Review paper

E-cadherin/CD34 double immunostaining in placental diagnosis

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Placental foetal vascular malperfusion (FVM) may be responsible for complicated foetal or neonatal condition. By highlighting endothelial fragmentation, the double E-cadherin/CD34 immunostain highlights distal villous endothelial fragmentation of recent FVM not seen on haematoxylin-eosin stained sections. We routinely perform the stain on a grossly unremarkable placental sections of placentas predominantly from pregnancies with mass-forming foetal anomalies and umbilical cord complications. The stain can upgrade the FVM and/or reveal its temporal heterogeneity, both useful in establishing the cause of foetal death or poor neonatal condition. It also highlights the basement membranes of syncytiotrophoblastic cells which, in conjunction with endothelial staining, is helpful in the diagnosis of widening thereof in distal villous hypomaturity. It can distinguish mineralised stem occluding thrombi from mineralised trophoblastic pseudo inclusions – the former outlined by CD34, the latter by E-cadherin – thus helping to differentiate FVM from placental aneuploidies. The E-cadherin component helps in the diagnosis of trophoblastic lesions of shallow placental implantation featuring an increased number of extravillous trophoblasts in placental membranes and chorionic disc. Therefore, the double immunostain is helpful in histological diagnosis of placental lesions and patterns of injury.

Key words: placenta, foetal vascular malperfusion, immunohistochemistry, CD34, E-cadherin.

Introduction

The value of placental examination in obstetrics and neonatology is well established [1–4], although sometimes authors express some reservations [5]. Most commonly, in addition to gross examination of the placenta, routine haematoxylin and eosin (HE) staining rarely needs to be supplemented by histochemical and/or immunohistochemical studies, usually for the diagnosis of placental infections, or molecular/genetic tests for a foetal genetic disease.

A few years ago, E-cadherin/CD34 double immunostaining was introduced to diagnose the widening of villous vasculosyncytial membranes of villous dysmaturity/hypomaturity, and the condition of villous capillaries in seemingly avascular/hypo vascular villi to more objectively diagnose the foetal vascular malperfusion (FVM) [6, 7]. With time, the routine application of the double immunostaining led to other possible applications.

This review aims at summarising the author's experience with double E-cadherin/CD34 immunostaining and its 2 components separately, not only for FVM but also for other patterns of placental injury.

Double E-cadherin/CD34 immunostaining protocol

Slides are stained using an automated platform, the Discovery XT (Ventana/Roche Tissue Diagnostics). Slides are pretreated with ethylenediaminetetraacetic acid at 95°C, and then rinsed with reaction buffer.

100 μl of primary antibody E-cadherin (Roche, 790-4497, RTU) is applied to the slides and incubated for 20 minutes. The slides are then rinsed with reaction buffer. 100 μl of second primary antibody CD34 (Roche, 760-2620, RTU) is applied to the slides and incubated for 60 minutes. The slides are then rinsed with reaction buffer. Slides are detected using a combination of the UltraView Universal DAB and UltraView Red detection kits (Roche,760-500 and 760-501). Slides are counterstained with haematoxylin II (Ventana, #790-2208) for 12 minutes, and then rinsed, blued with bluing reagent (Ventana, #760-2037) for 4 minutes, and then rinsed, washed in soapy water, and run down through graded ethanol and xylene to dehydrate, and they are finally cover slipped using a xylene-based mounting medium.

Foetal vascular malperfusion

This constitutes the most common application of the double immunostain in our material. The CD34 component of the double immunostaining is most useful for the diagnosis, timing, and grading of the distal villous FVM, particularly recent (acute) FVM [7], which features endothelial fragmentation, not seen on HE placental sections (Fig. 1A) [8, 9]. The endothelial fragmentation is different than the stromal vascular karyorrhexis (SVK) diagnosable on HE staining (Fig. 1B) [10]. Both patterns are the earliest histological manifestations of distal villous FVM with overlapping time frame of appearance after foetal vascular obliteration. However, the CD34-highlighted endothelial fragmentation is more sensitive, being 3–4 times more common than SVK. In the former, while some villous capillary endothelium is still present, some is fragmented, while in SVK most villous endothelium is destroyed [8, 10–12]. If adjacent to SVK, the endothelial fragmentation involves more chorionic villi (larger area on slide) (Fig. 1C) than SVK (Fig. 1D) because it appears a little earlier [10]. Therefore, in most cases, it is the only histological feature of early FVM. The clustered endothelial fragmentation of distal villi is thus a very useful, relatively new histological pattern in the diagnosis of early FVM (2 days) [7], its grading [12], and revealing its temporal heterogeneity, i.e. co-existing with other types of FVM of various duration [13] (Fig. 1E, F).

