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Original article

Nodular fibromuscular villous stromal dysplasia (NFMVSD): forensic insights into fetal/neonatal outcomes

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Summary

Objective. To assess the frequency, morphological features, and perinatal/forensic relevance of nodular fibromuscular villous stromal dysplasia (NFMVSD) in a large retrospective placental series.

Methods. Placentas examined between 2014-2018 were retrospectively reviewed. Cases fulfilling diagnostic criteria for NFMVSD were re-evaluated macro- and microscopically, with smooth muscle actin and desmin immunostains when required. Placental weight centiles, lesion distribution, associated abnormalities, and pregnancy outcomes were recorded.

Results. NFMVSD was identified in 27 placentas (1.34%), mainly involving second-/third-order villi with multifocal nodular growth. Sixty-three percent were below the 25th weight percentile. Common findings included hypoxic distress (55%), stem vessel sclerosis (39%), and villous immaturity or dysmaturity (42%). Two intrauterine deaths (6%), four neonatal deaths (14%), and congenital anomalies (32%) occurred.

Conclusions. NFMVSD represents a distinct placental lesion with medicolegal significance, often associated with low placental weight, vascular changes, and hypoxic features. Its recognition may help clarify unexplained fetal or neonatal deaths. Standardized criteria and multicenter studies are required to refine its clinical and forensic implications.

Keywords: placenta/pathology, fetal Death, hypoxia, forensic pathology, vascular malformations

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Introduction

Nodular fibromuscular villous stromal dysplasia (NFMVSD) is a rare and complex placental lesion first described by Drut[1] in 2010.

The terminology used to define this lesion deserves clarification. The entity originally described by Drut as "*nodular myofibroblastic mesenchymal dysplasia*" emphasizes the nodular architecture and the myofibroblastic nature of the stromal proliferation.

However, in our experience, the immunohistochemical profile of the lesion is not consistent with a purely myofibroblastic proliferation. Myofibroblasts are typically positive for smooth muscle actin but lack desmin expression, whereas in our cases the stromal cells showed positivity for both smooth muscle actin and desmin, supporting a fibromuscular differentiation of the villous stromal cells[2,5].

Therefore, the term "*fibromuscular villous stromal dysplasia*" better reflects the nature of the lesion as a dysplastic process involving the fibro-

muscular stromal axis of stem villi rather than a purely myofibroblastic process.

Considering both the original description and our findings, the definition "*nodular fibromuscular villous stromal dysplasia*" represents a more comprehensive and pathologically terminology, as it preserves the nodular architectural feature while more accurately describing the underlying stromal differentiation.

Histologically, it is characterized by a dysplastic proliferation of small leiomuscular and fibro-leiomuscular elements within the stroma of the stem villi, with a typically nodular and multifocal pattern. It does not cause evident macroscopic alterations and is diagnosed exclusively by histological examination, mainly in the second and third trimester of pregnancy.

The stroma of stem villi contains a variable number of smooth muscle cells depending on the caliber of the villus[6]; this histological characteristic constitutes the physiological basis on which the lesion examined in this paper develops.

In recent literature, the distinction between NFMVSD, placental vascular dysplasia (PVD), and placental mesenchymal dysplasia (PMD) remains unclear[7,8]. PMD, in particular, has recently been the subject of several publications that have highlighted its diagnostic complexity, its association with intrauterine growth restriction (IUGR), and the variability of fetal outcomes[9,11].

PVD affects only the main placental blood vessels and is characterized by the presence of tortuous, ectatic, or, in some cases, aneurysmal amniochorionic vessels. Placentas are generally enlarged, with a weight above the 90th percentile, and may present complications such as vessel thrombosis or rupture with hemorrhage and be associated with adverse outcomes such as intrauterine growth restriction (IUGR), neonatal anemia, and disseminated intravascular coagulation (DIC)[12].

PMD, on the other hand, represents a serious and rare placental pathology that mainly manifests in the first trimester and is frequently associated with the female sex of the fetus[13] and, in approximately 23% of cases, with Beckwith-Wiedemann syndrome. From a genetic point of view, it has been correlated with biparental androgenetic mosaicism with a diploid karyotype[14]. Histologically, it diffusely involves the chorionic villi, which show hyperplasia of the stromal cells, cystic dilations and thickening of the vascular wall. Macroscopically, the placenta often has a weight higher than the 90th percentile[15] and evident cystic villous dilations[16]. PMD enters into differential diagnosis with partial hydatidiform mole, from which it is distinguished by the absence of trophoblastic proliferation, trophoblastic stromal inclusions and a triploid karyotype. It is frequently associated with fetal complications such as IUGR and intrauterine fetal death[17,18], neonatal complications such as anemia and hepatic and pulmonary hamartomas[19,20], but in some cases it can be found in the absence of adverse outcomes[21].

