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Distal villous lesions are clinically more relevant than proximal large muscular vessel lesions of placental fetal vascular malperfusion

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Summary. Background. Fetal vascular malperfusion (FVM) can be diagnosed on placental examination based on histology of distal placental villi and large muscular placental vessels. While histology of both those placental compartments can be low grade or high grade, it is not known if these are clinically equivalent. This retrospective study aimed to compare the impact of placental distal villous and large vessel FVM lesions on clinical and placental phenotypes.

Methods. Clinical and placental phenotypes of 479 consecutive ≥20 weeks of gestation at delivery cases of placental FVM were analyzed among 3 groups: Group 1: 86 cases with distal FVM (clusters of sclerotic distal villi and/or those with stromal vascular karyorrhexis and/or mineralization, and/or endothelial fragmentation by CD34 immunostain) without large vessel lesions; Group 2: 186 cases with large vessel lesions (fetal vascular ectasia, vascular thrombi, stem vessel obliteration, intramural fibrin deposition) without distal villous lesions; and Group 3: 207 cases showing both distal villous lesions and large fetal vessel lesions.

Results. Statistically significant differences (Bonferroni correction) were observed in: average gestational age at delivery 31, 35, 34 weeks, fetal growth restriction 24, 9, 25%, average placental weight 318, 413, 366 g, postuterine pattern of chronic hypoxic placental injury 12, 2, 6%, luminal vascular abnormalities in stem vessels 16, 3, 11%, and high grade FVM 33, 16, 39%, among Groups 1-3, respectively.

Conclusion. Because of longer time needed for its development, distal FVM portends poorer prognosis for the fetus than large vessel FVM.

Key words: Endothelial fragmentation, Fetal vascular malperfusion, Mineralization, Distal villi, Proximal vessels, Placenta

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Introduction

Placental examination is the most valuable tool in determining the cause of perinatal complications, particularly stillbirth, followed by autopsy and cytogenetic analysis (The Stillbirth Collaborative Research Network Writing Group, 2011; Korteweg et al., 2012; Ptacek et al., 2014). The macroscopic morphological features of the placenta cannot predict the presence or absence of histological placental lesions in an unselected population near term (Pathak et al., 2011). Fetal vascular malperfusion (FVM), caused by thrombotic obliteration of placental villous blood flow, is one of the major histological placental correlates of adverse perinatal outcome, particularly due to the umbilical cord compromise, but also hypercoagulability or complications of cardiac dysfunction such as hypoxia (Redline, 2004; Stanek, 2015, 2016; Battarbee et al., 2017). 5% of placentas from live births and 1% of all third trimester placentas show features of FVM (Ernst, 2015). The lesion is frequently not visible grossly and, when small, may be missed on histological examination. Overall, the recurrence risk of FVM is low (Redline and Ravishankar, 2018).

The Amsterdam conference standardized the placental nomenclature, including that of FVM, the term suggested to replace the old term "fetal thrombotic vasculopathy" (Khong et al., 2016). The two general categories of FVM are distal (segmental), complete, and global, incomplete (partial) (Redline and Ravishankar, 2018). Although pathogenetically possibly different, both categories feature overlapping histomorphology, including large placental vessel lesions and distal villous lesions, therefore being difficult to separate in clinical placental material.

More appealing and relevant is a dichotomy into low grade and high grade FVM, as only the latter correlates with both short term perinatal outcome, particularly the NICU stay and neonatal ischemic encephalopathy (Stanek, 2020) and perinatal mortality, morbidity and future child development (Redline and Ravishankar, 2018). It was also suggested that non-severe lesions of

FVM may not result in a significant difference from control in regard to morbidity and neurological injury (Ernst et al., 2016; Stanek, 2020). FVM, usually low-grade, is more common with advanced maternal age (Torous and Roberts, 2020). The diffuse vs. focal nature of FVM may help to distinguish between histological pattern secondary to fetal death and FVM occurring prior to fetal death (Heider, 2017).

