Virchows Archiv (2021) 478:905–914
https://doi.org/10.1007/s00428-020-02916-3

ORIGINAL ARTICLE

Temporal heterogeneity of placental segmental fetal vascular malperfusion: timing but not etiopathogenesis

Jerzy Stanek[1]

Received: 18 February 2020 / Revised: 13 July 2020 / Accepted: 19 August 2020 / Published online: 12 September 2020

Abstract

Clinicopathologic correlations of segmental villous avascularity and other histological lesions of segmental fetal vascular malperfusion (SFVM) were analyzed retrospectively to determine whether lesions of various durations reflect different etiopathogeneses. The frequencies of 25 independent clinical and 43 placental phenotypes were statistically compared by ANOVA or Chi-square among 3 groups containing a total of 378 placentas with SFVM: group 1 contained 44 cases of recent SFVM (endothelial fragmentation, villous hypovascularity by CD34 immunostain, and/or stromal vascular karyorrhexis); group 2 contained 264 cases of established SFVM (clusters of avascular villi); and group 3 contained 70 cases of remote SFVM (villous mineralization). Statistically significant differences among the three study groups (p Bonferroni < 0.002) were found in four clinical variables (gestational age, frequencies of macerated stillbirth, induction of labor, and cesarean section) and in five placental variables (frequencies of fetal vascular ectasia, stem vessel luminal vascular abnormalities, diffusely increased extracellular matrix in chorionic villi, chorionic disk extravillous trophoblast microcysts, and excessive extravillous trophoblasts in the chorionic disc). In summary, the absence of statistically significant differences between the study groups regarding the most common causes of SFVM (hypertensive conditions of pregnancy, diabetes mellitus, fetal anomalies, and clinical and pathological features of umbilical cord compromise) is evidence that the three types of SFVM reflect temporal heterogeneity rather than etiopathogenesis. This evidence can be used to date the onset of fetal vascular malperfusion before delivery or stillbirth. The coexistence of different SVFM lesions of various durations indicates ongoing or repeat occurrences of FVM rather than single episodes.

Keywords Endothelial fragmentation · Fetal vascular malperfusion · Mineralization · Placenta · Stillbirth · Temporal heterogeneity · Umbilical cord

Introduction

Fetal vascular malperfusion (FVM) is a well-known subtype of a postuterine pattern of chronic hypoxic placental injury [1] that can be associated with complicated perinatal outcome and remote neonatal and developmental sequelae [2–6]. FVM can be segmental (SFVM) or global [7]. SVFM (previously known as fetal thrombotic vasculopathy) is best documented by studying the avascular terminal villi from placentas of children born alive [8] (Fig. 1). Global FVM is best documented by studying the histology of fetal vessels and villous sclerosis of placentas from retained stillbirth [9, 10, 11] (Fig. 2). However, scattered small clusters of sclerotic villi may be caused by partially obstructed umbilical blood flow and may also be observed in global FVM [7].

The earliest SFVM lesions feature segmental villous endothelial fragmentation, stromal vascular karyorrhexis, or hypovascularity (identified by CD34 immunostain) (Fig. 1a–1c) [12, 13]. The established lesions feature clusters of avascular villi (Fig. 1d) [7], and the more advanced

Presented at the Fall Meeting of the Society for Pediatric Pathology in Pittsburgh, PA, October 17-19, 2019

This article is part of the Topical Collection on *Quality in Pathology*

Electronic supplementary material The online version of this article (https://doi.org/10.1007/s00428-020-02916-3) contains supplementary material, which is available to authorized users.

✉ Jerzy Stanek
jerzy.stanek@cchmc.org

[1] Division of Pathology, Cincinnati Children's Hospital Medical Center, 3333 Burnet Avenue, Cincinnati, OH 45255, USA