As opposed to endothelial fragmentation by CD34 immunostaining, the established distal villous segmental avascularity by HE staining is of several days to a couple of weeks duration. If it does not evolve, it is usually associated with a good neonatal condition without hypoxia or metabolic acidosis. To the author, it is therefore unlikely to be blamed for the poor foetal/neonatal condition unless high grade or co-existing with other patterns of placental injury (overlap hypoxic/inflammatory/thrombotic lesions) [6, 14]. On the other hand, the diagnosis of FVM temporal heterogeneity is more important in the investigation of poor neonatal condition/death than the classic and time-honoured isolated clustering of avascular/sclerotic/hyalinised chorionic villi [13], which is also more visible on the double immunostain than on HE-stained slides. Recognition of the CD34-highlighted endothelial fragmentation is particularly useful when co-existing with the FVM lesions of longer duration (sclerotic and/or mineralised clusters of distal villi [remote FVM]) [14]. Such temporal heterogeneity [13] is indicative of an on-going FVM process until the time of birth, probably contributing to or responsible (if high grade) for poor condition and/or death of the foetus/neonate. As mentioned above, the FVM lesions are focal [15]. Diffuse placental villous endothelial fragmentation is usually evidence of recent stillbirth (up to 2 days' duration). However, the author observed diffuse endothelial fragmentation in a case of neonatal death of hypoxic ischaemic encephalopathy on day 2 of life (Fig. 1G, H). The newborn showed nuchal cord 3×, which probably caused a global foetal malperfusion producing the lethal diffuse foetal hypoperfusion of chorionic villi.

Villous endothelial fragmentation of unknown significance

Sclerotic chorionic villi enmeshed in intervillous fibrin are not uncommonly seen in term placentas (Fig. 2F) [4], but they can be a part of, or be seen in association with, other than FVM placental lesions and patterns. It is therefore understandable that their earliest precursor, the villi with endothelial fragmentation and can be seen with villitis of unknown aetiology (Fig 2A, B) [4], chorangioma/chorangiomatosis (Fig. 2C), massive perivillous fibrinoid deposition (Fig. 2D) [16], or intervillous thrombi (Fig. 2E). Like with associated classic sclerotic chorionic villi, the significance of these patterns remains unknown.

Stillbirth

Stillbirth-evoked regressive/involutional placental changes may significantly limit the accuracy of histological diagnosis of FVM [4]. Those changes range from intravascular karyorrhectic debris, through endothelial fragmentation, stromal vascular karyorrhexis, luminal vascular abnormalities of stem villi resembling recanalising thrombi, distal villous hypovascularity, distal villous avascularity, sclerosis, and scattered distal villous clustered mineralisation, the predominant type of lesion useful in the determination the timing of stillbirth [17, 18]. These still-

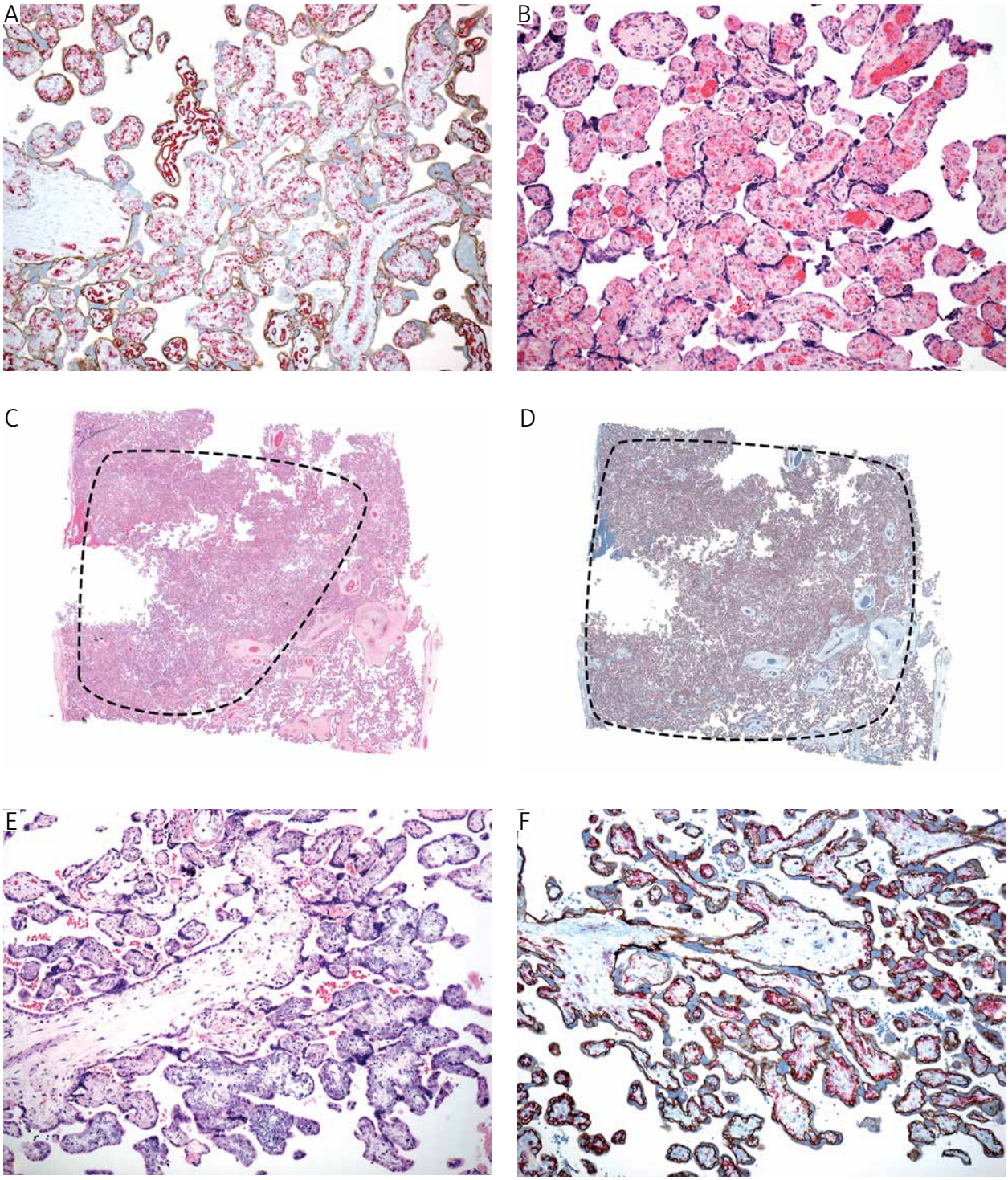
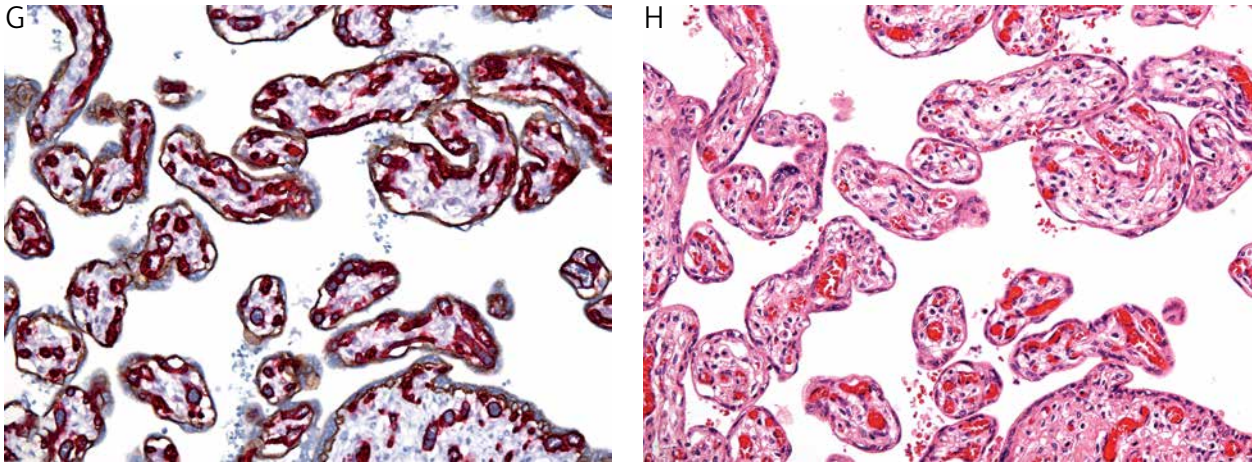