The Amsterdam consensus conference has also defined the qualitative and quantitative histologic diagnostic and grading criteria of placental FVM. The intention was that the nomenclature would be used by pathologists to standardize and improve the value of placental pathology and perinatal autopsy reports. High grade FVM is based on number of involved terminal villi and/or occluding/nonoccluding thrombi in large muscular placental vessels. Histological evidence of vascular thrombi are not required for the diagnosis but is used for grading (Khong et al., 2016). The high grade FVM is defined as a placenta exhibiting at least one of the following histopathological scenarios: more than one focus of avascular villi (a cumulative involvement of >45 avascular villi over three sections examined or an average of >15 per section) with or without thrombus, or 2 or more occluding or nonoccluding thrombi in chorionic plate or major stem villi, or multiple nonoccluding thrombi (Khong et al., 2016). The relative importance of the quantitative estimate of involvement of proximal muscular vessels by intramural fibrin deposition, vascular ectasia and stem vessel obliteration in comparison with distal villous changes is not clear. The author's previous results indicate that the quantitative grade rather than the qualitative type of FVM correlates with short time perinatal outcome (Stanek, 2020).

This analysis has been undertaken to clarify if the impact of the two feature categories of FVM (the involvement of distal villi, i.e. terminal or intermediate, vs proximal vessels, i.e. chorionic or stem) on short term perinatal outcome and other placental pathology, as it has never been reported. Likewise, it has never been determined, if the high grade FVM diagnosed by small villous vessel involvement is equivalent to that of large vessel involvement. For the sake of completeness we will include also other large vessel FVM lesions (fetal vascular ectasia, stem vessel obliteration and intramural fibrin deposition) which are not included in the grading system, as well as small vessel FVM lesions which were described only after the Amsterdam conference (villous hypovascularity, endothelial fragmentation and segmental mineralization).

Materials and methods

This is a single institution review experience in which clinical data were retrieved from the hospital computer database. The placentas were received for examination at a discretion of obstetricians in years 2016-2021 because of high-risk/complicated pregnancy or were a part of autopsy material. The year 2016 was adopted as a starting point because at that time E cadherin/CD34 immunostain was implemented as a diagnostic test of incipient FVM. All gross abnormalities were sampled and, in addition, at least 2 sections of membrane rolls and the umbilical cord and 2 paracentral sections of grossly unremarkable placenta were taken. Formalin-fixed and paraffin-embedded sections were stained with H&E (hematoxylin-eosin) and all were reviewed by the author. 479 consecutive cases fulfilling the minimum quantitative criteria of placental FVM were reviewed. They were analyzed together with distal villous FVM by the traditional criteria with sclerotic chorionic villi and/or stromal vascular karyorrhexis, using same quantitative criteria as described by the Amsterdam conference (Khong et al., 2016), i.e. at least 3 or more foci of 2 to 4 terminal villi involved (stromal vascular karyorrhexis, total avascularity, hypovascularity, endothelial fragmentation, mineralization) (Boyd et al., 2019; Stanek and Abdaljaleel, 2019; Stanek, 2019a, 2020), as opposed to diffuse involvement by these lesions characteristic of retained stillbirth. Iron and/or von Kossa stains were used particularly in retained stillbirths with placental regressive changes to disclose potential segmental villous mineralization. Distal villous changes (avascular or hypo vascular) villi of chronic villitis were not considered for the purpose of diagnosis or grading FVM. Apart from the gestational age <20 weeks at delivery, there were no other exclusion criteria, particularly stillbirth and fetal anomalies were not excluded.

Three groups of cases were compared: Group 1: 86 cases with distal FVM (at least 3 or more foci of 2 to 4 terminal villi with sclerotic/hypo vascular/mineralized distal villi or villi with stromal vascular karyorrhexis seen on H&E and/or clusters of hypo vascular distal villi or mineralized villi or villi with endothelial fragmentation on CD34 immunostain and/or iron or von Kossa stain) without large vessel lesions (Fig. 1); Group 2: 186 cases with large vessel lesions (fetal vascular ectasia, occluding/non-occluding thrombi, intramural fibrin deposition, stem vessel obliteration) without distal villous lesions (Fig. 2); and Group 3: 207 cases showing both distal villous lesions and large fetal vessel lesions, i.e. combined features of FVM seen in both Group 1 and Group 2.

