg, Marjolijn J. L., Kremer, Hannie, Koolen, David A., van de Warrenburg, Bart P. C., Cremers, Frans P. M., Marcelis, Carlo L. M., Smeitink, Jan A. M., Wortmann, Saskia B., van Zelst-Stams, Wendy A. G., Veltman, Joris A., Brunner, Han G., Scheffer, Hans, & Nelen, Marcel R. (2013). A post-hoc comparison of the utility of sanger sequencing and exome sequencing for the diagnosis of heterogeneous diseases. *Human Mutation*, *34*(12), 1721–1726. https://doi.org/10.1002/humu.22450

Nickel, R. E. (1988). Maternal floor infarction: An unusual cause of intrauterine growth retardation. *American Journal of Diseases of Children*, *142*(12), 1270–1271. https://doi.org/10.1001/archpedi.1988.02150120024020

Ouzzani, M., Hammady, H., Fedorowicz, Z., & Elmagarmid, A. (2016). Rayyan—a web and mobile app for systematic reviews. *Systematic Reviews*, *5*(1), 4. https://doi.org/10.1186/s13643-016-0384-4

Pathak, S., Lees, C. C., Hackett, G., Jessop, Flora, & Sebire, Neil J. (2011). Frequency and clinical significance of placental histological lesions in an unselected population at or near term. *Virchows Archiv*, *459*(6), 565–572. https://doi.org/10.1007/s00428-011-1157-z

Qi, M., En Chang, K. T., Lian, D. W. Q., Khoo, C. K., & Tan, K. H. (2016). Placental massive perivillous fibrinoid deposition is associated with adverse pregnancy outcomes: A clinicopathological study of 12 cases. *Case Reports in Perinatal Medicine*, *5*(1), 35–39. https://doi.org/10.1515/crpm-2015-0087

Redline, R. W. (2020). Extending the spectrum of massive perivillous fibrin deposition (maternal floor infarction). *Pediatric and Developmental Pathology*, *24*(1), 10–11. https://doi.org/10.1177/1093526620964353

Redline, R. W., Jiang, J. G., & Shah, D. (2003). Discordancy for maternal floor infarction in dizygotic twin placentas. *Human Pathology*, *34*(8), 822–824. https://doi.org/10.1016/S0046-8177(03)00288-0

Redline, R. W., & O'Riordan, M. A. (2000). Placental lesions associated with cerebral palsy and neurologic impairment following term birth. *Archives of Pathology and Laboratory Medicine*, *124*(12), 1785–1791. https://doi.org/10.5858/2000-124-1785-PLAWCP

Romero, R., Whitten, A., Korzeniewski, S. J., Than, N. G., Chaemsaithong, P., Miranda, J., Dong, Zhong, Hassan, Sonia S., & Chaiworapongsa, Tinnakorn (2013). Maternal floor infarction/massive perivillous fibrin deposition: A manifestation of maternal antifetal rejection? *American Journal of Reproductive Immunology*, *70*(4), 285–298. https://doi.org/10.1111/aji.12143

Sebire, N. J., Backos, M., Goldin, R. D., & Regan, L. (2002). Placental massive perivillous fibrin deposition associated with antiphospholipid antibody syndrome. *BJOG: An International Journal of Obstetrics and Gynaecology*, *109*(5), 570–573. https://doi.org/10.1111/j.1471-0528.2002.00077.x

Seburn, K. L., Nangle, L. A., Cox, G. A., Schimmel, Paul, & Burgess, Robert W. (2006). An active dominant mutation of Glycyl-tRNA synthetase causes neuropathy in a charcot-marie-tooth 2D mouse model. *Neuron*, *51*(6), 715–726. https://doi.org/10.1016/j.neuron.2006.08.027

Siekierska, Aleksandra, Stamberger, Hannah, Deconinck, Tine, Oprescu, Stephanie N., Partoens, Michèle, Zhang, Yifan, Sourbron, Jo, Adriaenssens, Elias, Mullen, Patrick, Wiencek, Patrick, Hardies, Katia, Lee, Jeong-Soo, Giong, Hoi-Khoanh, Distelmaier, Felix, Elpeleg, Orly, Helbig, Katherine L., Hersh, Joseph, Isikay, Sedat, Jordan, Elizabeth, Karaca, Ender, Kecskes, Angela, Lupski, James R., Kovacs-Nagy, Reka, May, Patrick, Narayanan, Vinodh, Pendziwiat, Manuela, Ramsey, Keri, Rangasamy, Sampathkumar, Shinde, Deepali N., Spiegel, Ronen, Timmerman, Vincent, von Spiczak, Sarah, Helbig, Ingo, Weckhuysen, Sarah, Francklyn, Christopher, Antonellis, Anthony, de Witte, Peter, & De Jonghe, Peter (2019). Biallelic VARS variants cause developmental encephalopathy with microcephaly that is recapitulated in vars knockout zebrafish. *Nature Communications*, *10*(1), 708. https://doi.org/10.1038/s41467-018-07953-w

Sival, D. A., Visser, G. H., & Prechtl, H. F. (1990). Does reduction of amniotic fluid affect fetal movements? *Early Human Development*, *23*, 233–246. https://doi.org/10.1016/0378-3782(90)90014-A

Sival, D. A., Visser, G. H., & Prechtl, H. F. (1992). The effect of intrauterine growth retardation on the quality of general movements in the human fetus. *Early Human Development*, *28*(2), 119–132. https://doi.org/10.1016/0378-3782(92)90107-R

Sival, D. A., Visser, G. H., & Prechtl, H. F. (1992). The relationship between the quantity and quality of prenatal movements in pregnancies complicated by intra-uterine growth retardation and premature rupture of the membranes. *Early Human Development*, *30*, 193–209. https://doi.org/10.1016/0378-3782(92)90069-S

Skaria, P., Dahl, A., & Ahmed, A. (2019). Arthrogryposis multiplex congenita in utero: Radiologic and pathologic findings. *The Journal of Maternal-Fetal & Neonatal Medicine*, *32*(3), 502–511.