Fig. 1. Recent distal villous foetal vascular malperfusion. A, B) 39 weeks, double nuchal cord, body and foot, bladder outlet obstruction, different sites on same slides. 10×. A) E-cadherin/CD34, endothelial fragmentation. B) Haematoxylin and eosin (HE), stromal vascular karyorrhexis. C, D) 39 weeks, 2 days stillbirth, tight nuchal cord, early foetal vascular malperfusion (FVM), whole slide scans. C) Stromal vascular karyorrhexis (HE). D) Endothelial fragmentation, same case, 2-fold larger area. E, F) Temporal heterogeneity of FVM, 10×, 39 weeks, 2 day's stillbirth, tight nuchal cord. E) Remote distal villous FVM (clustered mineralisation) (HE). F) Same site, recent distal villous FVM (endothelial fragmentation by CD34). G, H) 25 weeks, hypoxic-ischemic encephalopathy, delivery at home, early neonatal death on day 2 of life, diffuse endothelial fragmentation, same site, 20×. G) Endothelial fragmentation by E-cadherin CD34 H) Negative for FVM by HE



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birth-related changes are diffuse, i.e. the same type of lesion is present throughout the placenta [8, 17], depending on the time elapsed from stillbirth to delivery. Diffuse placental villous endothelial fragmentation is evidence of recent stillbirth (up to 2 days duration) (Fig. 3A). However, a similar pattern may be present in placentas from the intrapartum foetal death as mentioned previously and depicted in Figure 1G, H. The diffuse distal villous endothelial fragmentation by CD34 may be seen in association with COVID-19 placentitis [16].

The above-mentioned various diffuse involutional villous changes can obscure the antemortem focal villous lesions (inflammatory lesions, maternal vascular malperfusion (MVM), and of FVM). Nevertheless, in many cases, the diagnosis of FVM is still possible in placentas from stillbirths, particularly recent stillbirths [8]. In intrapartum foetal death and stillbirths of up to a few days' duration, the focal histological changes of FVM are not different than in placentas from live births because the diffuse regressive changes of stillbirth are not developed yet, at least not fully (Fig. 3B, C). Foetal vascular malperfusion lesions of various duration may therefore be seen, the recent ones highlighted with the CD34 immunostain (recent, recent-on-established, recent-on-remote FVM). The endothelial fragmentation can be seen adjacent to avascular distal villi or totally separately on the same slide or on other slides. The temporal heterogeneity of stillbirth regressive changes and co-existing FVM changes may be helpful in establishing whether and the extent to which the FVM may have contributed to foetal death [8]. Foetal vascular malperfusion, particularly low-grade, significantly preceding the stillbirth is less likely to contribute to foetal death than the on-going changes developing until the time of foetal death, because in the former case the foetus was still alive for weeks or several days after a vascular thrombotic event. CD34 immunohistochemistry plays, therefore, a role in the evaluation of stillbirth placentas [7, 8]. Diffusely hypovascular distal villi by CD34 in stillbirth may appear as total villous avascularity on HE staining, thus timing the foetal death to less than 2 weeks [17]. Even in these cases, clusters of mineralised chorionic villi (remote FVM), forming more than 2 weeks before foetal death [18], as opposed to diffuse villous mineralisation of prolonged retained stillbirth, permits the timing not only of stillbirth but also of focal FVM lesions (Fig. 3D).