Although we performed CD34 immunostain in all cases analyzed here, the indications for performing the CD34 immunostain have been otherwise: (1) high risk conditions for FVM, such as clinical evidence of cord compromise, EXIT (ex-utero intrapartum treatment procedure), unexplained stillbirth, and mass forming fetal anomalies when H&E sections are negative for segmental FVM or there was a large vessel component without distal villous changes, or (2) low grade villous changes (a potential for upgrading). We perform the CD34 immunostain on the least abnormal H&E slide of grossly normal placenta to potentially discover the

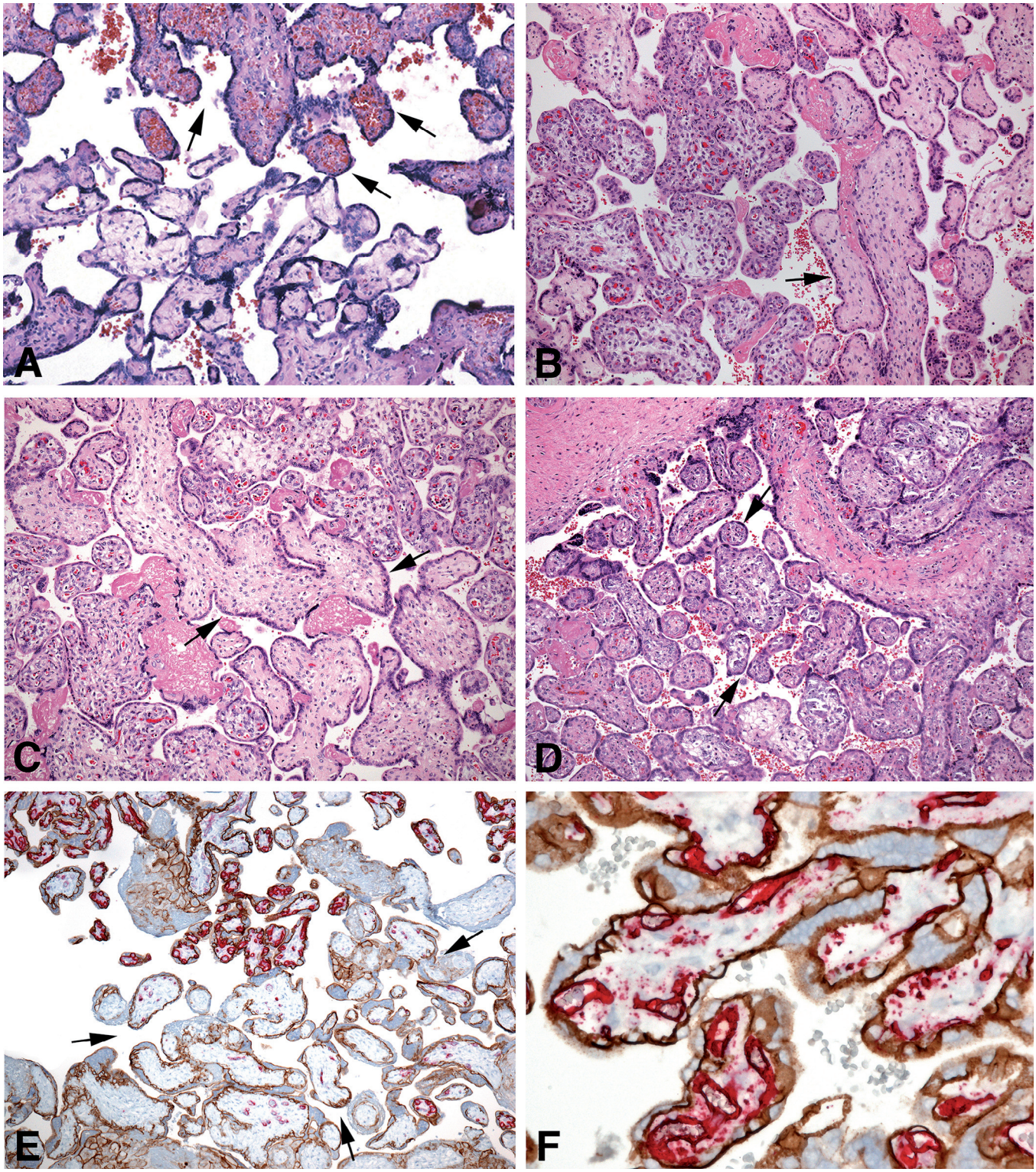

Fig. 1. Distal villous (terminal, intermediate) change, stains and objective magnifications in parentheses. **A.** Stromal vascular karyorrhexis, hematoxilin-eosin (H&E). **B.** Cluster of avascular chorionic villi (H&E). **C.** Cluster of hypovascular chorionic villi (H&E). **D.** Segmental distal dusty villous mineralization (H&E). **E.** Cluster of hypovascular chorionic villi not seen on H&E (E cadherin-CD34, brown-red). **F.** Cluster of distal villi with endothelial fragmentation (E cadherin/CD 34, brown-red). A-E, x 10; F, x 40.

earliest changes not yet diagnosable on H&E staining. We do not perform the stains on all placentas or on all blocks of a given placenta, particularly when there is no increased risk or clinicopathologic suspicion of FVM (Stanek and Abdaljaleel, 2019).

