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CD34 immunostain increases the sensitivity of placental diagnosis of fetal vascular malperfusion in stillbirth

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ABSTRACT

Introduction: Postmortem regressive placental changes of stillbirth may obscure the pre-existing placental histomorphology. The objective is to find out whether the use of CD34 immunostain can increase the sensitivity of placental examination in the diagnosis of fetal vascular malperfusion (FVM).

Methods: Twenty six independent clinical and 46 placental variables of 46 placentas from stillbirths were statistically compared to those of 92 placentas from livebirths. One histologically most unremarkable section per case was stained using double *E*-cadherin/CD34 immunostain (ECCD34). Clusters of avascular/hypovascular chorionic villi on hematoxylin and eosin (H&E) staining system and/or CD34 immunostaining, the latter also including endothelial CD34 positive debris in the villous stroma, were regarded as evidence of FVM.

Results: The gestational age and cesarean section rate were statistically significantly lower and the induction of labor and mild erythroblastosis of fetal blood was higher, but the frequencies of clinical and placental features of umbilical cord compromise were not statistically significant between stillbirths and livebirths, respectively. By using H&E stain, 9 (19.6%) of stillbirths and 30 (32.6%) of livebirths showed clusters of avascular villi on H&E. By CD34, the rates of FVM increased to 23 (50%) and 34 (40%), respectively. The increase was statistically significant for stillbirths only (Chi square = 9.4, p = 0.002). By CD34, new clusters of hypovascular chorionic villi or villi with endothelial fragmentation were found in 23 stillbirth cases (50%) as opposed to livebirths (29 cases, 31.5%)(Chi square = 9.4, p = 0.002).

Discussion: When compared with H&E stain, the CD34 increases sensitivity and/or upgrades FVM in placental examination in stillbirths but not in livebirths.

1. Introduction

The diagnosis of focal placental fetal vascular malperfusion (FVM), previously called "fetal thrombotic vasculopathy," is most commonly made in cases of umbilical cord compromise, the second most common cause of stillbirth after placental insufficiency [1,2], but it can also be made in fetal blood hypercoagulability (e.g., infections, maternal pre-eclampsia, maternal diabetes mellitus, maternal humoral, and fetal genetic coagulopathies), fetal growth restriction (FGR), fetal disruption sequences, cerebral palsy, poor neurological outcome, neonatal stroke, severe perinatal liver disease, perinatal mortality, and fetal cardiac dysfunction [3–21]. However, it can occur also in an unselected population at or near term [22]. Its most important histological feature is clusters of avascular chorionic villi [23,24], but FVM may sometimes be suspected on gross placental examination. The ability to accurately make the diagnosis is, therefore, vital in understanding the etiopathogenesis of stillbirth, neonatal risks, and poor postnatal outcomes.

The stillbirth-related diffuse postmortem regressive placental changes because of all-placental cessation of blood flow [25] has similar pathomechanism and likely the same timetable to develop as FVM and may obscure the pre-existing histomorphology of focal fibrosis/hypovascularity of the latter [26]. As in stillbirth, total villous fibrosis likely takes 2 or more weeks to develop [25]. Therefore, the early stages of villous hypovascularity can be difficult to diagnose with confidence in stillbirth on H&E stain only, hence may be overlooked.

The *E*-cadherin/CD34 immunostain (ECCD34) has been used by the senior author for more than 3 years in the differential diagnosis of chronic hypoxic patterns of placental injury to assess vasculosyncytial membranes, villous vascularity, and density of villous cytotrophoblasts [27–29]. While doing this, we noticed that its CD34 component may highlight segmental (lobular) villous hypovascularity/avascularity and