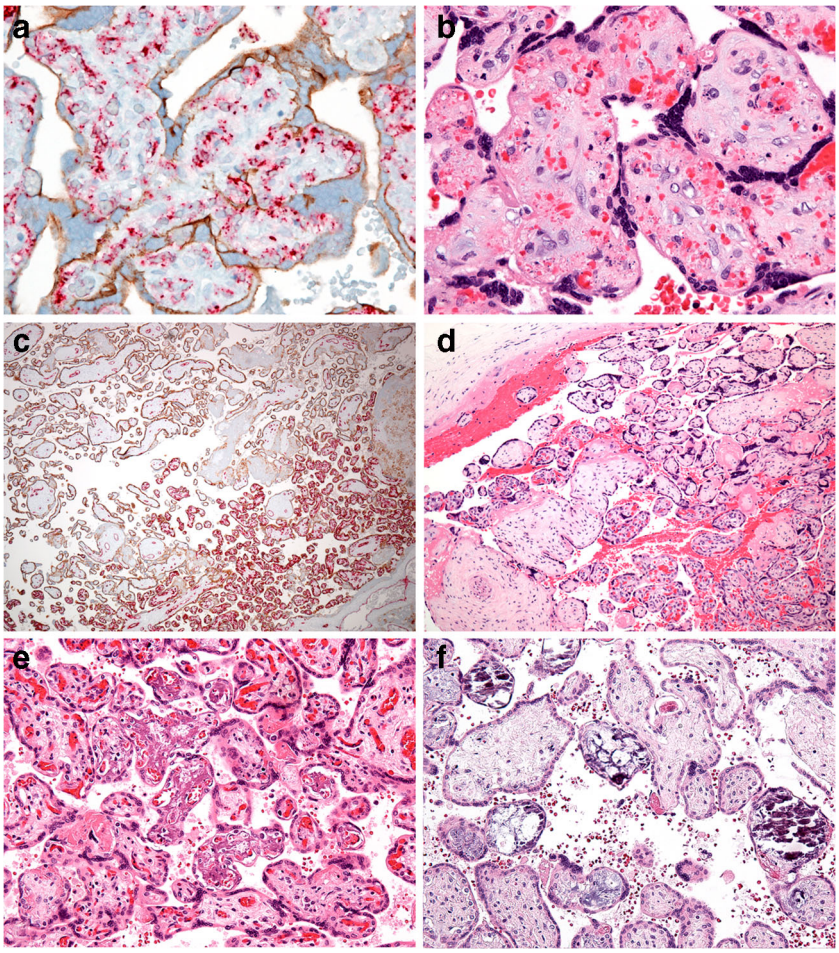

Fig. 1 Lesions of SFVM, objective magnifications given. **a** Endothelial fragmentation, E cadherin (brown)/CD34 (red) immunostain, × 40, 39 weeks, umbilical cord compromise, fetal growth restriction, bladder outlet obstruction, prune belly syndrome. **b** Stromal vascular karyorrhexis, H&E, × 40, same case as A. **c** Villous hypovascularity, E cadherin/CD34, × 4, 36 weeks, amniotic sac infection syndrome, nonmacerated stillbirth. **d** Avascular villi, H&E, × 10, 36 weeks, fetal growth restriction, multicystic kidneys. **e** Villous vascularity and stromal speckled mineralization, H&E, × 20, 36 weeks, nonmacerated stillbirth. **f** Diffuse villous avascularity and segmental stromal mineralization, H&E, × 20, 27 weeks, grade 3 macerated stillbirth [9]

lesions feature segmental villous mineralization (Fig. 1e, f) [13, 14–16]. The significance has not yet been determined for SFVM lesions other than clusters of totally sclerotic chorionic villi (segmental villous endothelial fragmentation, stromal vascular karyorrhexis, hypovascularity, and mineralization). All types of SFVM are potentially low or high grade [2, 7, 8].

This retrospective analysis compares clinicopathologic correlations of segmental villous avascularity and other histological types of SFVM to determine whether SFVM of various durations reflects different etiopathogeneses or temporal heterogeneity independent of etiology.

Materials and methods

Obstetricians submitted placentas for examination because of high-risk pregnancy or its complications, gross abnormality, or involvement in an autopsy. Histology examination was performed on at least two sections of the membrane roll and the umbilical cord and two paracentral sections of grossly unremarkable placentas. All gross focal abnormalities were also sampled. After sectioning, formalin fixation, and paraffin embedding, slides were stained with H&E and reviewed by the author. At least one most unremarkable slide on the H&E block was stained by E-cadherin/CD34 immunostain to highlight segmental villous hypovascularity or chorionic villi with segmental endothelial fragmentation. Selected slides were stained by iron and/or von Kossa immunostain to disclose a possible segmental mineralization of chorionic villi and its pattern [15]. This study used nomenclature recommended by the 2016 Amsterdam consensus conference [7] or nomenclature used in the author's previous publications (Table 1) [1, 17,18–20].

In this study, 378 consecutive placentas with SFVM and gestational ages > 19 weeks were divided into 3 groups and statistically compared:

Group 1 contained 44 cases of recent SFVM (30 cases of segmental endothelial fragmentation and/or hypovascular chorionic villi identified by CD34 immunostain, and 14 cases of stromal vascular karyorrhexis). For the purpose of this study, segmental hypovascular villi are clusters of chorionic villi that contrast sharply with adjacent normovascular villi with regard to the number of villous