Maternal vascular malperfusion

Chronic hypoxic placental injury may feature diffuse/global hypervascularity/chorangiosis (pre-uterine hypoxic pattern) or focal hypervascularity/chorangiosis as a component of the uterine hypoxic pattern, both better highlighted by CD34 [6, 19]. Of note, normal vascularity in the third trimester features 2–5 vessels *per* terminal villus, and distal villus hypervascularity of more than 5 capillaries *per* distal villus, reaching at least 10 capillaries *per* 10 villi *per* 10 × 10 – power fields in chorangiosis [1–3]. Focal hypervascularity, not necessarily meeting Altshuler's criteria for chorangiosis, is a feature of the uterine patterns of chronic hypoxic placental injury [6] (Fig. 4A). The patterns may be evaluated on HE-stained slides but are better highlighted with the CD34 immunostain. However, villous capillaries counted on CD34 immunostained slides are more numerous than those counted on HE-stained slides (Fig. 4A); at least 20 vessels *per* villus is therefore needed if chorangiosis is to be diagnosed by CD34 [20]. It is also worth mentioning that the chorangiosis is a meaningful placental diagnosis only when accompanied by other cytological features of the chronic hypoxic placental injury, such as increased syncytial knotting, increased villous cytotrophoblasts (cytotrophoblast hyperplasia), abnormal (increased or decreased) extracellular matrix of chorionic villi, and abnormal