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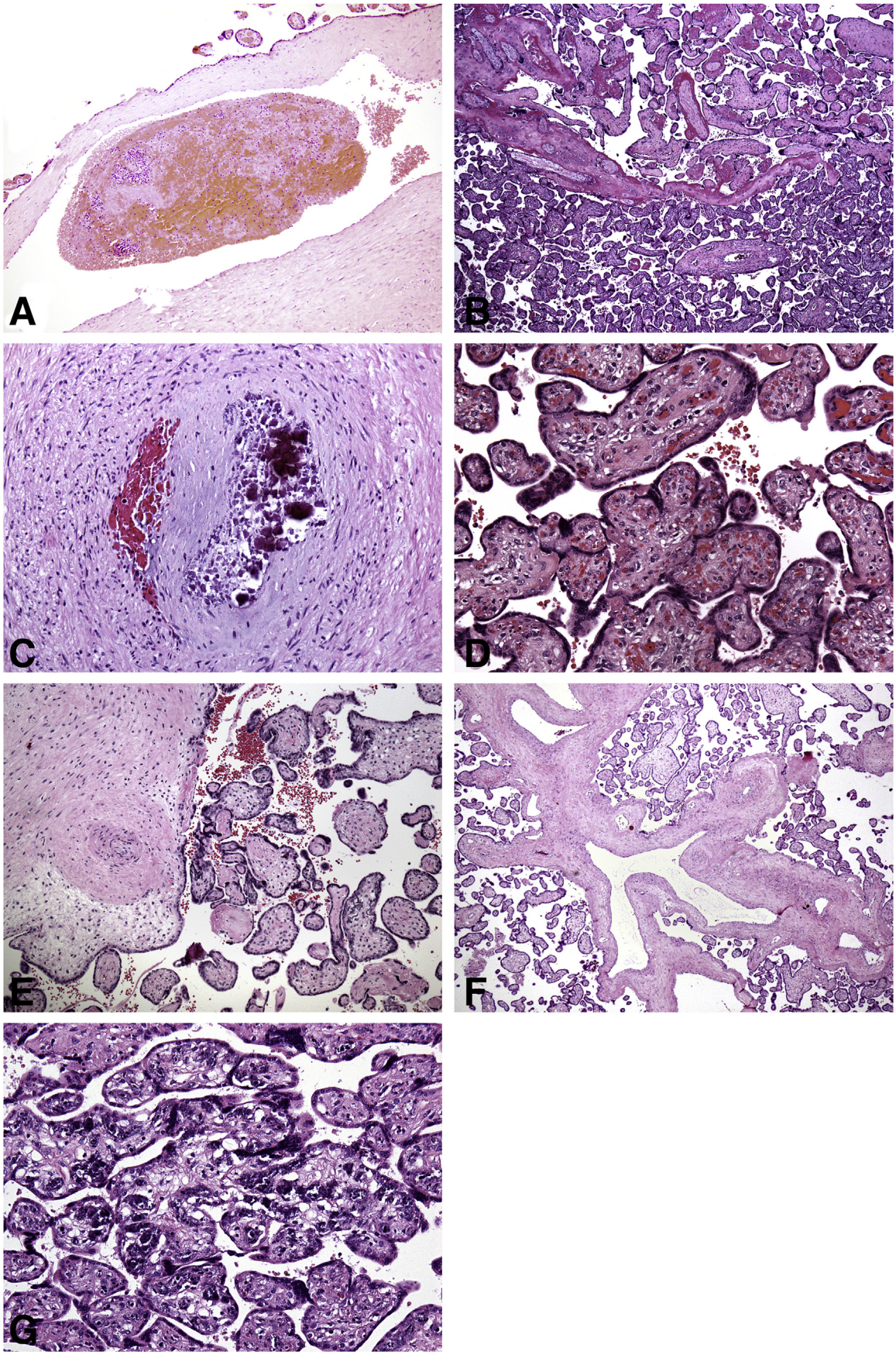

Fig. 1. Conventional hematoxylin-eosin histology of FVM. Objective magnifications are given in parentheses. A. Nonoccluding thrombus in a stem vessel (x10). Multiple nonocclusive thrombi suffice to define high grade FVM even in the absence of placental villous changes. B. Clusters of sclerotic villi (high grade FTV) (x4). C. Mineralized intramural fibrin deposition (x20). D. Villous stromal vascular karyorrhexis (x20). E. Stem vessel obliteration (fibromuscular sclerosis) (x10). F. Stem vascular ectasia (x4). G. Clustered lobular mineralization (x20).