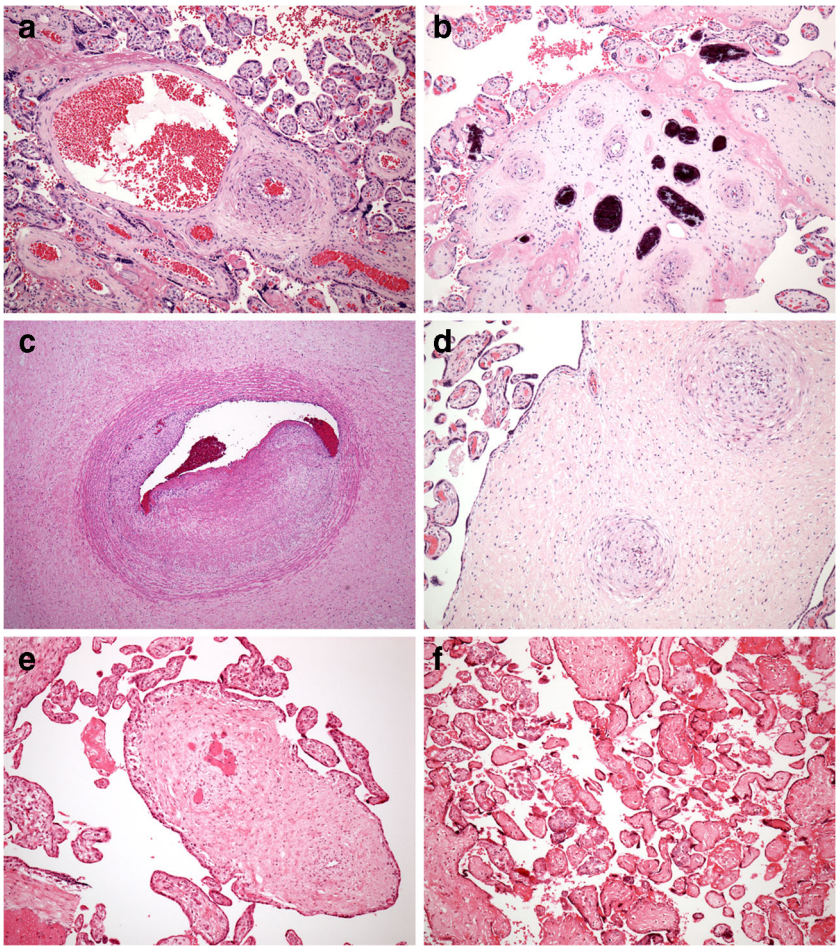

Fig. 2 Other FVM lesions, H&E, objective magnifications given. **a** Stem vascular ectasia, × 10, 37 weeks, ECMO for sacrococcygeal teratoma, pregnancy-induced hypertension, fetal hydrops, a chorangioma. **b** Occluding calcified venous stem thrombi, the focal calcification at the periphery of the right upper corner villus is in the perivillous fibrin, the arteries are not thrombosed, × 10, 35 weeks, polyhydramnios, ECMO for congenital diaphragmatic hernia. **c** Umbilical vein intramural fibrin deposition, × 4, 33 weeks, nonmacerated fetal death. **d** Stem vessel obliteration, × 10, 39 weeks, maternal diabetes mellitus, nonmacerated fetal death. **e** Stem luminal vascular abnormalities, × 10, 25 weeks, fetal death 2 days before delivery. **f** Total villous fibrosis, × 10, 26 weeks, retained stillbirth

capillaries. The normal vascularity of terminal villi is 2 to 5 capillaries [21]. This contrast is best seen on the CD34 immunostain, but it can occasionally be appreciated on the H&E stain [13]. Although the CD34 immunohistochemistry highlights mature villous endothelial cells, it can also stain progenitor cells [22]. However, progenitor cells have no segmental distribution, are described mostly in animals, and occur mostly during the first trimester of pregnancy. Therefore, from a practical point of view, CD34 immunostain can be used for highlighting vascular endothelium to distinguish segmental (lobular) hypovascularity (Fig. 1c) or segmental endothelial fragmentation (Fig. 1a). Occasionally, totally sclerotic chorionic villi on H&E stain turn out to be hypovascular on CD34 immunostain. That is, squeezed villous capillaries may not be appreciated on H&E stain (Fig. 1e); but they are seen on CD34 immunostain, as it is reasonable to assume that the segmental villous hypovascularity is the stage preceding total segmental villous avascularity [17].

Group 2 contained 264 cases of established SFVM (clusters of completely avascular villi chorionic villi on H&E stain).

Group 3 contained 70 cases of remote SFVM with segmental villous mineralization (Fig. 1e, f). Segmental villous mineralization includes segmental linear mineralization of basement membranes (Fig. 3e, f) [23], segmental speckled villous core mineralization (Fig. 1e) [24], and segmental perivascular mineralization (Fig. 1f). Qualitatively, all types of mineralization may be associated with etiologies other than FVM (stillbirth, villous edema, and aneuploidies) [25]; but such cases would not be segmental but diffuse [9, 14]. Because those etiologies may be complicated by FVM, we used iron or von Kossa stains to highlight the segmental nature of mineralization, as reported previously [12].

More recent FVM lesions were permitted in groups 2 and 3. Therefore, group 1 contained no clusters of avascular terminal villi or clusters of mineralized chorionic villi, and group 2 contained no clusters of mineralized chorionic villi.

The quantitative criteria for SFVM in all groups were consistent with the Amsterdam criteria, which require "3 or more foci of 2-4 terminal villi showing total loss of villous capillaries and bland hyaline fibrosis of the villous