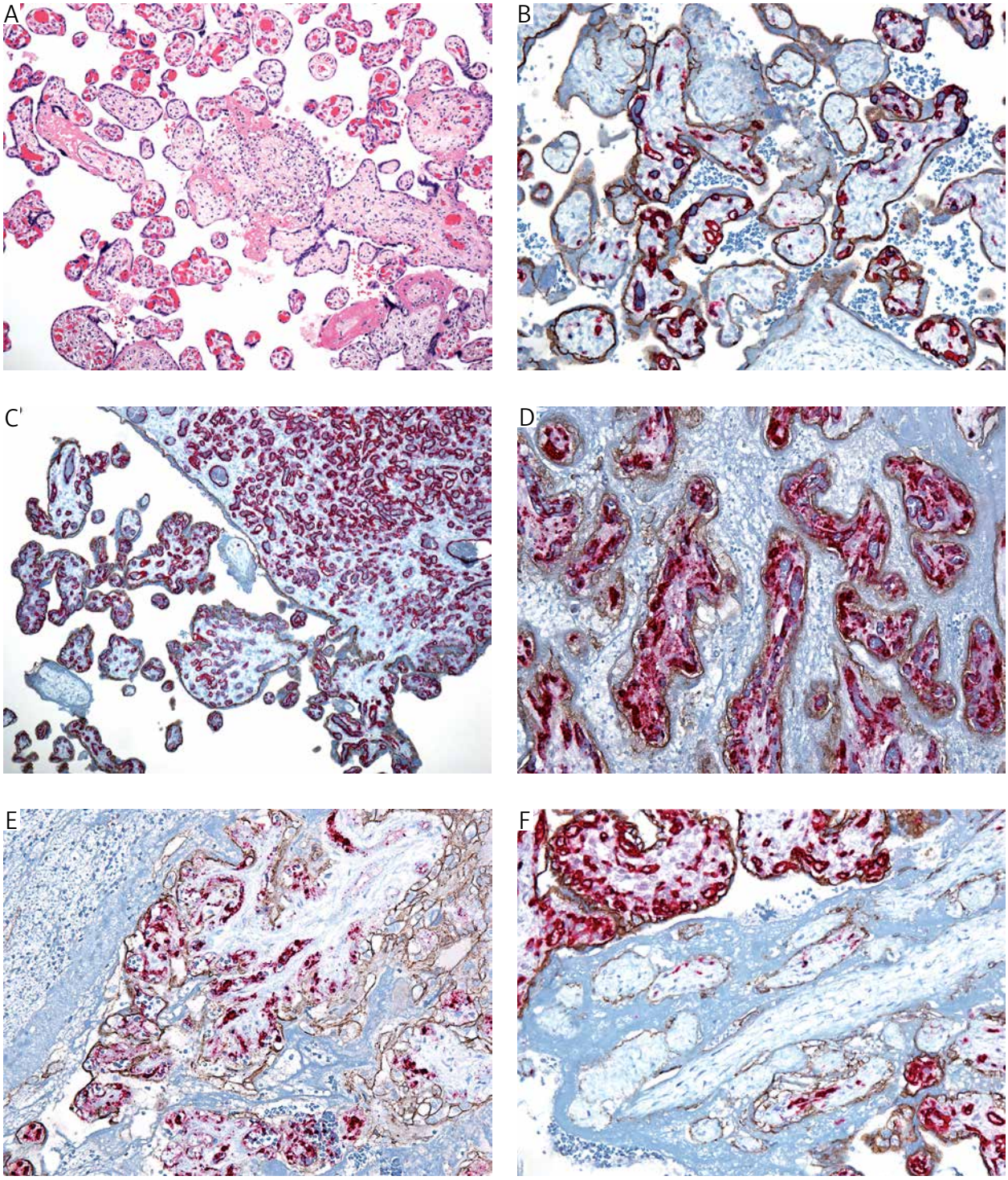


Fig. 2. Villous endothelial fragmentation of unknown significance. A, B) Villitis of unknown aetiology, 38 weeks, 10×, different sites on same slide. A) Haematoxylin and eosin, sclerotic distal villi. B) E-cadherin/CD34 immunostain, endothelial fragmentation. C) 37 weeks, bladder outlet obstruction, anhydramnios, 10×, chorangiomatosis with adjacent avascular villi, and endothelial fragmentation in chorangiomatosis and adjacent villi. D) 33 weeks, decreased fetal movements, cesarean section, massive perivillous fibrin deposition, 20×, endothelial fragmentation by E-cadherin/CD34. E) 36 weeks, gestational hypertension, preterm premature rupture of membranes, E-cadherin CD34, 20×, intervillous thrombus with adjacent endothelial fragmentation of distal villi. F) 36 weeks, immune hydrops, avascular villi and villi with endothelial fragmentation in fibrin