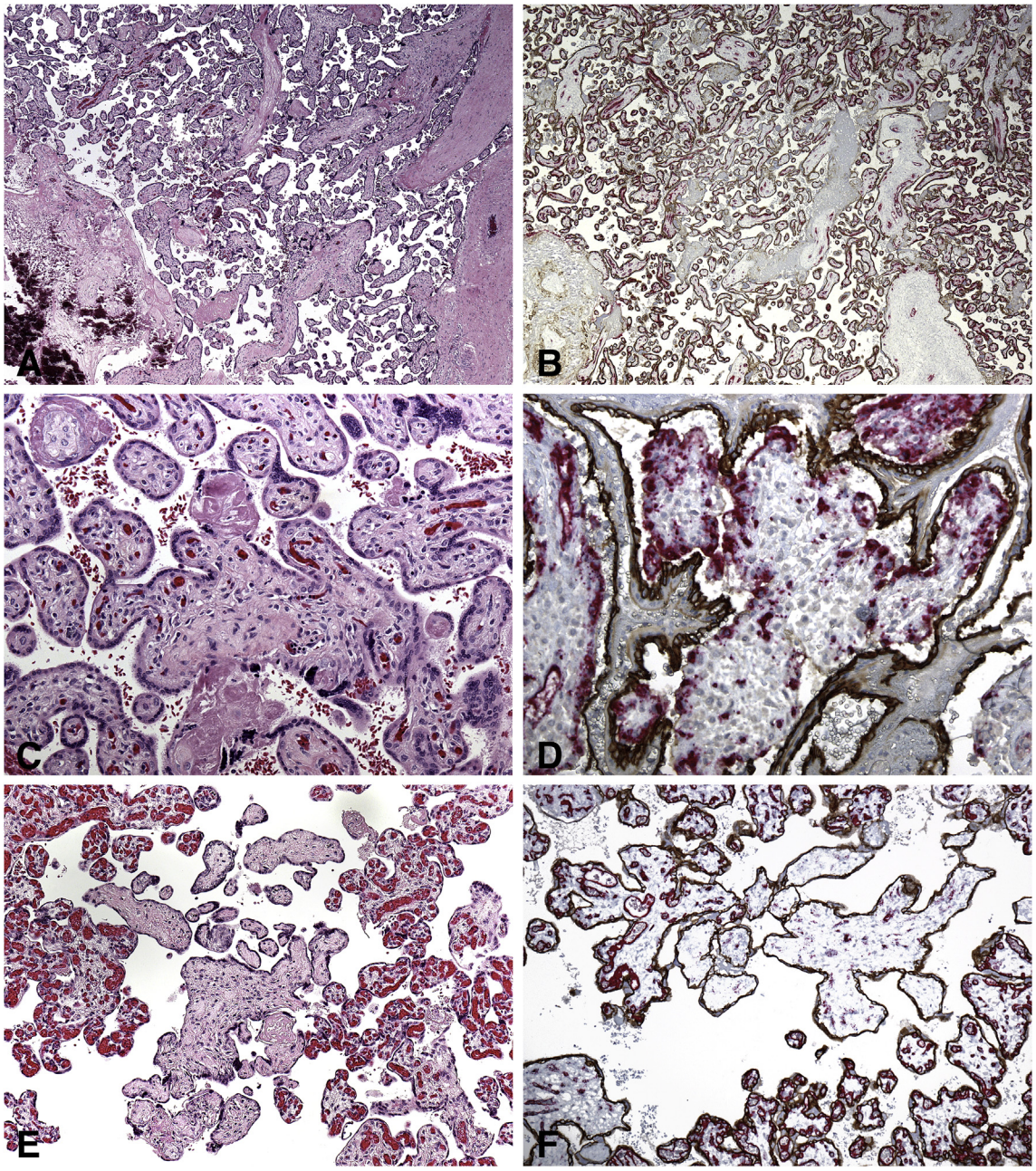

Fig. 2. FVM diagnosed or upgraded by ECCD34 immunostain. A,B. Incipient FVM: No avascular villi on H&E stain (A), lobular hypovascularity on CD34 (B)(x4). C,D. Incipient FVM: No stromal vascular karyorrhexis in villi on H&E stain (C), clustered villi with endothelial fragmentation on CD34 (D) (x20). There is a split artifact between the trophoblastic shell and the villous core diagnostic of villous edema. E,F. FVM upgraded by CD34 immunostain: One focus of avascular villi on hematoxylin-eosin stain (E), more clustered foci of villous hypovascularity on another section on CD34 (F), potentially upgrading FVM to high grade. (x10).

villous endothelial fragmentation in cases that they were not easily appreciable on H&E, and we started to regard it as a possible incipient FVM [30]. As a systematic statistical review of the approach has not been published yet, our objective was to analyze whether the use of CD34 immunostain could increase the sensitivity of placental examination in this respect and to assess the value of this stain to detect the early stages of FTV not clearly seen on H&E slides.

2. Materials and methods

The study was approved by the institutional review board (IRB #2016–7942). Of all 205 placentas examined by the author at the Division of Pathology and Laboratory Medicine in years 2015–2018, ECCD34 had been performed in 138 placentas, mainly to help in differential diagnosis of chronic hypoxic patterns of diffuse placental injury. The components of ECCD34 included E. Cadherin (clone 36): Roche, Ms. Monoclonal, 790-and CD34 (clone QBEnd/10): Roche, Ms Monoclonal, 760-for the purpose of this analysis, only the CD34 component was evaluated.

The placentas were available for examination at the discretion of the obstetricians because of a high risk-pregnancy or its complications such as fetal distress, operative delivery, poor condition of the neonate, or grossly abnormal placenta or were a part of autopsy. At least 2 sections of membrane roll and the umbilical cord and 2 paracentral sections of grossly unremarkable placenta were examined, but all grossly abnormal areas were also sampled. After sectioning, formalin fixation, and paraffin embedding, the sections were stained with H&E and were reviewed by the author using the same diagnostic criteria as in previous

Table 1
Clinical phenotypes.