Table 1 Definitions of placental lesions and patterns

Term	Definition
Acute chorioamnionitis	Polymorphonuclear leukocytes present in the Langhans fibrinoid and/or amniochorion of placental membranes and/or in wall of umbilical vessels or chorionic vessel of the chorionic disc
Villitis of unknown etiology	Presence of chronic inflammatory cells (histiocytes, lymphocytes) in the villous stroma
Plasma cell deciduitis	Plasma cells seen in the decidua parietalis or basalis
Erythroblastosis of fetal blood	At least 2 nucleated red blood cells per 40× objective seen in villous vessels
Shallow meconium penetration	Meconium macrophages seen in the amniochorion of placental vessels
Deep meconium penetration	Meconium macrophages present in the decidua or Wharton jelly
Intravillous hemorrhage	Recent hemorrhage into villous core, usually underlying a retroplacental hematoma
Villous infarction	A non-marginal focus of coagulative necrosis of chorionic villi (> 5% of placental parenchyma)
Retroplacental hemorrhage	Blood accumulation causing indentation of maternal floor grossly and dissection the decidua microscopically
Hypertrophic decidual arteriolopathy	Preservation of muscular wall of spiral arterioles > 20 weeks of pregnancy
Hyaline necrosis, including atherosis of spiral arterioles	Dilatation and fibrinoid degeneration with histiocytes of decidual spiral arterioles
Laminar necrosis of membranes	A band of coagulative necrosis of choriodecidual interface of placental membranes (at least 10% of membrane roll)
Preuterine hypoxic pattern	Diffuse homogeneous villous hypomaturity with hypervascularity, decrease of extracellular matrix of chorionic villi, increased density of villous cytotrophoblasts, Hofbauer cells, and syncytial knots
Uterine hypoxic pattern	Diffuse heterogeneous hypermaturity of chorionic villi with other histological features as above
Postuterine hypoxic pattern	Diffuse homogeneous villous hypermaturity with increased extracellular matrix of chorionic villi and smudgy syncytial knotting, decreased villous vascularity, cytotrophoblasts and Hofbauer cells, sometimes with elongated pencil-like chorionic villi (distal villous hypoplasia)
Excessive amount of extravillous trophoblasts	≥ 5 cell islands and/or placental septa with ≥ 50 extravillous trophoblasts ≥ 5 per placental section or membrane migratory trophoblastic layer > 7 cells thick
Membrane/chorionic microcysts	≥ 3 microscopic chorionic lakes per section of a membrane roll or a section of grossly unremarkable placental parenchyma
Maternal floor clusters of multinucleate trophoblasts	Clusters > 3 trophoblastic cells with > 3 nuclei in decidua basalis or parietalis
Placenta creta (including basal plate myometrial fibers)	Deficiency of the decidua with myometrial fibers at the maternal floor (clinical or incidental microscopic)
Chorangiosis	Villous vascular profiles of at least 10 per ten terminal villus in 10 chorionic villi in 10 fields × 10 in 3 non-ischemic areas of placenta
Placental hydrops	Edematous villi with splits between the trophoblastic shell and villous cores
Fetal vascular ectasia	Fetal muscular vessel lumen ≥ 4 times the luminal diameter of the adjacent vessel.
Fetal vascular thrombosis	Arterial or venous thrombus, occluding or nonoccluding
Stem vessel obliteration	Marked thickening of the vessel wall with resulting obliteration of the vascular lumen
Stem vessel luminal abnormalities	Fibroblast septation of stem villous vessels
Diffusely increased extracellular matrix of chorionic villi	Diffuse fibrosis of villous cores with hypovascularity, including terminal villous hypoplasia
Segmental avascular villi	Clusters of 3 or more foci of avascular villi
Stromal vascular karyorrhexis	Clusters of 3 or more foci of terminal villi with karyorrhexis of fetal cells with preservation of surrounding trophoblasts
Intramural fibrin deposition	Venous intimal fibroblastic growth with a fibrin cap
Segmental villous mineralization	Linear mineralization/ferrugination of basement membranes of chorionic villi and/or stromal accumulation of hemosiderin or siderophages and or perivascular mineralization
Abnormal coiling of umbilical cord	Hypocoiled cord – coiling index < 0.1 coils/cm, hypercoiled cord – coiling index > 0.3 coils/cm
Dilatation of chorionic/stem vessels	Vascular dilatation to at least 4 times the diameter of an adjacent muscular vessel
Perivascular stem edema	Rings of edema around stem arteries
Intervillous thrombus	Villus-free nodular focus of coagulated blood in the intervillous space
Choriodecidual hemosiderosis	Siderophages and/or hemosiderin granules in placental membranes or decidua basalis
Massive perivillous fibrin deposition	> 30% of placental parenchyma occupied by lacy deposits of perivillous fibrinoid

stroma" [7], but for the purpose of this study, the quantitative criteria were expanded to include hypovascular villi, villi with stromal-vascular karyorrhexis, and mineralization. Other lesions or patterns of FVM (vascular thrombi in large vessels, stem vessel obliteration, intramural fibrin deposition, stem luminal vascular abnormalities, and diffuse villous avascularity) were analyzed as dependent covariates (Table 1), as they did not affect inclusion in groups 1–3 because of their global origin or nature.

Frequencies of 25 independent clinical and 43 placental variables were statistically compared among the 3 groups by ANOVA or Chi-square where appropriate, with Bonferroni correction for multiple comparisons.

Results

Of the 378 cases of SFVM, 160 cases (42.3%) ended in perinatal mortality, including 88 cases (23.2%) of macerated stillbirth. Among the three study groups, statistically significant differences (p Bonferroni < 0.002) were found in four independent clinical variables: gestational age, macerated