In 2013, we published the first case of NFMVSD associated with intrauterine death in the Journal of Forensic Sciences[22], helping to draw the scientific community's attention to this rare placental lesion.

In our previous 2013 report, the lesion was interpreted within the spectrum of mesenchymal villous dysplasia. However, subsequent observations and immunohistochemical characterization allowed a more precise definition of the lesion as a fibromuscular stromal alteration. Therefore, the current terminology does not represent a conceptual shift but rather a refinement of the same pathological entity.

Over the following five years, we continued systematically collecting and analyzing cases, observing that not all NFMVSD diagnoses were correlated with adverse fetal outcomes. These data reinforced the need to clarify the true clinical relevance of the lesion and motivated the initiation of a systematic neonatal follow-up, with the aim of more precisely defining the possible implications on fetal and neonatal well-being.

The aim of the study is to retrospectively analyze the cases of NFMVSD diagnosed in our center, evaluating the incidence, associated placental lesions, and fetal and neonatal outcomes, to clarify the clinical and medicolegal impact of this entity.

Materials and Methods

Study design and inclusion criteria

We conducted a retrospective observational study of placentas submitted for histopathological examination between 2014 and 2018. During this period, 2019 placentas were analyzed, submitted based on specific selection criteria: fetal death, pathological pregnancy, intrauterine growth abnormalities, abnormal birth history, malformations in live births, significant neonatal pathology, or macroscopic alterations of the adnexa.

Study population and comparative reference

The placentas included in this analysis were derived from a selected cohort of cases referred for histopathological evaluation between 2014 and 2018 based on specific clinical and/or medicolegal indications (*e.g.*, fetal/neonatal death, severe perinatal pathology, intrauterine growth restriction [IUGR], malformative anomalies, macroscopic alterations of the adnexa). In this context, non-NFMVSD placentas available in

the same period represent a heterogeneous group with variable lesions and reasons for referral, and with non-systematic availability of neonatal clinical outcomes. It should also be noted that the presence of lesions concentrated at early gestational ages (including extreme prematurity) reflects the characteristics of the center dedicated to the management of high-risk pregnancies.
For this reason, an internal "control group" was not defined for comparative analyses, in order to avoid biased conclusions due to selection and referral bias. The aim of the present study is the clinical histopathological characterization of NFMVSD and its medicolegal relevance in a consecutive series of cases.

Histopathological examination

All study placentas were processed following a standardized protocol that included proper preservation, formalin fixation, and macroscopic and microscopic evaluation. This protocol, in line with international recommendations[23,25], was applied to ensure an accurate and uniform histological diagnosis.
After macroscopic evaluation, each specimen was sectioned and examined histologically with routine hematoxylin and eosin (H&E) staining; as a diagnostic criterion of certainty, cases in which lesions were demonstrated on transverse sections of stem villi were evaluated (Fig. 1-3). In suspicious cases, immunohistochemical investigations aimed at identifying fibromuscular cells were also performed, using antibodies against smooth muscle actin (SMA) (Fig. 4) and desmin (Fig. 5). This is in line with comparative morphological studies that have highlighted the evolution of contractile elements in placental villi, supporting the hypothesis of a myofibroblastic stromal origin[26].
Immunohistochemical staining was performed using an automatic stainer (BenchMark Ultra – Roche

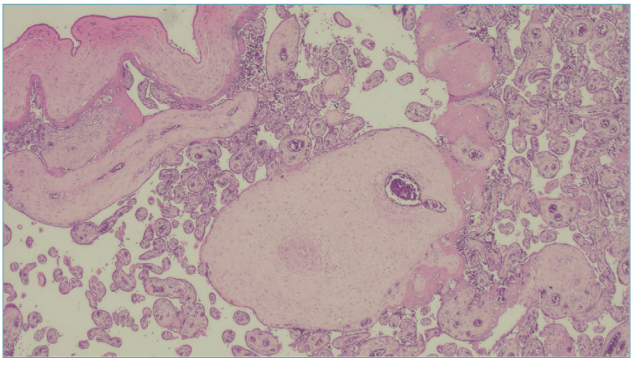

Figure 1. Hematoxylin-eosin stain of a first-order stem villus with NFMVSD (H&E 10x).