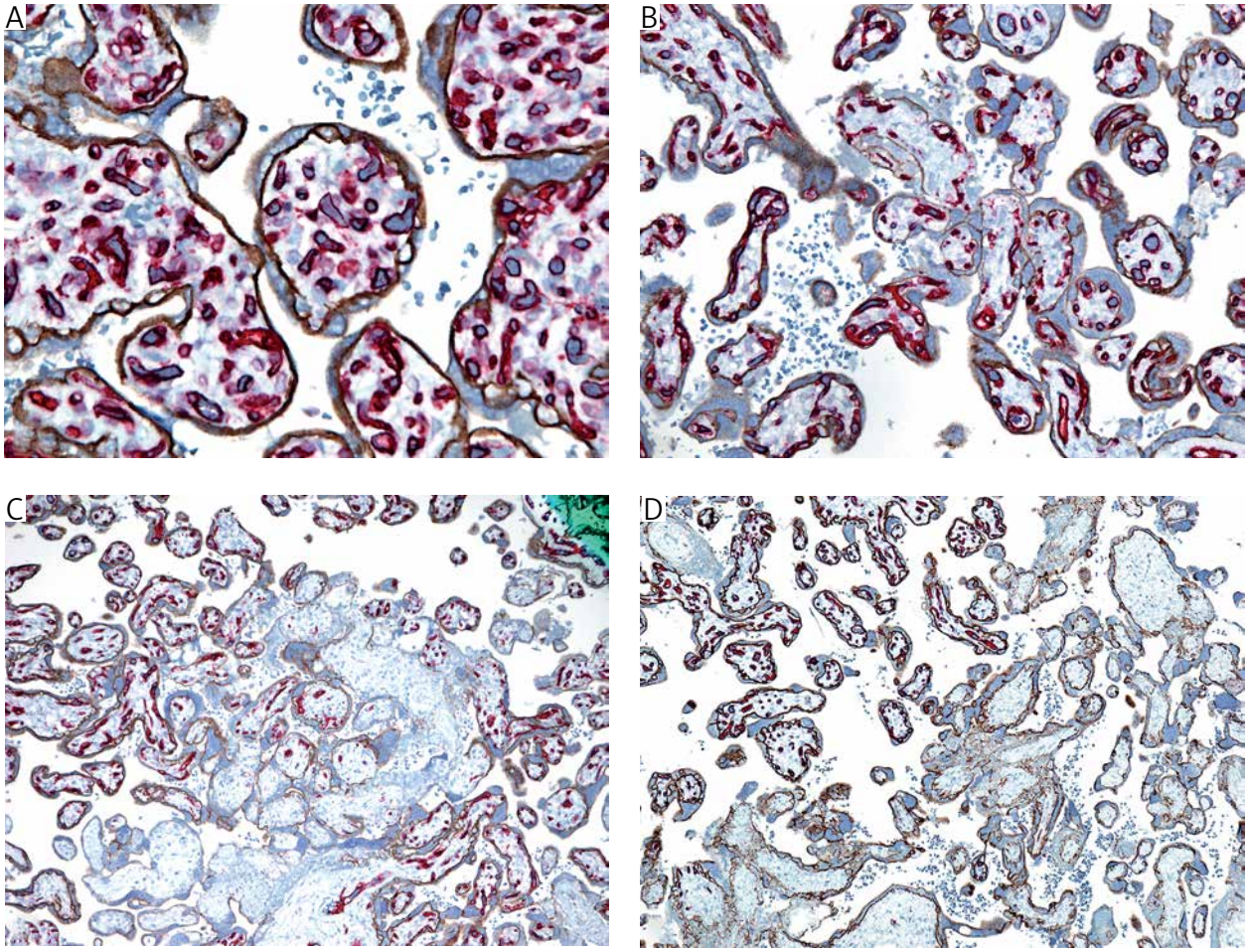


Fig. 3. Stillbirth. A) 37 weeks, foetal growth restriction, skeletal dysplasia, recent stillbirth, E-cadherin/CD34, 40×, diffuse endothelial fragmentation, no foetal vascular malperfusion (FVM). B, C) 40 weeks, true knots and body encirclement of umbilical cord, E-cadherin/CD34, on-going FVM with temporal heterogeneity. B) Endothelial fragmentation, 20×. C) Sclerotic distal villi (other area on slide) (10×). D) 32 weeks, recent stillbirth of one monochorionic twin at 24 weeks, 20×, extensive segmental distal villous FVM (hypovascularity and endothelial fragmentation)

(increased or decreased) number of Hofbauer cells [6, 21]. The isolated villous hypervascularity, even reaching the threshold of chorangiosis, is not a sensu stricto placental lesion, but an adaptive villous change to low-grade hypoxia, usually without any identifiable associations [22]. Villous hypovascularity, or inconspicuous distal villous vessels, are a feature of the post-uterine pattern of chronic hypoxic placental injury, not always easy to evaluate on HE staining [6].

Placental infarction is an acute lesion of MVM [6]. In infarction of longer duration, the tightly packed chorionic villi are avascular [1]. However, CD34 immunostaining can highlight villous capillaries even in the placental infarction that is seemingly avascular on HE staining, which is evidence of a recent onset of the lesion (2 days), thus serving an additional feature in timing the villous infarction, as well as local neutrophilic response [1–3](Fig. 4B). Sometimes, an unexpected zone of endothelial fragmentation of recent FVM is seen at the periphery of placental infarction (Fig. 4C, D).

Trophoblastic lesions

The E-cadherin component of the double immunostain highlights basement membranes of extravillous and villous cytotrophoblasts. More than 7 rows of extravillous trophoblastic cells in placental membranes [23], and more than 5 cell islands or placental septa *per* placental section, with possible chorionic microcyst formation [24] (Fig, 5A–D), is evidence of increased extravillous trophoblasts in the chorionic disc of shallow placental implantation [25, 26]. A rare differential diagnosis includes metastatic carcinoma to the placenta, which also shows the intervillous space location (Fig. 5E, F). E-cadherin may be an alternative immunostain to cytokeratin in that situation, particularly if the double immunostain is used on the block anyway. In mature placenta, villous cytotrophoblasts are commonly seen in 20% of terminal villi, rarely up to 40%, but they never form for a complete mantle around the distal villus under the syncytiotrophoblastic shell [1]. Villous