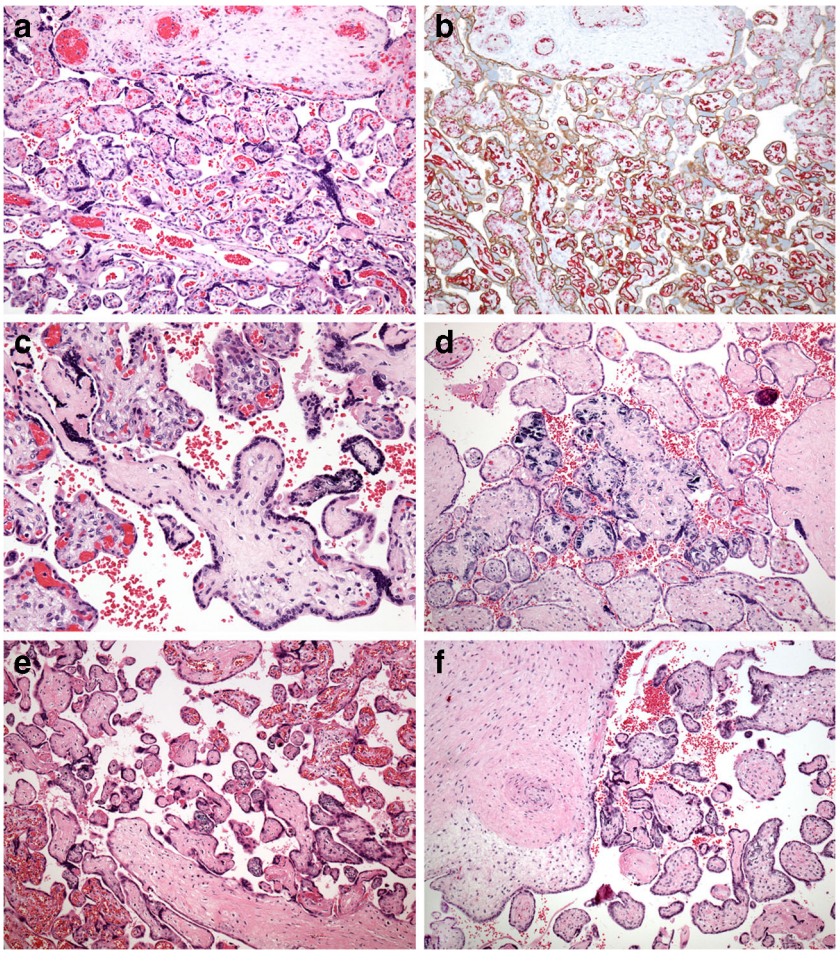

Fig. 3 Temporal heterogeneity of SFVM lesions (objective magnifications given). **a**, **b** Same site on the slide, 39 weeks, umbilical cord 2× around neck and 1× around body, and 1× around foot, anhydramnios, × 10. **a** Stromal vascular karyorrhexis, H&E, upper part of microphotograph. **b** Endothelial fragmentation involving larger area of placental tissue down to the bottom half of the microphotograph, E cadherin/CD34 immunostain. **c** Stromal vascular karyorrhexis, partial villous avascularity, and trophoblast basement membrane mineralization, × 20, 36 weeks, multicystic kidneys. **d** Hypovascularity, avascularity, and endothelial mineralization, × 0, 35 weeks, macerated and growth restricted stillbirth. **e** Segmental villous avascularity and basement membrane mineralization, × 10, 41 weeks, intrapartum fetal death. **f** Obliterated stem vessel, villous avascularity, and basement membrane mineralization, × 10, 30 weeks, amniotic sac infection syndrome, neonatal death, multicystic encephalomalacia

stillbirth, induction of labor, and cesarean section (Table 2). Notably, no statistically significant differences were found in the frequencies of hypertensive conditions of pregnancy, congenital anomalies, or clinical cord compromise.

Statistically significant differences were found in the frequencies of five independent placental features (Table 3): two lesions of shallow placental implantation (chorionic disk extravillous trophoblast microcysts and excessive extravillous trophoblasts in the chorionic disk), and three lesions of global vascular malperfusion (luminal vascular abnormalities of stem villi [multifocal or extensive], diffusely increased extracellular matrix in chorionic villi, and fetal vascular ectasia). The first four lesions were most common in group 3, and the fifth lesion was most common in group 1. However, no statistically significant differences were found in the frequencies of anatomical placental cord abnormalities, fetal vascular thrombosis, stem vessel obliteration, or intramural fibrin deposition.

Various FVM lesions commonly coexisted in the same cases and even on the same slides, thus indicating their temporal heterogeneity and the ongoing nature of the process. This information permitted us to date the beginning of the FVM inciting event before delivery or stillbirth and to determine its duration. The recently described clustered villous mineralization was observed mostly in preterm births with 1 month lower-than-average gestational ages at birth. This observation was particularly associated with macerated retained stillbirth, induction of labor, and features of global FVM, as expected.

Discussion

Placental examination is the most valuable tool for determining the cause of fetal death and explaining pregnancy complications [25–28]. Along with hypoxic and inflammatory lesions, FVM lesions are major correlates of fetal and neonatal pathology. In one database of high-risk pregnancy, the prevalence of SFVM was 7%, based on clusters of avascular chorionic villi seen on H&E stain [10]. In this study, the Amsterdam criteria for SFVM were expanded by including other recently described segmental placental lesions, the endothelial fragmentation and hypovascularity visualized by CD34 immunostain [12, 13], and villous mineralization usually identifiable by H&E stain but better highlighted by iron or