	Group 1 Stillbirth	Group 2 Livebirth	F or Chi square	p < 0.05, (statistically significant p Bonferroni < 0.0018519)
Number of cases	46	92		
Gestational age (weeks, average ± standard deviation)	27.6 ± 8.1	32.6 ± 5.5	18.1	**3.78E-05**
Preeclampsia	9 19.6%	18 19.6%		
Gestational hypertension	6 13.0%	6 6.5%		
Mild preeclampsia	1 2.2%	1 2.2%		
Severe preeclampsia	2 4.3%	7 7.6%		
HELLP	2 4.3%	3 3.3%		
Chronic hypertension (including superimposed preeclampsia)	5 10.9%	7 7.6%		
Poor or absent prenatal care	2 4.3%	2 2.2%		
Substance abuse	9 19.6%	9 9.8%		
Maternal diabetes mellitus	5 10.9%	13 14.1%		
Oligohydramnios	6 13.0%	10 10.9%		
Polyhydramnios	1 2.2%	7 7.6%		
Premature rupture of membranes	5 10.9%	16 17.4%		
Antepartum hemorrhage	2 4.3%	7 7.6%		
Meconium (clinical)	4 8.7%	8 8.7%		
Thin	3 6.5%	7 7.6%		
Thick	1 2.2%	1 1.1%		
Abnormal fetal heart rate tracing[a]	4 8.7%	16 17.4%		
Abnormal umbilical artery Doppler	2 4.3%	9 9.8%		
Induction of labor	27 58.7%	7 7.6%	43.1	**0**
Cesarean section	12 26.1%	61 66.3%	19.9	**0.00008**
Multiple pregnancy	6 6.5%	4 4.3%		
Perinatal mortality	46 100.0%	31 33.7%		**N/A**
Neonatal mortality	0 0%	31 33.7%		**N/A**
Nonmacerated stillbirth	13 28.3%	0		N/A
Macerated stillbirth	33 71.7%	0		**N/A**
Fetal growth restriction[b]	18 39.1%	20 21.7%	4.6	0.031
Umbilical cord compromise[c]	6 13.0%	11 12.0%		
Congenital malformations	12 26.1%	39 42.4%		
Abnormal third stage of labor (prolonged, hemorrhage)	2 4.3%	8 8.7%		

Bold font: differences that remained statistically significant after Bonferroni correction for multiple comparisons.
N/A: not applicable.
[a] Abnormal nonstress test and/or abnormal contraction stress test and/or abnormal intrapartum cardiotocography (prolonged bradycardia and/or prolonged tachycardia and or decrease in fetal heart rate variability and/or late decelerations).
[b] Birth weight < 10 centile.
[c] Variable decelerations, encirclement, true knot, or prolapse.

publications [31–33]. The nomenclature adopted by the 2016 consensus of the Amsterdam Conference was used when possible, in particular high-grade FVM was diagnosed by the finding of more than one focus of avascular villi (a cumulative assessment of ≥45 avascular villi over 3 sections examined or an average of ≥15 villi per section), or 2 or more thrombi in chorionic plate or major stem villi, or multiple non-occlusive thrombi [34].

The material was divided into 46 stillbirths and 92 livebirths. In addition to the standard H&E stained sections, one histologically most unremarkable section per case was stained with CD34. Clusters of avascular/hypovascular chorionic villi on H&E (Fig. 1) and/or CD34 immunostain (Fig. 2), the latter including also endothelial CD34 positive debris in the villous stroma in lobular distribution, were regarded as evidence of FVM. The H&E findings diagnostic of FVM were also compared to the CD34-stained slide to find out whether the stain was diagnostic of FVM not seen on H&E or upgraded FVM from low grade to high grade. Frequencies of 26 independent clinical and 46 placental phenotypes were statistically compared between the stillbirths and livebirths.

3. Results

3.1. Clinical phenotypes

The gestational age and cesarean section rate were statistically significantly lower, and the induction of labor was higher in stillbirths than in livebirths (p Bonferroni < 0.0018519). The frequencies of clinical phenotypes known to be classically associated with poor obstetric outcome, particularly hypertensive conditions in pregnancy, maternal diabetes mellitus, premature rupture of membranes, and umbilical cord compromise, were not statistically significant between the 2 groups, but maternal substance abuse/smoking, poor prenatal care, and FGR were twice more common in the stillbirth group, and abnormal fetal heart rate, abnormal Dopplers, and congenital malformations were higher in the livebirth group (Table 1).

3.2. Placental examination

Only mild erythroblastosis of fetal blood and villous edema were statistically significantly more frequent in the stillbirth group (p Bonferroni < 0.0010204). The individual components of the FVM complex identified grossly or by H&E stain were not statistically significantly different (Table 2). In some cases, the CD34 either highlighted FTV not appreciated on the H&E stained sections alone or demonstrated additional areas involved by FVM that permitted us to upgrade FVM from low grade to high grade [34]. Of the FVM complex (Table 2) by H&E, 9 (19.6%) of stillbirths and 30 (32.6%) of livebirths showed clusters of avascular villi (statistically not significant). However, with the addition of CD34, the rates of FVM increased to 23 (50%) and 34 (40%) in both groups, respectively. The increase was statistically significant for stillbirths only (Chi square = 9.4, p = 0.002). By CD34, new clusters of hypovascular chorionic villi or villi with endothelial fragmentation were found in 23 stillbirth cases (50%) as opposed to livebirths (29 cases, 31.5%)(Chi square = 9.4, p = 0.002),

Table 2
Placental variables.