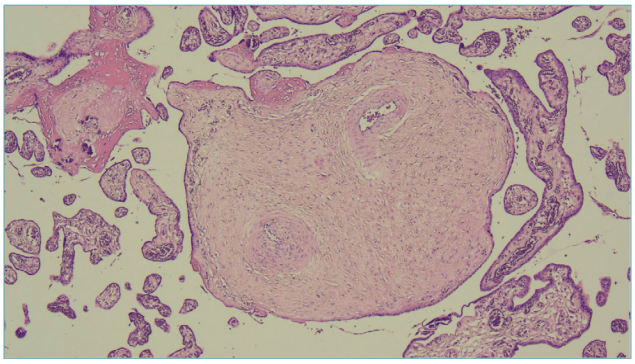

Figure 2. Hematoxylin-eosin stain of a second-order stem villus with NFMVSD (H&E 20x).

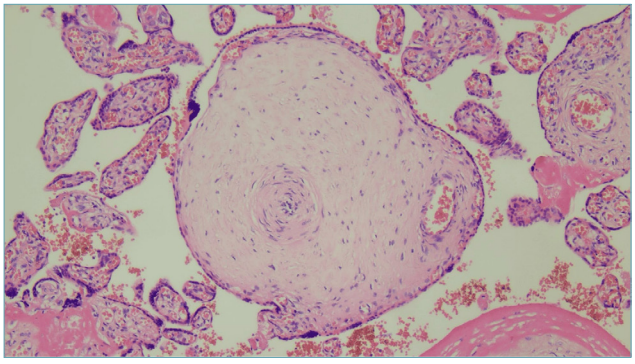

Figure 3. Hematoxylin-eosin stain of a third-order stem villus with NFMVSD (H&E 20x).

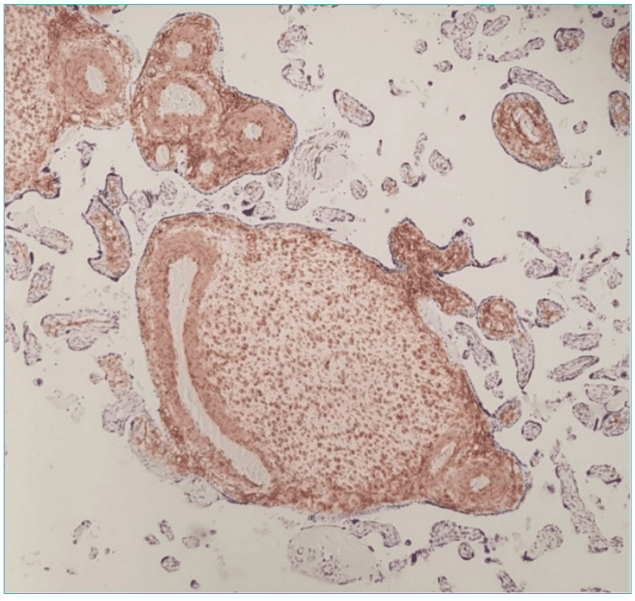

Figure 4. Immunohistochemistry for smooth muscle actin in a second-order villus with NFMVSD (SMA 40x).

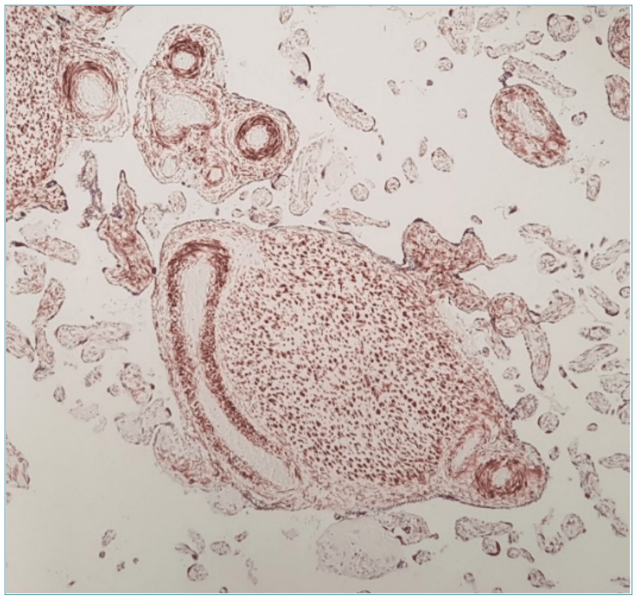

Figure 5. Immunohistochemistry for desmin in a second-order villus with NFMVSD (DESMIN 40x).