Grade of FVM was not considered for sub classification of this material as it was reported earlier (Stanek, 2020), but was evaluated as a dependent variable according to the Amsterdam criteria (Khong et al., 2016); therefore, in Group 1 the grade was determined based solely on the extent of distal villous changes, while in Group2, solely on the presence of occluding or non-occluding thrombi in large fetal vessels. In Group 3, both patterns were used for grading.

Frequencies of 26 clinical and 38 independent placental phenotypes were statistically compared among the groups by Chi-square or analysis of variance applying the Bonferroni correction.

Results

The material consisted of highly pathological pregnancies (Table 1). Statistically significant differences (p Bonferroni≤0.002) were noted among Groups 1-3 phenotypes, respectively: average gestational age at delivery (weeks) 31±7, 35±5, 34±6, and fetal growth restriction (FGR) 24%, 9%, 25% (Table 1), and average placental weight (grams) 318±167, 413±196, 366±174, postuterine pattern of chronic hypoxic placental injury 12%, 2%, 6%, luminal vascular abnormalities in stem vessels 16%, 3%, 11%, and high grade FVM 33%, 16%, 39% (Table 2). Placentas with only proximal vascular changes came thus statistically significantly from more advanced pregnancies and showed the least common frequency of FGR. Notably, there were no statistically significant differences in perinatal mortality, clinical cord compromise, congenital