Table 2 Clinical phenotypes

	Group 1 early FVM	Group 2 late FVM	Group 3 remote FVM	F or Yates Chi-square groups 1 vs 2 vs 3, *df* 2	Groups 1 vs 2 vs 3 $p < 0.05$, 2 df (statistically significant p Bonferroni < 0.003)
Number of cases	44	264	70		
Gestational hypertension	3 (6.8%)	16 (6.1%)	4 (5.7%)		
Preeclampsia	4 (9.1%)	28 (10.6%)	7 (10%)C		
Chronic hypertension	1 (2.3%)	8 (3.0%)	6 (8.6%)		
Gestational age (weeks, average ± standard deviation)	33.8 ± 4.9	33.4 ± 5.7	29.6 ± 5.8	18.9	*< 0.0001*
Poor or absent prenatal care	1 (2.3%)	6 (2.3%)	4 (5.7%)		
Substance abuse	5 (11.4%)	21 (7.9%)	16 (22.9%)	11.0	0.00406
Maternal diabetes mellitus	6 (13.6%)	27 (10.2%)	8 (11.4%)		
Oligohydramnios	4 (9.1%)	34 (12.9%)	13 (18.6%)		
Polyhydramnios	4 (9.1%)	30 (11.4%)	8 (11.4%)		
Premature rupture of membranes	7 (15.9%)	40 (15.1%)	5 (7.1%)		
Antepartum hemorrhage	2 (4.5%)	27 (10.2%)	3 (4.3%)		
Meconium-stained amniotic fluid	1 (2.3%)	40 (15.1%)	6 (8.6%)		
Abnormal fetal heart rate tracing[a]	5 (11.4%)	66 (25.0%)	9 (12.9%)	6.6	0.034
Abnormal umbilical artery Dopplers	2 (4.5%)	23 (8.7%)	8 (11.4%)		
Induction of labor	10 (22.7%)	48 (18.2%)	32 (45.7%)	21.6	*< 0.0001*
Cesarean section	30 (68.2%)	157 (59.5%)	17 (24.3%)	29.7	*< 0.0001*
EXIT	11 (25.0%)	22 (8.3%)	4 (5.7%)	11.2	0.0036
Multiple pregnancy	2 (4.5%)	18 (6.8%)	10 (14.3%)		
Perinatal mortality	12 (27.3%)	88 (33.3%)	60 (85.7%0	66.8	< 0.0001
Neonatal mortality	5 (11.4%)	13 (4.9%)	4 (5.7%)		
Nonmacerated stillbirth	2 (4.5%)	13 (4.9%)	4 (5.7%)		
Macerated stillbirth	5 (11.4%)	37 (14.0%)	46 (65.7%)	83.2	*< 0.0001*
Fetal growth restriction[b]	6 (13.6%)	72 (27.3%)	23 (32.9%)		
Umbilical cord compromise[c]	6 (13.6%)	25 (9.5%)	10 (14.3%)		
Congenital malformations	21 (47.7%)	61 (23.1%)	17 (24.3%)	10.7	0.0048
Abnormal 3rd stage of labor (prolonged, hemorrhage)	3 (6.8%)	28 (10.6%)	2 (2.9%)		

Italics, differences that remained statistically significant after Bonferroni correction for multiple comparisons (independent variables). Perinatal mortality is not and independent variable

[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

von Kossa histochemistry stains when needed [15, 16]. The lesions are on opposite ends of the SVFM time spectrum: the endothelial fragmentation is the most recent lesion, with the shortest duration; and clustered villous mineralization is the most remote lesion, spanning the time interval of a couple of days to more than 2 weeks after the inciting event [17]. The high-grade SFVM diagnosed by CD34 immunohistochemistry and/or mineralization histochemistry worsens the short-term neonatal outcome measured by the Neonatal Intensive Care Unit stay. This outcome is the same as that of high-grade SFVM diagnosed by H&E only; thus, the sensitivity of placental examination for SFVM is increased [8].

It must be stressed that CD34 immunostain is a reliable marker for villous endothelium despite two facts: (1) CD34/CD45-positive progenitors may be identified in the mesenchymal compartment of chorionic villi during the first trimester of pregnancy and in the chorionic plate of mouse [22] and (2) the c-kit/CD34-positive cells may be observed in the mid-gestation placenta [29]. Endothelial colony-forming cells from human chorionic villi only partially express CD34 [30], but