Ventana) with the use of pre-diluted sera (anti-Desmin DE-R-11- primary antibody 5 µg/ml), (anti-Actin, Smooth Muscle 1°4- primary mouse monoclonal antibody 0.03 µg/ml) according to standard procedures.
This analysis identified 27 placentas (1.34% of the total examined, 27/2019) compatible with NFMVSD. Of these, 23 were from singleton pregnancies and 4 from dichorionic and diamniotic twin pregnancies. No cases were attributable to medically assisted pregnancies.

Macro- and microscopic morphological criteria

In our study, the diagnosis of NFMVSD was made exclusively on histological grounds. At the macroscopic level, it was not possible to identify specific lesions affecting the villous branches nor non-specific signs that could suggest a diagnostic suspicion, confirming the impossibility of reliable identification based solely on clinical-macroscopic examination.
Microscopically, the lesions appeared as homogeneous nodular formations, with diameters ranging from 0.2 to 1.2 mm, multifocally distributed within the stromal axis of the stem villi. They consisted of spindle-shaped cells with abundant cytoplasm and small nuclei, arranged in interlacing or whorled patterns, lacking mitotic figures. The lesions lacked a capsule or pseudocapsule and did not exhibit necrotic, hemorrhagic phenomena or associated inflammatory infiltrates. The nodular expansion tended to compress the surrounding tissues without causing vasculitic reactions, degenerative changes, or endothelial damage.
Immunohistochemical investigations confirmed the fibromuscular origin of the cellular proliferations, demonstrating positivity for smooth muscle actin and desmin. The combination of these features allowed us to distinguish NFMVSD from other conditions with potentially similar histological presentations, such as placental mesenchymal dysplasia and placental vascular dysplasia.

Data collection and analysis

For each placenta diagnosed with NFMVSD, a systematic collection of clinical and anatomopathological data was carried out.
First, the fresh placental weight was recorded, relating it to the gestational age to calculate the relative centile according to the reference tables published by Pinar et al.(1996)[27]. This information was considered particularly relevant since a low placental weight often represents an indicator of functional insufficiency.
During microscopic analysis, the location of the lesion within the villous tree was described for each case, specifying the order of the affected villi and the extent of distribution. At the same time, any associated placental lesions were documented, using as a reference the classification proposed by the Amsterdam Placental Workshop Group Consensus Statement[25]. According to these criteria, the observed lesions were grouped into four main categories. The first included pathologies of infectious origin, such as chorioamnionitis, funisitis, vasculitis of the amniochorionic vessels and fetal inflammatory response (FIR). The second included vascular alterations of maternal origin, such as retroplacental hemorrhages, acute atherosis of the decidual vessels, ischemic cotyledonary infarctions and severe hypoxic conditions (attributable to maternal vascular malperfusion). The third category consisted of fetal vascular pathologies, which included sclerosis of the stem vessels, thrombotic vasculopathies, ischemic necrosis of the villi branches, as well as intervillous and subamniotic hemorrhages (attributable to fetal vascular malperfusion). Finally, the fourth category focused on placental maturation anomalies, such as dysmaturity of metabolic or endocrine origin, placental immaturity, and cases of inadequate implantation.
To link placental characteristics with clinical outcomes, data were collected from all pregnancies with NFMVSD. A total of two cases of stillbirth and 29 live births (including twins) were identified.
Maternal information was obtained from the medical history forms received with the placental samples and included: maternal age, obstetric history, and pathologies during the ongoing pregnancy.
For each newborn, the following were recorded: sex,

gestational age, mode of delivery, presence of intrauterine growth restriction (IUGR), birth weight and percentile[28,29], Apgar score at the first and fifth minutes, and any presence of congenital malformations.
In the two cases of stillbirth, clinical information was integrated with data from diagnostic findings (fetal autopsy), which allowed us to define sex, gestational age, and final autopsy diagnosis.