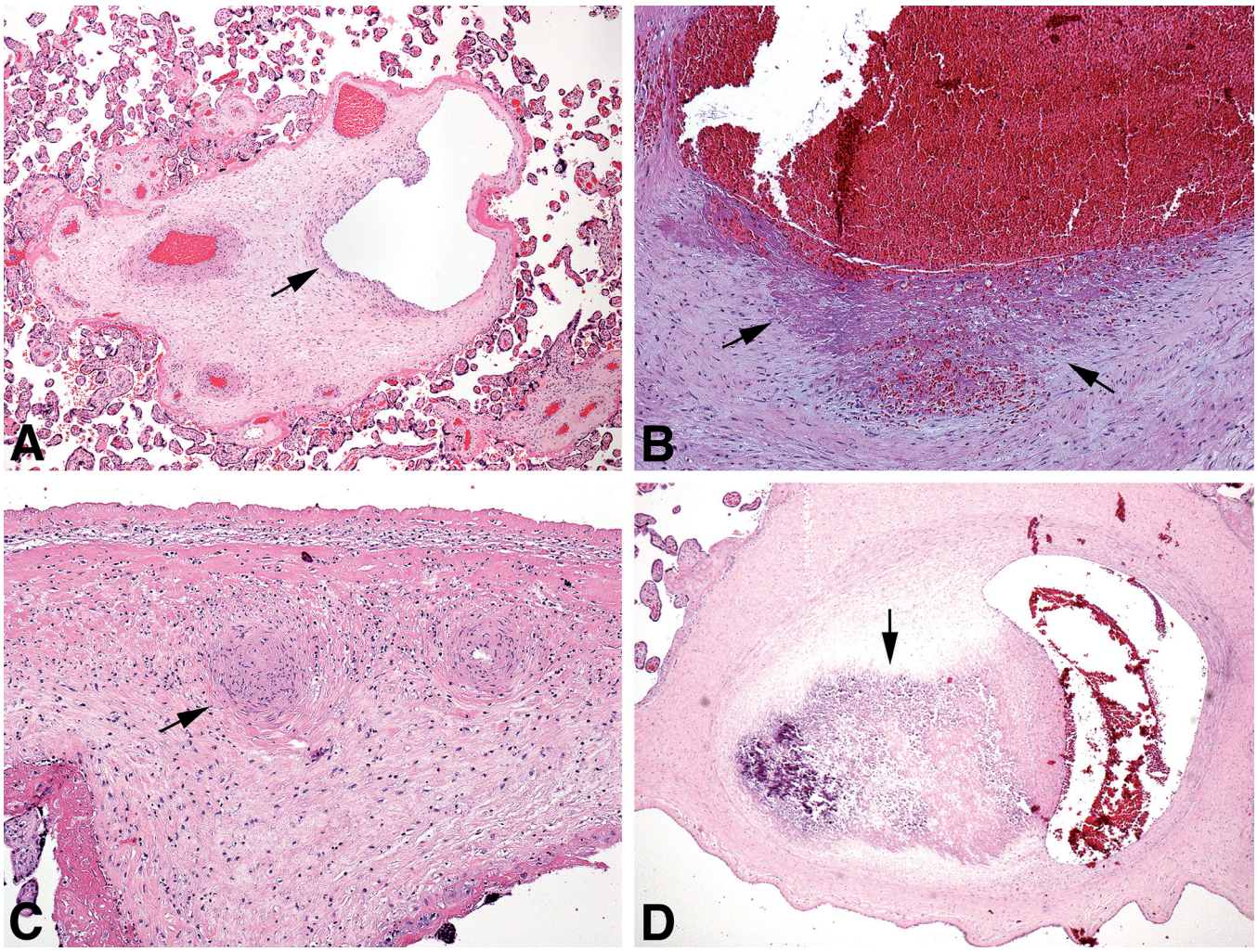

Fig. 2. Proximal vessel involvement, H&E. **A.** Stem fetal vascular ectasia. **B.** Intramural fibrin deposition (recent). **C.** Chorionic vessel obliteration (H&E). **D.** Calcified mural non-occluding stem thrombus. A, D, x 4; B, C, x 10.

malformations, anatomical cord abnormalities or abnormal cord attachment, other acute and chronic placental hypoxic lesions, and lesions of shallow placental implantation among Groups 1-3 (Tables 1, 2).

Discussion

The diagnosis of FVM is most frequently retrospective and histological as it is usually grossly unapparent. To the author's knowledge, this is the first analysis comparing the clinical and placental phenotypes associated with small vessel and large vessel FVM. This terminology was adopted by the author, because histological diagnosis of segmental and global FVM according to the Amsterdam criteria would be difficult to reproduce as both may feature fetal small vessel and large vessel lesions, although with different distribution, therefore more impacted by sampling. The time-honored lesions of FVM (focal postuterine hypoxic pattern) (Stanek, 2013), are clusters of avascular chorionic villi. This analysis incorporated new distal vessel FVM lesions that were reported only after the Amsterdam conference (segmental villous hypovascularity, endothelial fragmentation and mineralization) (Stanek, 2019a). The use of CD34 immunohistochemistry and iron/phosphate histochemistry increases the sensitivity of placental examination for distal villous FVM (more cases diagnosed) (Stanek, 2018, 2019a; Stanek and Abdaljaleel, 2019). For the purpose of this analysis, the Amsterdam, criteria were thus qualitatively expanded, with preservation of the quantitative thresholds.

Because of the adopted grouping criteria, only the numerical criteria based on number of distal villi involved were used for grading in Group 1 and only the number of large vessels with thrombi in Group 2. Both criteria were used for Group 3. Similar to the Amsterdam criteria, the extent of stem vascular ectasia, stem vessel obliteration and intramural fibrin deposition has not been used for grading. The above lesions are usually global in distribution, usually found in the central part of the placenta that may lead to capillary level villous changes (Boyd et al., 2019). The lesions should not be confused with the changes secondary to fetal death (luminal vascular abnormalities of chorionic villi) (Genest, 1992), which were initially characterized as erythrocytes and erythrocyte fragments trapped by strands of fibrous tissue (Fox and Sebire, 2007). Stem luminal vascular abnormalities were statistically

Table 1. Clinical phenotypes.