	Group 1 Stillbirth	Group 2 Livebirth	F or Chi square	p < 0.05, (statistically significant p Bonferroni < 0.0010204)
Number of cases	46	92		
Placental weight (grams, average ± standard deviation)	265.7 ± 175.2	361.1 ± 173.4	8.8	0.004
Inflammatory lesions/patterns				
Acute chorioamnionitis	18 39.1%	23 25.0%		
Maternal inflammatory response	13 28.3%	11 12.0%	5.7	0.017
Fetal inflammatory response	5 10.9%	12 13.0%		
Chronic villitis of unknown etiology	6 13.0%	13 14.1%		
Plasma cell deciduitis	5 10.9%	11 12.0%		
Hypoxic lesions/patterns				
Erythroblastosis of fetal blood	18 39.1%	9 9.8%	16.8	**0.0000419**
Meconium (histological)	15 32.6%	30 32.6%		
Deep (decidual)	4 8.7%	4 4.3%		
Shallow (amnionic or chorionic)	11 23.9%	26 28.3%		
Villous infarction (> 5% of placental parenchyma)	7 15.2%	11 12.0%		
Hypertrophic decidual arteriolopathy	13 28.3%	31 33.7%		
Atherosis of spiral arterioles	5 10.9%	7 7.6%		
Laminar necrosis of membranes[a]	11 23.9%	26 28.3%		
Patterns of chronic hypoxic injury	18 39.1%	34 40.0		
Preuterine	6 13.0	6 6.5%		
Uterine	11 23.9%	26 28.3%		
Postuterine	1 2.2%	8 8.7%		
Retroplacental hematoma	2 4.3%	4 4.3%		
Intravillous hemorrhage	2 4.3%	5 5.4%		
Intervillous thrombus	9 19.6%	22 23.9%		
Lesions of shallow placental implantation				
Membrane chorionic microcysts[b]	3 6.5%	19 20.6%	4.57	0.0325
Chorionic disc chorionic microcysts[c]	6 13.0%	16 17.4%		
Clusters of maternal floor multinucleate trophoblastic giant cells	11 23.9%	27 29.3%		
Excessive amount of extravillous trophoblasts in chorionic disc	13 28.3%	25 27.2%		
Placenta accreta (including basal plate myometrial fibers)	2 (4.3%)	13 14.1%		
Fetal vascular malperfusion complex				
Fetal vascular ectasia	13 28.3%	39 42.4%		
Intramural fibrin deposition in stem/chorionic veins	2 4.3%	5 5.4%		
Clusters of avascular/hypovascular villi by H&E	9 (7/2) 19.6%	30 (16/14) 32%		
Thrombi (nonoccluding/occluding) in fetal circulation	9 (4/5) 19.6%	34 (19/15) 40%	4.324	0.038
Fetal vascular malperfusion by CD34	23 (16/7) 50.0%	34 (24/10) 40%	2.152	0.15
Upgrading of fetal vascular malperfusion by CD34	23 50%	29 31.5%	3.707	0.034
Stem vessel obliteration	3 6.5%	11 12.0%		
Lobular villous hemosiderosis	4 8.7%	4 4.3%		
Villous stromal vascular karyorrhexis	3 6.5%	3 3.3%		
Luminal vascular abnormalities of chorionic villi	19 41.3%	1 1.1%		N/A
Diffusely increased extracellular matrix of chorionic villi	21 45.6%	7 7.6%		N/A
Other				
Massive perivillous fibrin deposition (> 30% of placental parenchyma)	1 2.2%	5 5.4%		
Chorangiosis	7 15.2%	17 18.5%		
Choriodecidual hemosiderosis	5 10.9%	7 7.6%		
Villous edema	12 26.1%	3 3.3%	16.5	**0.0000488**
Two-vessel umbilical cord	5 10.9%	6 6.5%		
Hypercoiled umbilical cord	16 34.8%	24 26.1%		
Hypocoiled umbilical cord	6 13.0%	7 7.6%		
Perivascular stem edema	5 10.9%	11 12.0%		
Marginal insertion of umbilical cord	3 6.5%	4 4.3%		
Velamentous insertion of umbilical cord	1 2.2%	4 4.3%		
Other umbilical cord abnormalities[d]	16 34.8%	22 23.9%		
Amnion nodosum/chorion nodosum	6 13.0%	7 7.6%		
Marginate or vallate placenta	0	9 9.8%	4.8	0.0287
Gross chorionic cyst(s)	0	3 3.3%		
Succenturiate lobe	0	2 2.2%		

Bold font: differences that remained statistically significant after Bonferroni correction for multiple comparisons.
N/A: not applicable.
[a] At least 10% of membrane rolls.
[b] At least 3 pseudocysts per membrane roll.
[c] At least 3 pseudocysts per section of grossly unremarkable chorionic disc.
[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.