Results

The collected data are summarized in Table I, which describes the distribution of placentas based on weight percentile and the main maternal, fetal, and neonatal clinical data.
The analysis of the 27 placentas diagnosed with NFMVSD highlighted a prevalence of low placental weight. Specifically, 41% of cases (11/27) had a weight below the 10th percentile for gestational age, while a further 22% (6/27) fell between the 10th and 25th percentiles. Only 18% of placentas (5/27) exceeded the 90th percentile, while the remainder were distributed in the intermediate percentiles. These data suggest a significant association between NFMVSD and low placental weight.
Regarding the distribution of the villous tree lesion, a total of 31 chorionic discs were analyzed, including both single and diamniotic placentas, as detailed in Table II, which reports the distribution of the involved stem villi in the different orders.
An overall evaluation demonstrated that the lesion was never present in the first-order stem villi or in the amniochorionic vessels; it was present in the second, third, and fourth-order stem villi in 6 of the 27 total cases; in 3 of the 27 cases, the lesion was present in the third- and fourth-order stem villi; and in 14 cases, it was present in the second- and third-order stem villi. This latter finding, combined with the six cases where the lesion was present in all orders, allows us to confirm that the second- and third-order villi are primarily involved (20 out of 27 cases).
In all cases examinated, the lesions showed a multifocal distribution within the villous tree.
In one case, the lesion was demonstrated only in the second-order villi; in two cases, only in the third-order villi; and in only one case, in the fourth-order villi.
The analysis of associated placental lesions, reported in Table III, highlighted the frequent coexistence of other pathological conditions. Severe hypoxic distress was detected in over half of the discs (55%), while chorioamnionitis and placental immaturity were each present in approximately 42% of cases. Stem vessel sclerosis was observed in 39% of the discs, while maturational alterations of a metabolic or endocrine nature were documented in 35%.
The analysis of maternal anamnesis data allowed the assessment of predisposing factors that are sometimes reported in the literature as associated with adverse pregnancy outcomes. In our sample, no cases of chronic or gestational hypertension, nor episodes of alcohol or drug abuse, were documented. Regarding metabolic alterations, three cases of gestational diabetes (11%) were identified, all adequately managed with obstetric monitoring. From an infectious standpoint, a single case of HCV positivity was detected, not associated with evident clinical complications during gestation. Regarding lifestyle habits, only one patient (6%) reported habitual smoking; in most pregnancies, no significant exposure to environmental or behavioral risk factors was reported.
An additional element emerging from the anamnesis is the frequent presence of PROM (preterm rupture of membranes), documented in multiple cases (9/27, i.e., 33%) without showing particular concentration at specific gestational weeks. Although this finding does not demonstrate a direct correlation with NFMVSD, it represents a clinically relevant observation, as PROM is a well-known risk factor for obstetric and neonatal complications and may have contributed to aggravating the clinical picture in some pregnancies.
Overall, the distribution of these maternal conditions was limited and did not show statistically significant correlations with the occurrence of NFMVSD or the observed fetal and neonatal outcomes.
This suggests that, although representing elements of epidemiological interest, maternal anamnesis factors do not constitute a primary determinant in the genesis or evolution of placental lesions in our sample.
Regarding the distribution of lesions in relation to gestational age at delivery, no significant concentration within specific weeks emerged. In detail, the identified cases were as follows: 2 cases at 23 weeks, 1 case at 24 weeks, 1 case at 27 weeks, 1 case at 30 weeks, 5 cases at 32 weeks, 4 cases at 33 weeks, 2 cases at 34 weeks, 3 cases at 35 weeks, 3 cases at 36 weeks, 1 case at 37 weeks, 1 case at 38 weeks, and 3 cases at 39 weeks.
Regarding perinatal outcomes, two fetuses (6% of the total) suffered intrauterine death. Placental diagnoses and autopsy results for these two cases are shown in Table IV. No congenital malformations were identified at autopsy. Considering live births, the neonatal population was predominantly preterm: 55% (16/29) were born before the 34th week and a further 28% (8/29) between the 34th and 37th weeks, while only 17% (5/29) reached term. The overall gestational age of the fetuses and newborns analyzed was, in 74% of

Table I. Clinical data of cases (mother – fetus – newborn)