Sobreira, N., Schiettecatte, F., Valle, D., Hamosh, A. (2015). GeneMatcher: A matching tool for connecting investigators with an interest in the same gene. *Human Mutation*, *36*(10), 928–930.

Spinillo, Arsenio, Gardella, Barbara, Muscettola, Giulia, Cesari, Stefania, Fiandrino, Giacomo, & Tzialla, Chryssoula (2019). The impact of placental massive perivillous fibrin deposition on neonatal outcome in pregnancies complicated by fetal growth

restriction. *Placenta*, *87*, 46–52. https://doi.org/10.1016/j.placenta.2019.09.007

Taweevisit, Mana, Tansatit, Montakarn, Sutthiruangwong, Piriya, Siranart, Noppachai, & Thorner, Paul Scott (2020). Combined placental maternal floor infarction and cytomegalovirus placentitis: A case report. *Fetal and Pediatric Pathology*, 1–6. https://doi.org/10.1080/15513815.2020.1857487

Taweevisit, Mana, Thawornwong, Nutchanok, & Thorner, Paul Scott (2021). Massive perivillous fibrin deposition associated with placental syphilis: A case report. *Pediatric and Developmental Pathology*, *24*(1), 43–46. https://doi.org/10.1177/1093526620957523

Taweevisit, M., & Thorner, P. S. (2010). Maternal floor infarction associated with oligohydramnios and cystic renal dysplasia: Report of 2 cases. *Pediatric and Developmental Pathology*, *13*(2), 116–120. https://doi.org/10.2350/09-06-0669-CR.1

Taweevisit, M., & Thorner, P. (2015). Maternal floor infarction associated with umbilical cord hypercoiling. *Virchows Archiv*, *467*, S100–S101.

Taweevisit, M., & Thorner, P. S. (2016). Maternal floor infarction/massive perivillous fibrin deposition associated with hypercoiling of a single-artery umbilical cord: A case report. *Pediatric and Developmental Pathology*, *19*(1), 69–73. https://doi.org/10.2350/15-07-1673-CR.1

Tjon, Jill K., Tan-Sindhunata, Gita M., Bugiani, Marianna, Witbreuk, Melinda M., van der Sluijs, Johannes A., Weiss, Marjan M., van de Pol, Laura A., van Weissenbruch, Mirjam M., van der Knoop, Bloeme J., & de Vries, Johanna I. (2019). Fetal akinesia deformation sequence, arthrogryposis multiplex congenita, and bilateral clubfeet: Is motor assessment of additional value for in utero diagnosis? A 10-year cohort study. *Prenatal Diagnosis*, *39*(3), 219–231. https://doi.org/10.1002/pd.5411

Viero, S., Chaddha, V., Alkazaleh, F., Simchen, Mj, Malik, A., Kelly, E., Windrim, R., & Kingdom, Jcp (2004). Prognostic value of placental ultrasound in pregnancies complicated by absent end-diastolic flow velocity in the umbilical arteries. *Placenta*, *25*(8-9), 735–741. https://doi.org/10.1016/j.placenta.2004.03.002

Warrander, Lynne K., Batra, Gauri, Bernatavicius, Giovanna, Greenwood, Susan L., Dutton, Philip, Jones, Rebecca L., Sibley, Colin P., & Heazell, Alexander E. P. (2012). Maternal perception of reduced fetal movements is associated with altered placental structure and function. *PLoS One*, *7*(4), e34851. https://doi.org/10.1371/journal.pone.0034851

Weber, Martin A., Nikkels, Peter G. J., Hamoen, Karen, Duvekot, Johannes J., & de Krijger, Ronald r (2006). Co-occurrence of massive perivillous fibrin deposition and chronic intervillositis: Case report. *Pediatric and Developmental Pathology*, *9*(3), 234–238. https://doi.org/10.2350/06-01-0019.1

Whitten, A. E., Romero, R., Korzeniewski, S. J., Tarca, A. L., Schwartz, A. G., Yeo, L., Dong, Z., Hassan, S. S., & Chaiworapongsa, T. (2013). Evidence of an imbalance of angiogenic/antiangiogenic factors in massive perivillous fibrin deposition (maternal floor infarction): A placental lesion associated with recurrent miscarriage and fetal death. *American Journal of Obstetrics and Gynecology*, *208*(4), 310.e1–310.e11. https://doi.org/10.1016/j.ajog.2013.01.017

Wilcox, Sara M., Arora, Hitesh, Munro, Lonna, Xin, Jian, Fenninger, Franz, Johnson, Laura A., Pfeifer, Cheryl G., Choi, Kyung Bok, Hou, Juan, Hoodless, Pamela A., & Jefferies, Wilfred A. (2017). The role of the innate immune response regulatory gene ABCF1 in mammalian embryogenesis and development. *PLoS One*, *12*(5), e0175918. https://doi.org/10.1371/journal.pone.0175918

Yu, W., Tellier, R., & Wright, J. R. Jr (2015). Coxsackie virus A16 infection of placenta with massive perivillous fibrin deposition leading to intrauterine fetal demise at 36 weeks gestation. *Pediatric and Developmental Pathology*, *18*(4), 331–334. https://doi.org/10.2350/15-01-1603-CR.1

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