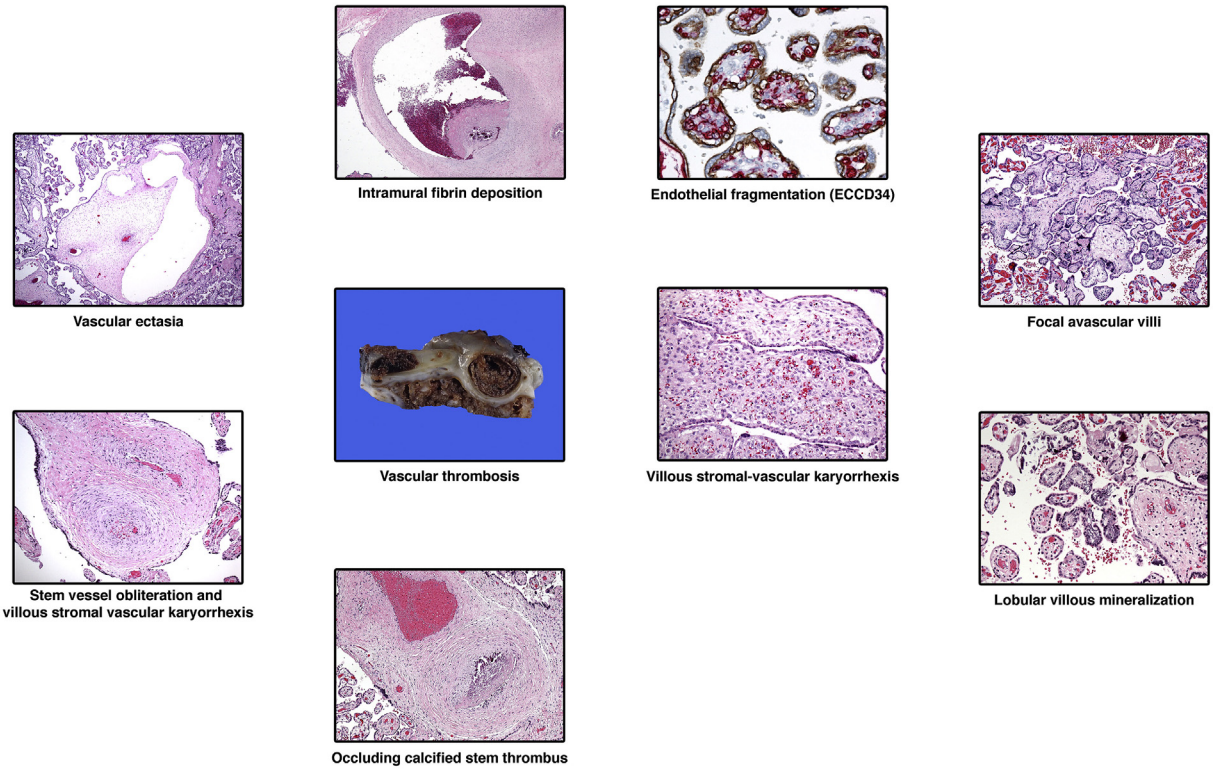

Fig. 3. FVM is an on-going process. Not all stages must be seen in a given placenta, particularly if FVM is not stasis-induced. The lesions on the left are usually earlier, and the lesions on the right later (older FVM).

thus upgrading FVM from none to low grade in 12 cases, from 0 to high grade in 6 cases, from low grade to high grade in 1 case, and additional abnormal clusters were found in 4 cases, however, falling short of upgrading low grade to high grade FVM. There were no statistically significant differences in other H&E components of the FVM complex (fetal vascular ectasia, fetal thrombosis, intramural fibrin deposition, villous stromal vascular karyorrhexis, lobular hemosiderosis, and stem vessel obliteration). The statistically significantly diffuse increase in the extracellular matrix of chorionic villi and luminal stem vessel abnormalities [25] were the obvious results of fetal death in the stillbirth group.

4. Discussion

We do not favor the term FVM over fetal thrombotic vasculopathy [34] as it is a functional/pathophysiological term and not a histopathological term [26], by the same token as we prefer the term "myocardial infarction" to "coronary artery malperfusion." Having said this, there are several histological components of the FVM complex (Table 2), of which only the quantitatively assessed clusters of sclerotic chorionic villi and fetal vascular thrombi are used for discrimination between low-grade and high-grade FVMs [34].