	Maternal Age	Parity	Placental weight (g)	Gestational age	Placental centile	Sex of the fetus or newborn	Weight g (Centile)	APGAR 1 min	APGAR 5 min	Neonatal outcome	Malformations
1	35	G1	573	33	10°-25°	Twin A: F	1740 (42°)	8	9		
						Twin B: F	1820 (52°)	8	9		
2	36	G4, P3	372	35+6	10°-25°	M	2670 (48°)	3	6	Neonatal death	Vertebral, cerebral, and cardiac malformations
3	39	G2, P1	342	35+1	<10°	F	2100 (23°)	8	9	Neonatal death	Tracheoesophageal fistula, pulmonary dysplasia, tetralogy of Fallot
4	33	G2	430	34+1	<10°	Twin A: M	1645 (6°)	8	9		
						Twin B: M	1465 (2°)	8	9		
5	29	G1	526	32	>90°	F	1610 (52°)	0	0	Intrauterine death	
6	23	G2, A1	305	31+6	25°-50°	F	1375 (22°)	3	7		Complex heart disease
7	39	G1	146	24+2	10°-25°	M	695 (72°)	6	7		Cerebral malformations
8	36	G2, P1	570	33+6	10°-25°	Twin A: M	1340 (1°)	7	9		
						Twin B: F	1760 (20°)	6	9		Patent foramen ovale, arterial vascular malformation (aortopulmonary collateral)
9	41	G2, P1	432	36+6	25°-50°	M	3300 (81°)	9	9		
10	39	G4, P2, IVG1	250	34+6	<10°	M	2780 (83°)	9	9		
11	36	G2, A1	420	38+5	10°-25°	M	3530 (68°)	8	8		
12	34	G3, A2	202	22+6	>90°	F	520 (47°)	6	8	Neonatal death	
13	42	G2	290	31+4	10°-25°	M	2080 (93°)	7	8		
14	28	G6, P3, IVG2	178	27+3	<10°	F	1020 (68°)	2	8		
15	39	G3, P1, IVG1	561	38+5	75°-90°	M	3070 (24°)	8	8		
16	22	G2, P1	323	36+1	<10°	M	2550 (33°)	9	9		
17	28	G1	272	35+6	<10°	M	2430 (33°)	8	8		
18	35	G2, P1	350	33	25°-50°	M	2185 (75°)	5	7		
19	38	G3, A2	336	31+5	<10°	Twin A: F	1200 (11°)	6	8		
						Twin B: F	1410 (28°)	8	9		Arterial vascular malformation (aortopulmonary collateral artery), hepatic lesion
20	29	G3, P1, A1	351	35+1	<10°	F	2190 (30°)	8	9		Cerebral malformations
21	32	G2, IVG1	736	37+4	>90°	F	3600 (97°)	9	10		Pulmonary valve stenosis/ atresia, tripartite right ventricle
22	37	G5, P2, A2	262	32	<10°	F	1652 (50°)	0	0	Intrauterine death	
23	36	G2, P1	382	39	<10°	F	3305 (65°)	6	8		Tetralogy of Fallot
24	41	G3, P2	187	23+1	50°-75°	F	506 (37°)	1	6	Neonatal death	
25	25	G1	466	32+4	>90°	F	2230 (94°)	9	9		
26	40	G3, A2	531	30	>90°	F	1335 (64°)	5	9		
27	23	G1	290	32+4	<10°	F	1610 (38°)	6	8		arterial vascular malformation (aortopulmonary collateral artery)

IVG = induced or spontaneous abortion

Table II. Distribution of affected villi

Affected villi	Number of placental discs	Percentage
No injury	2	6,5% (2/31)
Villi I order	0	0
Villi II order	1	3% (1/31)
Villi III order	2	6,5% (2/31)
Villi IV order	2	6,5% (2/31)
Villi II-III order	14	45% (14/31)
Villi II-III-IV order	6	19,5% (6/31)
Villi III-IV order	4	13% (4/31)

Table III. Associated placental lesions (rounded global percentages)

1) Infectious disease	
Chorioamnionitis	42% (13/31)
Funisitis	3% (1/31)
Amniochorionic vasculitis	6% (2/31)
Fetal inflammatory response (FIR)	3% (1/31)
2) Maternal vascular disease	
Retroplacental hemorrhages	13% (4/31)
Acute decidual vessel atherosclerosis	10% (3/31)
Ischemic cotyledonary infarcts	16% (5/31)
Severe hypoxic injury	55% (17/31)
3) Fetal vascular disease	
Stem-vessel sclerosis	39% (12/31)
Thrombotic vasculopathy	6% (2/31)
Ischemic villous necrosis	6% (2/31)
Intervillous hemorrhages	10% (3/31)
Subamniotic hemorrhages	3% (1/31)
4) Dysmaturative disease	
Immaturity	42% (13/31)
Metabolic and/or endocrine dysmaturity	35% (11/31)
Inadequate placental implantation	3% (1/31)

cases, between 30 and 36 weeks.