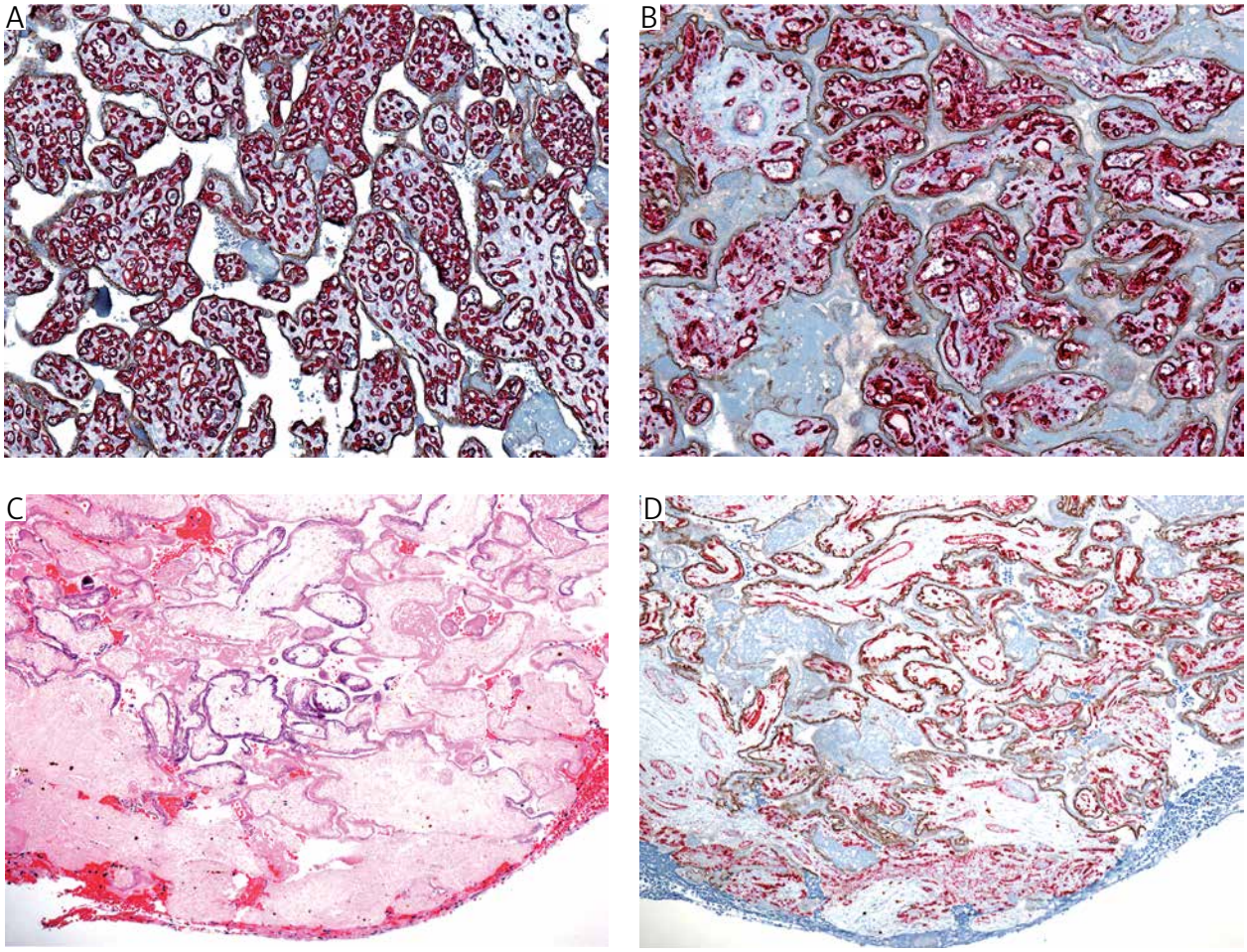


Fig. 4. Maternal vascular malperfusion. A) 37 weeks, double outlet right ventricle, E-cadherin/CD34 immunostain, 10×, chorangiosis. B) 38 weeks, recent infarction, 20×, E-cadherin/CD34 immunostain, endothelial fragmentation in infarcted distal villi. C, D) 34 weeks, double outlet right ventricle, 10×, infarction with peripheral endothelial fragmentation. C) Haematoxylin and eosin. D) E-cadherin/CD34 immunostain

trophoblastic hyperplasia is a feature of pre-uterine (diffusely) and uterine (focally) chronic hypoxic placental injury (Fig. 5G). E-cadherin can also confirm the presence of extravillous trophoblasts between the basal plate myometrial fibres and the Rohr fibrinoid/intervillous space, without the intervening decidua basalis (diagnosis of occult placenta accreta vs. basal plate myometrial fibres) (Fig. 5H). In spontaneously delivered placenta, this is another lesion of shallow placental implantation [26].

Both components of double immunostaining

Widening of the vasculosyncytial membrane, increasing the exchange distance between the maternal blood and foetal blood, is the feature of dysmature/hypomature placenta, a subtype of the pre-uterine pattern of hypoxic placental injury or as an isolated pattern of placental injury [6]. It may be diagnosable on HE staining but is better visualised with the double E-cadherin/CD34 immunostaining (Fig. 6A, B) [9]. Delayed distal villous maturation is characteristic of placentas of diabetic mothers or of pregnancies in which foetuses die "unexpectedly" at term [27– 30].

The double immunostaining can also help in the differential diagnosis of well demarcated, round to oval focal stem mineralization, which may be either a trophoblastic pseudo inclusion (more commonly) or mineralized occluding thrombus (less commonly). Both lesions may look deceptively similar on HE staining. The former will be outlined by the E-cadherin component of the double immunostaining (Fig. 6 C, D), while the latter by the CD34 component of the double immunostaining (Fig. 6E, F). The distinction is important because calcified occluding villous stem thrombi are diagnostic of the remote FVM [10, 15], while trophoblastic pseudo-inclusions may be non-specific, or seen in placental aneuploidies (e.g. partial hydatidiform mole and other aneuploidies, due to the convoluted villous outlines) [3].