Although the Amsterdam classification includes only H&E stained slides and not immunohistochemistry, the current manuscript presents a search for a novel approach and not new obligatory criteria for instantaneous implementation. For us, it is reasonable to assume that villous avascularity and sclerosis of FVM does not appear overnight, but develop gradually, approximately in 2 weeks, i.e., the minimum time needed for total villous sclerosis to develop in retained stillbirth [25]. On H&E, only villous stromal vascular karyorrhexis may be found at some point in this time gap, but it is not frequently present. Therefore, the FVM may not be diagnosed despite the vascular thrombotic obliterative process already in place with fetal systemic involvement with its potential serious consequences. Fetal damage may be severe shortly after an occurrence of vascular accident before diagnostic sclerotic chorionic villi would be visible on H&E stained slides. Therefore, the diagnosis of early phases of FVM seems to be desirable. The CD34 immunostain may offer a chance to highlight the gradual transition between normovascularity and total avascularity.

On the other hand, in retained stillbirths, progressively increasing diffuse villous extracellular matrix may blur the features of FVM. We believe that CD34 immunostain can also help in such situations. Previously, the stain was used to help in differential diagnosis of chronic hypoxic patterns of placental injury [27] by highlighting villous hypervascularity and chorangiosis [35]. It now appears that it is likewise helpful in evaluation of focal villous hypovascularity and villous endothelial fragmentation of FVM, the latter being different from karyorrhectic debris seen in stromal/vascular karyorrhexis ("hemorrhagic endovasculitis"), and both likely represent similar stage in the development of FVM [36].

As the minimal or even complete histological criteria for FTV feature low sensitivity [37], this analysis shows that the abnormal CD34 pattern is able to highlight early stages of FTV by showing incipient focal lesions of villous hypovascularity and endothelial disruption before clusters of avascular chorionic villi become manifest on H&E stained sections. Furthermore, even in the latter situation, the coexistent abnormal CD34 pattern could disclose the ongoing thrombotic process [30] (Fig. 3) High grade FVM is particularly associated with numerous fetal complications [34], but even low-grade FVM diagnosed on CD34 immunostain can be associated with calcified thrombi in brain vessels [29].

In this material, 50% of stillbirths showed evidence of FVM when CD34 immunostain was used, an increase by 30% in sensitivity as compared with H&E stain only. It is true that any increase in sensitivity of a test may be associated with a decrease in its specificity with subsequent potential lack of clinical relevance [38]. However, the use of CD34 does not increase the numbers of chorionic villi affected at the same time as sclerotic villi, but highlight those that were affected later in the disease process [25], thus reflecting the real extent of the on-