The analysis of fetal and neonatal sex did not reveal a clear predominance: 58% were female and 42% male. The mean Apgar score was 7 at the first minute and 8 at the fifth minute.

Four infants (14% of live births) died after birth. Two of these deaths occurred perinatally and involved severely premature female infants (23 and 23+1 weeks), both of whom died from complications of extreme prematurity. The other two deaths occurred within six months of life in infants with complex malformations.

Table IV. Two cases of intrauterine death

Placenta	Fetal sex	Gestational Age (weeks)	Placental histopathological diagnosis	Fetal autopsy diagnosis
5	F	32	- abnormal umbilical cord length - immature placenta - sclerosis of stem cell villi - ischemic villous necrosis	Death from acute cardiovascular failure due to tight constriction of an abnormally long cord around the neck
22	F	32	- underweight placenta - absolute short umbilical cord - retroplacental hematoma 20% of the surface - villous immaturity	Death from acute polyvisceral anemia due to massive subarachnoid hemorrahge and blood sequestration in the anterior, middle, and posterior cranial fossae

Table V. Associated congenital malformations.

Placenta	Malformations
2	VACTREL syndrome with: - imperforate anus - abnormalities in the formation and segmentation of the lumbar and sacral vertebrae - heart disease - severe Chiari II
3	Esophageal atresia with tracheoesophageal fistula and tetralogy of Fallot
6	Arterial and venous vascular malformation (right aortic arch with retroesophageal Kommerell's diverticulum and median descending aorta; persistent left vena cava not connected, draining into dilated coronary sinus)
7	Malformations of the cerebral cortex (asymmetry of the right occipital cortex and mild dysmorphism of the corpus callosum)
8B	Arterial vascular malformation (aortopulmonary collateral)
19B	Arterial vascular malformation (multiple aortopulmonary collateral arteries), 40x25mm hyperechoic lesion in the center of the liver with anechoic areas
20	Cerebral cortical malformation Left hemisphere, hypoplasia of the corpus callosum, hypoplasia of the vertebral arteries and basilar artery
21	Pulmonary valve atresia and tripartite right ventricle
23	Tetralogy of Fallot
27	Arterial vascular malformation (aortopulmonary colateral artery)

Out of 31 cases, 21 (68%) had no malformations, while the remaining 10 presented single or multiple anomalies, detailed in Table V. Specifically, 6 were cardiac malformations (19%), 3 cerebral malformations (9.6%), 3 vascular malformations (9.6%), 2 cases of pulmonary dysplasia, and one case each of vertebral, tracheoesophageal, and hepatic malformation. Overall, 32% of the products of conception (10/31) had congenital malformations.
In the two cases of intrauterine death, however, no fetal malformations were identified.