Table 3 Placental variables

	Group 1 early FVM	Group 2 lte	Group 3 remote FVM	Yates Chi-square groups 1 vs 2 vs 3, *df* 2	Groups 1 vs 2 vs 3, *df* 2 $P < 0.05$ (statistically significant < 0.00322
Number of cases	44	264	70		
Placental weight (grams, average ± standard deviation)	398.6 ± 173.0	384.2 ± 189.1	341.6 ± 332.0		
Inflammatory lesions					
Acute chorioamnionitis	12 (27.3%)	79 (29.9%)	35 (50.0%)	*10.9*	0.0044
Chronic villitis of unknown etiology	5 (11.4%)	59 (22.3%)	10 (14.3%)		
Plasma cell deciduitis	6 (13.6%)	17 (6.4%)	4 (5.7%)		
Hypoxic lesions					
Meconium (histological)	19 (43.2%)	104 (39.4%)	26 (37.1%)		
Deep (decidual)	3 (6.8%)	73 (27.6%)	9 (12.9%)		
Shallow (amnionic or chorionic)	16 (36.4%)	31 (11.7%)	17 (24.3%)		
Intravillous hemorrhage	1 (2.3%)	16 (5.7%)	3 (4.3%)		
Villous infarction (> 5% of placental parenchyma)	6 (13.6%)	42 (15.9%)	12 (17.3%)		
Laminar necrosis of membranes[a]	12 (27.3%)	83 (31.4%)	22 (31.4%)		
Erythroblastosis of fetal blood	6 (13.6%)	65 (24.6%)	17 (24.3%)		
Hypertrophic decidual arteriopathy	9 (20.4%)	73 (27.6%)	21 (30.0%)		
Hyaline necrosis, including atherosis, of spiral arterioles	4 (9.1%)	20 (7.6%)	8 (11.4%)		
Patterns of chronic hypoxic injury	10 (22.7%)	82 (31.1%)	25 (35.7%)		
Preuterine	1 (2.3%)	15 (5.7%)	7 (10.0%)		
Uterine	7 (15.9%)	41 (15.5%)	14 (20.0%)		
Postuterine	2 (4.5%)	26 (9.8%)	4 (5.7%)		
Retroplacental hematoma	1 (2.3%)	12 (4.5%)	6 (8.6%)		
Intervillous thrombus	10 (22.7%)	76 (28.8%)	20 (28.6%)		
Lesions of shallow placental implantation					
Membrane chorionic microcysts[b]	5 (11.4%)	39 (14.8%)	5 (7.1%)		
Chorionic disc extravillous trophoblast microcysts[c]	2 (4.5%)	32 (12.15%)	21 (30.0%)	18.2	*0.00011*
Maternal floor multinucleate trophoblastic giant cells	15 (34.1%)	66 (25.0%)	22 (31.4%)		
Excessive extravillous trophoblasts in chorionic disc	10 (22.7%)	54 (20.4%)	31 (44.3%)	16.8	*0.00022*
Placenta creta (including basal plate myometrial fibers)	9 (20.4%)	33 (12.5%)	5 (7.1%)		
Lesions of fetal vascular malperfusion					
Fetal vascular ectasia	21 (47.7%)	65 (24.6%)	27 (38.5%)	12.7	*0.0017*
Thrombosis	10 (22.7%)	102 (38.6%)	21 (30.0%)		
Stem vessel obliteration	6 (13.6%)	19 (7.2%)	5 (7.1%)		
Intramural fibrin deposition	3 (6.8%)	36 (13.6%)	17 (24.3)	7.5	0.024
Luminal vascular abnormalities of chorionic villi	5 (11.4%)	21 (7.9%)	43 (61.2%)	107.6	*< 0.0001*
Diffusely increased extracellular matrix of chorionic villi	9 (20.4%)	48 (18.2%)	32 (45.7%)	23.6	*< 0.0001*
Massive perivillous fibrin deposition (> 30% of placental parenchyma)	2 (4.5%)	15 (5.7%)	2 (2.9%)		
Other					
Chorangiosis	4 (9.1%)	44 (16.7%)	6 (8.6%)		
Choriodecidual hemosiderosis	4 (9.1%)	24 (9.1%)	6 (8.6%)		
Villous edema	3 (6.8%)	13 (4.9%)	14 (20.0%)		
Two-vessel umbilical cord	5 (11.4)	13 (4.9%)	6 (8.6%)		
Hypercoiled umbilical cord	11 (25.0%)	63 (23.8%)	17 (24.3%)		

Table 3 (continued)

	Group 1 early FVM	Group 2 lte	Group 3 remote FVM	Yates Chi-square groups 1 vs 2 vs 3, *df* 2	Groups 1 vs 2 vs 3, *df* 2 $P < 0.05$ (statistically significant < 0.00322
Hypocoiled umbilical cord	5 (11.4%)	24 (9.1%)	5 (7.1%)		
Marginal insertion of umbilical cord	2 (4.5%)	22 (8.3%)	4 (5.7%)		
Velamentous insertion of umbilical cord	2 (4.5%)	12 (4.5%)	3 (4.3%)		
Other umbilical cord abnormalities[d]	11 (25.0%)	64 (24.2%)	24 (34.3%)		
Amnion nodosum/chorion nodosum	4 (9.1%)	20 (7.6%)	7 (10.0%)		
Marginate or vallate placenta	2 (4.5%)	7 (2.6%)	4 (5.7%)		
Gross chorionic cyst(s)	0 (0.%)	1 (0.4%)	1 (1.4%)		
Succenturiate lobe	3 (6.8%)	8 (3.0%)	2 (2.9%)		

Italics, differences that remained statistically significant after Bonferroni correction for multiple comparisons

[a] At least 10% of membrane rolls

[b] At least three pseudocysts per membrane roll

[c] At least three pseudocysts per section of grossly unremarkable chorionic disk

[d] 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

the lymphangiogenesis markers PROX-1 and VEGFR3 are not expressed in the placenta [31]. However, the author has not observed CD34-positive cells that would be different from terminal villous capillary endothelium on routine placental examination.

This study addresses the correlation of FVM in its various stages of development; it does not address the issue of clinicopathologic correlations of FVM in general [8, 10, 32–35]. Some clinical and placental entities (Tables 2 and 3) are known to have an increased risk of fetal thrombosis and FVM (hypertensive conditions of pregnancy, diabetes mellitus, chorioamnionitis, mass-forming congenital anomalies, fetal growth restriction, and cord complications) [34, 36–39]. For example, both clinical cord compromise (average 11%) (Table 2) and various pathological cord abnormalities (average 26%) (Table 3) are almost three times more common in this material than in the unselected placental database of high-risk pregnancy [10]. However, the conditions were rather symmetrically distributed among the groups studied. This information proves that similar etiology of FVM was implicated in different groups, that the FVM is not pathognomonic for any clinical entity, and that various lesions of FVM reflect their temporal heterogeneity rather than a specific etiology.