	Group 1 Only distal villous FVM	Group 2 Only large vessel FVM	Group 3 Mixed (distal FVM and large vessel)	F or Yates chi square	p≤0.05, 2 df
Number of cases	86	186	207		
Maternal and fetal phenotypes					
Gestational hypertension	7 (8.1%)	13 (7.0%)	13 (6.3%)		
Preeclampsia	11 (12.8%)	14 (7.5%)	20 (9.7%)		
Chronic hypertension	6 (7.0%)	10 (5.4%)	7 (3.4%)		
Gestational age (*weeks, average ± standard deviation*)	31.3±7.0	34.8±4.9	33.7±5.8	10.891	2.37E-05
Poor or absent prenatal care	0	4 (2.1%)	6 (2.9%)		
Substance abuse	7 (8.1%)	17 (9.1%)	24 (11.6%)		
Maternal diabetes mellitus	12 (13.9%)	14 (7.5%)	22 (10.6%)		
Oligohydramnios	11 (12.8%)	14 (7.5%)	21 (10.1%)		
Polyhydramnios	5 (5.8%)	16 (8.6%)	18 (8.7%)		
Premature rupture of membranes	11 (12.8%)	22 (11.8%)	19 (9.2%)		
Antepartum hemorrhage	2 (2.3%)	10 (5.4%)	10 (4.8%)		
Meconium-stained amniotic fluid	9 (10.5%)	22 (11.8%)	21 (10.1%)		
Abnormal fetal heart rate tracing[a]	7 (8.1%)	32 (17.2%)	40 (19.3%)		
Abnormal umbilical artery Dopplers	9 (10.5%)	7 (3.8%)	15 (7.2%)		
Induction of labor	12 (13.9%)	30 (16.1%)	47 (22.7%)		
Cesarean section	43 (50.0%)	104 (55.9%)	119 (57.4%)		
EXIT procedure	6 (7.0%)	21 (11.3%)	21 (10.1%)		
Multiple pregnancy	5 (5.8%)	8 (4.3%)	12 (5.8%)		
Abnormal 3rd stage of labor (prolonged, hemorrhage)	8 (9.3%)	11 (5.9%)	17 (8.2%)		
Neonatal phenotypes					
Neonatal death	10 (11.6%)	26 (14.0%)	24 (11.6%)		
Nonmacerated stillbirth	3 (3.5%)	5 (2.7%)	13 (6.3%)		
Macerated stillbirth	21 (24.4%)	33 (17.7%)	32 (15.5%)		
Fetal growth restriction[b]	24 (24.4%)	16 (8.6%)	52 (25.1%)	22.34	0.000014
Umbilical cord compromise[c]	9 (10.5%)	17 (9.1%)	29 (14.0%)		
Congenital malformations	39 (45.3%)	117 (62.9%)	106 (51.2%)	9.10	0.0105

FVM fetal vascular malperfusion, [a]: abnormal non stress test and/or abnormal contraction stress test and/or abnormal intrapartum cardiotocography (prolonged bradycardia and/or prolonged tachycardia and or decrease of fetal heart rate variability and /or late decelerations), [b]: birth weight <10 centile, [c]: variable decelerations, encirclement, true knot, or prolapse. *Italics*, statistically significant after Bonferroni correction.

Table 2. Placental variables.