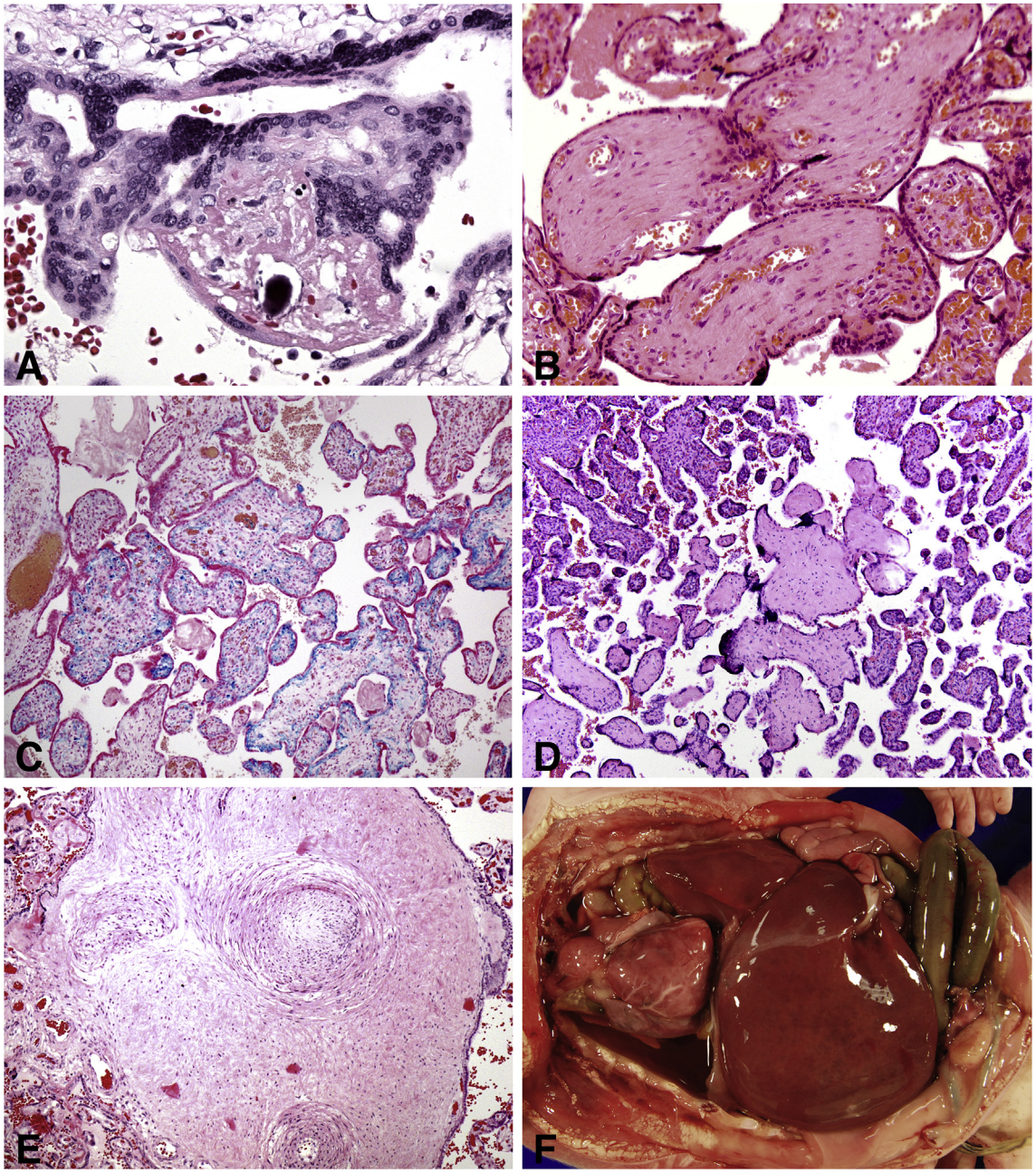

Fig. 4. Suggested indications for CD34 immunostaining if FVM is likely clinically and/or suspicious but not diagnostic on H&E, or if only low grade FVM is present (potential upgrading to high-grade FVM). None of the situations in Fig. 4 is sufficient to diagnose either FVM as such (Fig A, B), or high grade FVM (C–E). F represents an indication for performing CD34 based on clinical situation, even if the chorionic villi are normal on H&E. A. Unexplained stillbirth, calcified thrombus in a villous capillary (x40). B. Partial fibrosis in only 3 of chorionic villi (x20). C. A cluster of partial villous mineralization (iron stain) (potential for upgrading)(x20). D. A single cluster of avascular villi not meeting the criteria for high grade FVM (x10). E. Stem vessel obliteration and perivascular stem edema (x20). F. Stillbirth, large congenital diaphragmatic hernia (or other gross fetal or umbilical cord abnormalities).

going disease. In livebirths, the increase in CD34 sensitivity for the diagnosis of FVM was only 7.4% when compared with H&E immunostain. It is understandable because evaluation for hypovascular/avascular villi in livebirths is easier even on H&E without the background of diffuse villous fibrosis of retained stillbirth. Therefore, the CD34 immunostain is a particularly useful adjunct in the investigation of etiology of stillbirth, along with the iron stain for clustered villous hemosiderosis [39,40].

As other causes of FVM than the umbilical cord compromise are less common, we believe that the CD34 immunostaining has a potential to increase the sensitivity of placental examination mainly in retrospect diagnosing the umbilical cord compromise that frequently eludes the placental confirmation. Although some authors found correlation between gross umbilical abnormalities and histological FVM [41–49], this was not our experience, unless clinical features of cord compromise were also present [8]. In this material, the clinically observed signs of umbilical cord compromise (variable decelerations, encirclement, true knot, and prolapse) were equally common in stillbirths and livebirths. By comparison, without immunohistochemistry, only 11% of stillbirths showed placental features of umbilical cord obstruction [48], but various umbilical cord abnormalities and villous clusters of sclerotic/hemosiderotic villi were more common in macerated fetuses [29].

From this analysis, potential indications for placental CD34 immunostaining emerge (Fig. 4): unexplained stillbirth, increased risk for

fetal thrombophilia (clinical and/or gross umbilical cord abnormalities), recurrent pregnancy loss, suspicion for genetic thrombophilias, placentas from ECMO procedures, particularly those with partial villous fibrosis (cannonball, sausage type) [50], sclerotic chorionic villi not meeting quantitative criteria for FVM, low grade FVM (possibility for upgrading), and other histological features suggestive of umbilical cord abnormalities [51]. Only a strict prospective protocol can fully evaluate the value of the indication in diagnosing an occult FVM.

The limitation/weakness of this study is the case selection as mainly placentas associated with perinatal deaths, consults from high grade risk pregnancies, or children delivered by cesarean sections/EXIT procedure were studied, the latter showing by itself an increased risk for FVM [50]. Therefore, the risk of FVM was high in this material and may be smaller in an unselected population. Further, only one section of the least microscopically abnormal placental tissue was immunostained, but this would only attenuate and not exaggerate the differences in frequency of FVM. Also, the livebirth group is not a true control group but rather a comparative group, but this analysis was not intended to analyze the placental differences between livebirths and stillbirths, which was done previously [32], but rather to highlight the possible usefulness of the CD34 immunostain in diagnosing FVM.

We conclude that CD34 immunohistochemical staining can significantly improve the detection of focal or subtle findings of FVM in placental specimens, particularly in cases of high-risk pregnancy, placentas with hypoxic lesions [52], and poor fetal/infant outcome.

Declaration of competing interests

None to report.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.placenta.2019.02.001.

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