It must also be stressed that FVM lesions do not occur in isolation but are commonly associated with lesions of maternal vascular malperfusion and shallow placental implantation [10, 20, 40–42, 43]. Such lesions are characteristically observed in conditions such as preeclampsia or fetal growth restriction [44], as they are in this study (Table 3). Moreover, it is likely that lesions of maternal vascular malperfusion (decidual arteriopathy, acute hypoxic lesions, and chronic developmental patterns of hypoxic villous injury) may induce secondary changes in fetal vessels, which may be observed both clinically (abnormal uterine artery Dopplers) [45] and histologically (stem vessel obliteration) [44]. However, the histological lesions do not show then a segmental pattern. The secondary changes involving dedifferentiation of smooth muscle cells surrounding the fetal arteries within placental stem villi correlate with absent or reversed end-diastolic umbilical artery blood flow and with reduced fetal birth weight. The changes are more severe in the cases of fetal growth restriction associated with preeclampsia compared with the cases of isolated fetal growth restriction. This observation is consistent with the higher degree of maternal vasculopathy that occurred in the former cases along with more extensive macroscopic placental damage (infarcts, extensive fibrin deposition and microscopic villous developmental defects, atherosis, and noninfectious villitis) [44]. By contrast, FVM alone may be associated with normal uterine artery Doppler waveforms [46]. These observations show that the pathophysiologies of maternal and fetal vascular malperfusion overlap, at least in part.

The presence of SVFM lesions of various durations in the same placenta is the evidence that (1) instead of a single thrombotic event, an ongoing process exists or a new thrombus has formed, and (2) the time at which the most remote lesion occurs depends more on the interval between FVM onset and delivery or stillbirth than on the etiology of the process (Fig. 3). It is reasonable to assume that the most recent lesions would have progressed to more advanced lesions if the delivery had been delayed. However, the segmental endothelial fragmentation indicates that the onset of FVM is only about 2 days before delivery, stromal vascular karyorrhexis

is present a few days before delivery, hypovascular villi are present several days before delivery, clusters of totally sclerotic terminal villi are present up to 2 weeks before delivery, and clusters of mineralized chorionic villi are present more than 2 weeks before delivery [9, 12, 16]. Moreover, the presence of segmental villous mineralization in prolonged retained stillbirth, if present, can disclose the FVM even in a totally sclerotic placenta that might have escaped pathological identification because the preexisting lesions were obscured by villous sclerosis. Such segmental mineralization can be also seen in placentas from live births (24.3% of births in group 3 were live births) (Table 3). Some researchers believe that diagnosis of FVM is not possible in stillbirths because of obscuring villous regressive changes or fibrosis [8]. I agree that the antemortem presence of FVM cannot be diagnosed in all cases of stillbirth. However, most cases are not long-retained stillbirths associated with total villous sclerosis, so segmental total avascularity, hypovascularity, segmental stromal vascular karyorrhexis, and segmental endothelial fragmentation may still be helpful. The presence of fetal vascular thrombi also indicates a fetal antemortem event, as thrombi do not form postmortem. The temporal evolution discussed above permits the clinicopathologic correlation as to whether a known obstetric complication of known occurrence time could be responsible for the SFVM. FVM lesions with temporal heterogeneity developing until delivery are more likely to be responsible for perinatal complications and fetal death than a single remote FVM lesion followed by an uneventful pregnancy outcome. Although more studies are needed, analysis of the FVM spectrum may be helpful in medicolegal investigations of perinatal morbidity and mortality [47, 48].

The limitation of this analysis is that it may not be fully comparable with other populations of high-risk pregnancy from other institutions. The average gestational age of our cases is in the preterm pregnancy range. At term, umbilical cord compromise could be more common with the decreasing amount of amniotic fluid. Another shortfall of this study is that no known independent measure exists for timing placental lesions in general as they arise in utero. The same problem is encountered with other focal or diffuse placental lesions such as infarctions or hypoxic patterns of placental injury. The group segregation was therefore based on the author's observation of the mutual spatial relationships of the lesions themselves. For example, the adjacent coexisting stromal-vascular karyorrhexis is usually smaller and inside a larger lesion of the endothelial fragmentation by CD34, which indicates that the former is of longer duration than the latter (Fig. 3a, b).

In summary, the absence of statistically significant differences between the study groups regarding the most common causes of SFVM (hypertensive conditions of pregnancy, diabetes mellitus, fetal anomalies, and clinical and pathological features of umbilical cord compromise) is evidence that the three types of SFVM reflect temporal heterogeneity rather than etiopathogenesis. Like the global FVM of retained stillbirth, the SVFM lesions feature temporal evolution that can be used for dating the onset of FVM before delivery or fetal demise. Unlike the global FVM of retained stillbirth, SFVM lesions show histomorphology different from that of the adjacent nonlesional chorionic villi. The coexistence of various SFVM lesions of different durations in one placenta indicates ongoing or recurrent FVM rather than a single episode. Ongoing or recurrent FVM is more likely to explain a complicated perinatal outcome (including perinatal death) than the presence of a single remote FVM lesion. The author also believes that this approach could expand the criteria adopted by the Amsterdam panel; but further multi-institutional research is needed.

Author contributions The author is the only contributor.

Compliance with ethical standards

Conflict of interest The author declares that he has no conflict of interest.

Ethical approval This study was approved by the institutional review board (IRB #2016-7942) and complies with ethical standards.

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