	Group 1 Only distal vessel FVM	Group 2 Only large vessel FVM	Group 3 Mixed (distal FVM vessel and large vessel)	F	P<0.05 (2 df)
Number of cases	86	186	207		
Placental weight (*grams, average ± standard deviation*)	318.4±167.3	413.3±195.7	365.7±173.9	8.41	0.000257
Inflammatory pattern					
Acute chorioamnionitis	25 (29.1%)	42 (22.6%)	52 (25.1%)		
Chronic villitis of unknown etiology	16 (18.6%)	22 (11.8%)	32 (15.5%)		
Plasma cell deciduitis	5 (5.8%)	12 (6.4%)	16 (7.7%)		
Acute hypoxic pattern					
Meconium (histological)	33 (38.4%)	83 (44.6%)	83 (40.1%)		
Deep (decidual)	5 (5.8%)	8 (4.3%)	12 (5.8%)		
Shallow (amnionic or chorionic)	28 (32.6%)	75 (40.3%)	71 (34.3%)		
Intravillous hemorrhage	3 (3.5%)	5 (2.7%)	8 (3.9%)		
Villous infarction (>5% of placental parenchyma)	16 (18.6%)	12 (6.4%)	33 (15.9%)	11.19	0.0037
Laminar necrosis of membranes[a]	28 (32.6%)	49 (26.3%)	75 (36.2%)		
Chronic hypoxic pattern					
Erythroblastosis of fetal blood	14 (16.2%)	33 (17.7%)	50 (24.1%)		
Hypertrophic decidual arteriopathy	30 (34.9%)	40 (21.5%)	51 (24.6%)		
Hyaline necrosis, including atherosis, of spiral arterioles	5 (5.8%)	10 (5.4%)	22 (10.6%)		
Diffuse patterns of chronic hypoxic injury[b]	22 (25.6%)	32 (17.2%)	44 (21.3)		
Preuterine	2 (2.3%)	8 (4.3%)	7 (3.4%)		
Uterine	10 (11.6%)	21 (11. 3%)	25 (12.1)		
Postuterine	10 (11.6%)	3 (1.6%)	12 (5.8%)	12.17	0.0023
Retroplacental hematoma	4 (4.6%)	8 (4.3%)	7 (3.4%)		
Intervillous thrombus	25 (29.1%)	60 (32.3%)	78 (37.7%)		
Shallow placentation					
Membrane chorionic microcysts[c]	11 (12.8%)	32 (17.2%)	24 (11.6%)		
Chorionic disc extravillous trophoblast microcysts[d]	5 (5.8%)	33 (17.7%)	25 (12.1%)		
Maternal floor multinucleate trophoblastic giant cells	21 (24.4%)	39 (30.0%)	44 (21.3%)		
Excessive extravillous trophoblasts in chorionic disc	20 (23.3%)	37 (19.9%)	52 (25.1%)		
Clinically occult placenta creta (including basal plate myometrial fibers)	14 (16.3%)	32 (17.2%)	29 (14.0%)		
Fetal vascular malperfusion					
Sclerotic/hypovascular chorionic villi (on H&E)	63 (73.2%)		141 (68.1%)	N/A	
Stromal vascular karyorrhexis (on H&E)	5 (5.8%)		26 (12.6%)	N/A	
Endothelial fragmentation only or upgrading from low grade H&E	37 (43.0%)		84 (40.6%)	N/A	
Clustered mineralization (H&E or histochemistry)	7 (8.1%)		35 (16.9%)	N/A	
Fetal vascular thrombi	0		104 (50.2%)	N/A	
Stem vessel obliteration	0		82 (39.6%)	N/A	
Intramural fibrin deposition	0		40 (19.3%)	N/A	
Fetal vascular ectasia	0		146 (70.5%)	N/A	
Luminal abnormalities of stem vessels	14 (16.3%)	6 (3.2%)	23 (11.1%)	14.29	0.000787
Diffusely increased extracellular matrix of chorionic villi	18 (20.9%)	21 (11.3%)	31 (15.0%)		
High grade fetal vascular malperfusion	28 (32.6%)	30 (16.1%)	81 (39.1%)	25.8	0.0000025
Other					
Massive perivillous fibrin deposition (>30% of placental parenchyma)	1 (1.2%)	5 (2.7%)	9 (4.3%)		
Chorangiosis	11 (12.8%)	29 (15.6%)	22 (10.6%)		
Chorangioma	3 (3.5%)	2 (1.1%)	6 (2.9%)		
Choriodecidual hemosiderosis	6 (7.0%)	3 (1.6%)	6 (2.9%)		
Villous edema	11 (12.8%)	13 (7.0%)	15 (7.2%)		
Two-vessel umbilical cord	8 (9.3%)	13 (7.0%)	20 (9.7%)		
Hypercoiled umbilical cord	22 (25.6%)	59 (31.7%)	60 (30.0%)		
Hypocoiled umbilical cord	9 (10.5%)	11 (5.9%)	24 (11.6%)		
Stem perivascular edema	2 (2.3%)	14 (7.5%)	23 (11.1%)		
Marginal insertion of umbilical cord	6 (7.0%)	7 (3.8%)	7 (3.4%)		
Velamentous insertion of umbilical cord	3 (3.5%)	9 (4.8%)	5 (2.4%)		
Other umbilical cord abnormalities[e]	16 (18.6%)	33 (17.7%)	39 (18.9%)		
Amnion nodosum/chorion nodosum	7 (8.1%)	10 (5.4%)	14 (6.8%)		
Marginate or vallate placenta	3 (3.5%)	21 (11.3%)	27 (13.0%)		
Gross chorionic cyst(s)	2 (2.3%)	2 (1.1%)	2 (1.0%)		
Succenturiate lobe	2 (2.3%)	6 (3.2%)	4 (1.9%)		

[a]: at least 10% of membrane rolls, [b]: developmental patterns (Stanek, 2013), [c]: at least 3 pseudocysts per membrane roll, [d]: at least 3 pseudocysts per a section of grossly unremarkable chorionic disc, [e]: too long, too short, too thin, stricture, aneurysm, varix, hematoma, vessel unprotected by Wharton jelly, chorda, ulcer, barber pole funisitis, amniotic band, meconium toxicity, furcate insertion, edema. *Italics*, differences that remained statistically significant after Bonferroni correction for multiple comparisons.

significantly more frequent in this material in distal vessels involvement, likely due to more cases of prolonged stillbirth (Table 2).