Discussion

The data emerging from our study confirm that NFMVSD represents a histologically well-defined placental lesion distinct from PMD and PVD. The observed incidence (1.34%) appears higher than that reported for PMD, estimated at around 0.02%[4]. This difference suggests that NFMVSD may be a more frequent condition than previously believed, likely underdiagnosed due to the absence of specific macroscopic findings and the need for accurate histological analysis. This finding has relevant medico-legal implications: failure to identify the lesion could, in fact, prevent the documentation of a potential pathogenic factor in cases of unexplained intrauterine death or unfavorable outcomes.
From a pathophysiological standpoint, the lesion is predominantly localized to the third-order villi and, to a lesser extent, to the second-order villi, resulting in the formation of multifocal stromal nodules. This fibromuscular proliferation may disrupt the architecture of the villous axis, thereby compromising fetoplacental perfusion and contributing to irregular or intermittent blood flow. The frequent association with severe hypoxic conditions (55%) and sclerosis of the stem vessels (39%) confirms the possible functional relevance of this alteration. In the cases examined, 63% of the placentas affected by NFMVSD had a weight below the 25th percentile; this finding, if evaluated in isolation, could suggest placental insufficiency.
In the forensic field, these elements take on particular importance.
Although NFMVSD is frequently associated with adverse outcomes, it should not be interpreted as a direct and independent cause of fetal or neonatal death. Rather, it may represent a contributing factor within a broader spectrum of placental pathology, particularly in the context of fetal vascular malperfusion (FVM)[30-32]. According to current placental pathology guidelines[33], FVM is broadly divided into two main categories: lesions involving the major vessels (umbilical cord and amniochorionic vessels) and those involving the intra-cotyledonary vascular compartment.
Within the intra-cotyledonary compartment, the predominant condition is fetal thrombotic vasculopathy. However, the mechanisms underlying intrinsic vascular wall damage remain incompletely understood, and even less is known about vascular compromise due to extrinsic factors, such as mechanical distortion associated with nodular fibromuscular villous stromal dysplasia.
The severity of vascular damage should be interpreted in relation to the extent of the lesions, using criteria analogous to those applied in the grading of FVM.
One possible mechanism involves mechanical distortion and compression of intravillous vessels caused by nodular stromal proliferation, potentially leading to altered fetoplacental perfusion. The clinical impact of this alteration likely depends on the extent of the lesion and the presence of associated placental abnormalities.
In our study, two intrauterine deaths (6%) and four postnatal deaths (14%) were observed, but it was not always possible to attribute an exclusive or predominant role to NFMVSD. However, the percentage of adverse events is still high compared to the total number of placentas examined, suggesting that this lesion represents an important risk marker.
In particular, in the two cases of intrauterine death, additional significant pathological findings were identified, including umbilical cord abnormalities and placental immaturity. In this context, NFMVSD should be interpreted as a possible contributing factor rather than the primary cause of death. Notably, these abnormalities alone would likely not have been sufficient to account for fetal demise in the setting of villous immaturity, in the absence of NFMVSD.
In determining the cause of death, the correlation between NFMVSD and fetal vascular anomalies can provide useful information to reconstruct the etiopathogenesis of the event and to distinguish cases due to intrinsic fetal pathologies from those related to placental insufficiency.
The identification of NFMVSD takes on even greater significance in medicolegal disputes, for example in cases of unexplained intrauterine death or hypoxic neurological damage to the newborn. A documented histological diagnosis allows for better delineation of responsibility and clarification of whether the event can be attributed to an underlying placental condition rather than inadequate obstetric care.
Despite the interest of these data, our case series-although being the largest described to date-is numerically limited and single-center. Neonatal follow-up was brief, preventing the assessment of any long-term consequences. Multicenter studies with larger sample

sizes and standardized protocols are needed to define more precisely the true impact of NFMVSD in the genesis of adverse fetal and neonatal events.
Considering our observations, we believe that in cases of intrauterine death or severe neonatal compromise, it is essential to actively search for NFMVSD during placental examination. Its diagnosis can not only help explain the event but can also be a key element in forensic evaluations, allowing for the correct attribution of causes and responsibilities.

Conclusions

NFMVSD is a complex placental lesion, diagnosable only histologically and with different characteristics from PMD and PVD. While not always a direct cause of fetal death, NFMVSD is frequently associated with chronic hypoxia, low placental weight, congenital malformations, and adverse perinatal outcomes.
In the forensic field, identifying this lesion is crucial. In cases of unexplained intrauterine death, severe neonatal compromise, or suspected hypoxic injury, histological diagnosis of NFMVSD can help clarify the dynamics of the event and identify any predisposing factors.
NFMVSD may represent a relevant contributing factor in the interpretation of adverse outcomes, particularly in forensic contexts, where it can support the reconstruction of the etiopathogenetic framework when integrated with other clinical and pathological findings.
It is recommended to include NFMVSD in histological examinations of placentas with IUGR, immaturity/dysmaturity, or fetal vascular abnormalities. Although our series is the largest reported to date, larger multicenter studies and longer neonatal follow-ups are needed to further clarify the prognostic and medicolegal implications of NFMVSD. Standardization of histological diagnostic criteria and integration with genetic and clinical investigations will be essential to fully understand the role of this lesion in fetal and neonatal pathology.

Conflicts of interest statement

The authors declare that they have no known competing financial or nonfinancial interests that could have appeared to influence the work reported in this paper.

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Ethical consideration

This retrospective study used anonymized archival placental samples collected for routine clinical and medicolegal purposes; ethics committee review was not required.

Statement of human and animal rights

Not applicable – no identifiable human subjects or animal experimentation were involved.

Data sharing

The datasets generated and/or analyzed during the current study are not publicly available due to privacy and ethical considerations but are available from the corresponding author on reasonable request.

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