We proved that the distal villous FVM changes were more frequently associated with earlier gestations, fetal growth restriction, chronic hypoxic placental injury, and high grade FVM than large vessel FVM (Tables 1, 2), but not significantly associated with other phenotypes. Interestingly, the lesions of shallow placental implantation (Stanek, 2021a) showed no statistically significant differences among the groups. As expected, polyhydramnios was not statistically significantly different among the groups studied. FVM in mass-forming congenital fetal anomalies with or without fatal genetic abnormalities (Stanek, 2019b) and umbilical cord compromise (Stanek, 2016) were discussed previously. The observed associations may be explained by the longer time needed for the distal FVM to develop than for the proximal FVM. The chronic placental hypoxic pattern and FGR are also chronic placental and clinical phenotypes, respectively, needing longer time to develop. Cases of group 1 were born earlier, so the fetuses and placentas weighed less and the outcomes could have been worse by virtue of gestational age alone.

According to the literature, the most common etiology of FVM is umbilical cord obstruction leading to stasis, ischemia and in some cases thrombosis (Heider, 2017). Cord entanglement and pathological cord abnormalities are significantly more common in fetuses with FVM who go on to develop cerebral palsy and those placentas were reported to show chorangiosis and nucleated red blood cells (Redline, 2004; Chan and Baergen, 2012). In our previous report on placentas from high-risk pregnancy, umbilical cord abnormalities grouped with dilatation of umbilical, chorionic, and stem veins, but not with clusters of avascular villi or stromal vascular karyorrhexis which clustered separately together (Stanek and Biesiada, 2012). What is striking by the current analysis, is that frequencies of neither clinical nor pathological umbilical cord compromise/abnormalities are statistically significantly different among the groups. The longer time of umbilical cord compromise was most probably operative in Group 1, overlapping the chronic hypoxic placental injury and showing the temporal heterogeneity of distal villous lesions (Stanek, 2021b) not seen in Group 2.

Apart from the umbilical cord compromise, other contributing factors to FVM include maternal gestational hypertensive conditions, diabetes mellitus, fetal cardiac insufficiency or blood hyper viscosity, and inherited or acquired thrombophilias, particularly Factor V Leiden mutation and prothrombin mutation (Vern et al., 2000; Lepais at al., 2014; Simcox et al., 2015; Freedman et al., 2017; Boyd et al., 2019). Placental hypoxic lesions in general, and maternal vascular malperfusion in particular, predispose to thrombotic lesions (hypoxic/thrombotic overlap lesions) (Stanek, 2015). Although retained stillbirth-associated placental histological changes can obscure the pre-existing histological features of FVM, the CD34 immunostain-revealed segmental endothelial fragmentation and clustered villous mineralization (H&E or histochemistry) may actually unmask the time sequence of the thrombotic process.

We have previously found that high grade FVM is associated with increased likelihood of admission to NICU and neurological complications, no matter if diagnosed only by H&E stain, or by immunohisto-chemistry and/or histochemistry. We therefore confirmed that the grade of FVM is the most important short-term prognostic factor (Stanek, 2020) and also that the severe or high grade FVM is also an important long-term risk factor for adverse outcomes including fetal growth restriction, central nervous system injury, and stillbirth (Redline and Ravishankar, 2018). The analysis showed therefore that the impact of distal and proximal vascular lesions of FVM is not equivalent: distal lesions are more likely to be associated with high grade FVM than the isolated large vessel lesions of FVM, particularly chronic hypoxia,

The apparent limitations of the study is not excluding stillbirths (particularly macerated) and congenital malformations, but this could be regarded as an advantage of this all-inclusive analysis which now applies to all placental cases. Also, while type 1 error (the mistaken rejection of an actually true null hypothesis (also known as a "false positive" finding or conclusion) was probably avoided by using the Bonferroni correction, the type 2 error (the mistaken acceptance of an actually false null hypothesis (also known as a "false negative" finding or conclusion) was still a possibility.

In summary, the results of this analysis could supplement the Amsterdam Placental Workshop Group report. We agree that once distal FVM is recognized, the significance of associated global FVM is diagnostically and prognostically not that crucial (Redline and Ravishankar, 2018). The large proximal fetal vascular component of FVM alone is of shorter duration and may not portend a significant fetal/neonatal morbidity. These observations still need to be further investigated and validated, however.

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