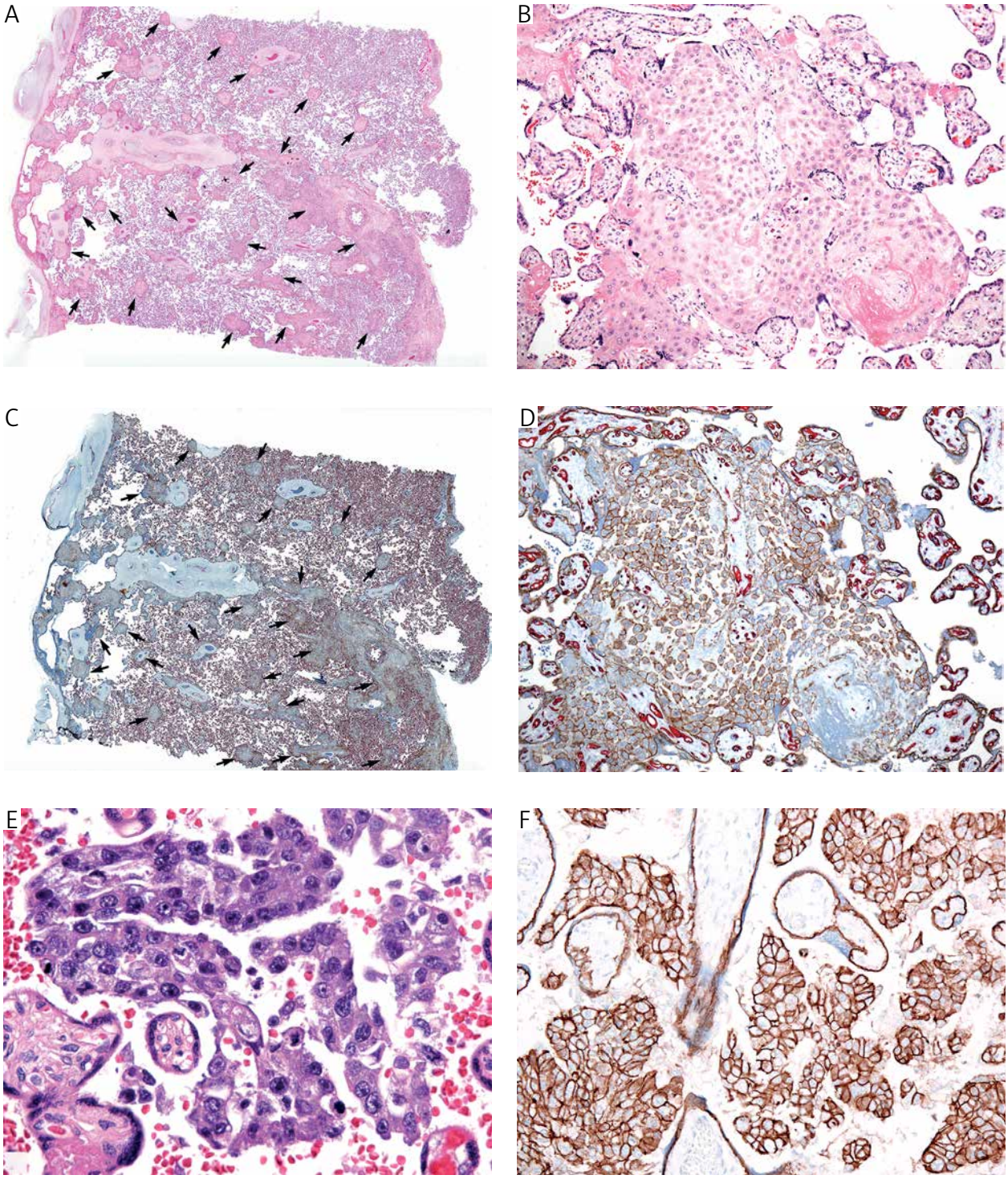
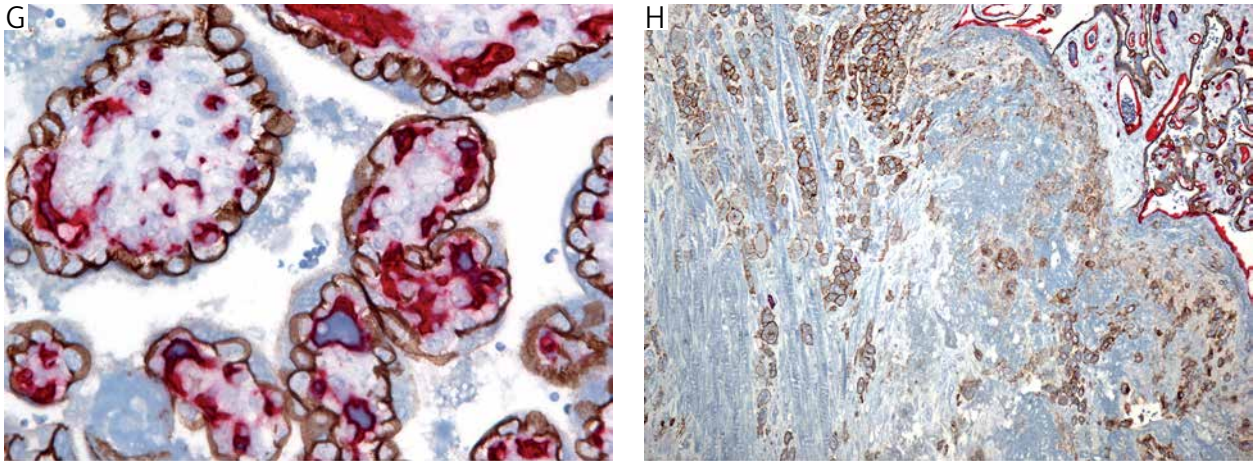


Fig. 5. Non-foetal vascular malperfusion trophoblastic lesions and mimics. A–D) 38 weeks, foetal growth restriction, lobar holoprosencephaly, cleft lip and palate, increased extravillous trophoblasts. A, C) Whole mount slides, arrows – cell islands/placental septa. B, D) A single cell island 10×. A, B) Haematoxylin-eosin. C, D) E-cadherin/CD34 immunostain. E, F) 31 weeks, preeclampsia, metastatic breast carcinoma, 10×. E) Haematoxylin and eosin. F) E-cadherin CD34. G) 35 weeks, diabetes mellitus, chronic hypertension, foetal omphalocele, almost circumferential villous trophoblastic hyperplasia and endothelial fragmentation, E-cadherin CD34, 40×. H) 34 weeks, gastroschisis, occult placenta accreta, E-cadherin CD34, 10× absence of decidua between basal plate myometrial fibres and extravillous trophoblasts of maternal floor



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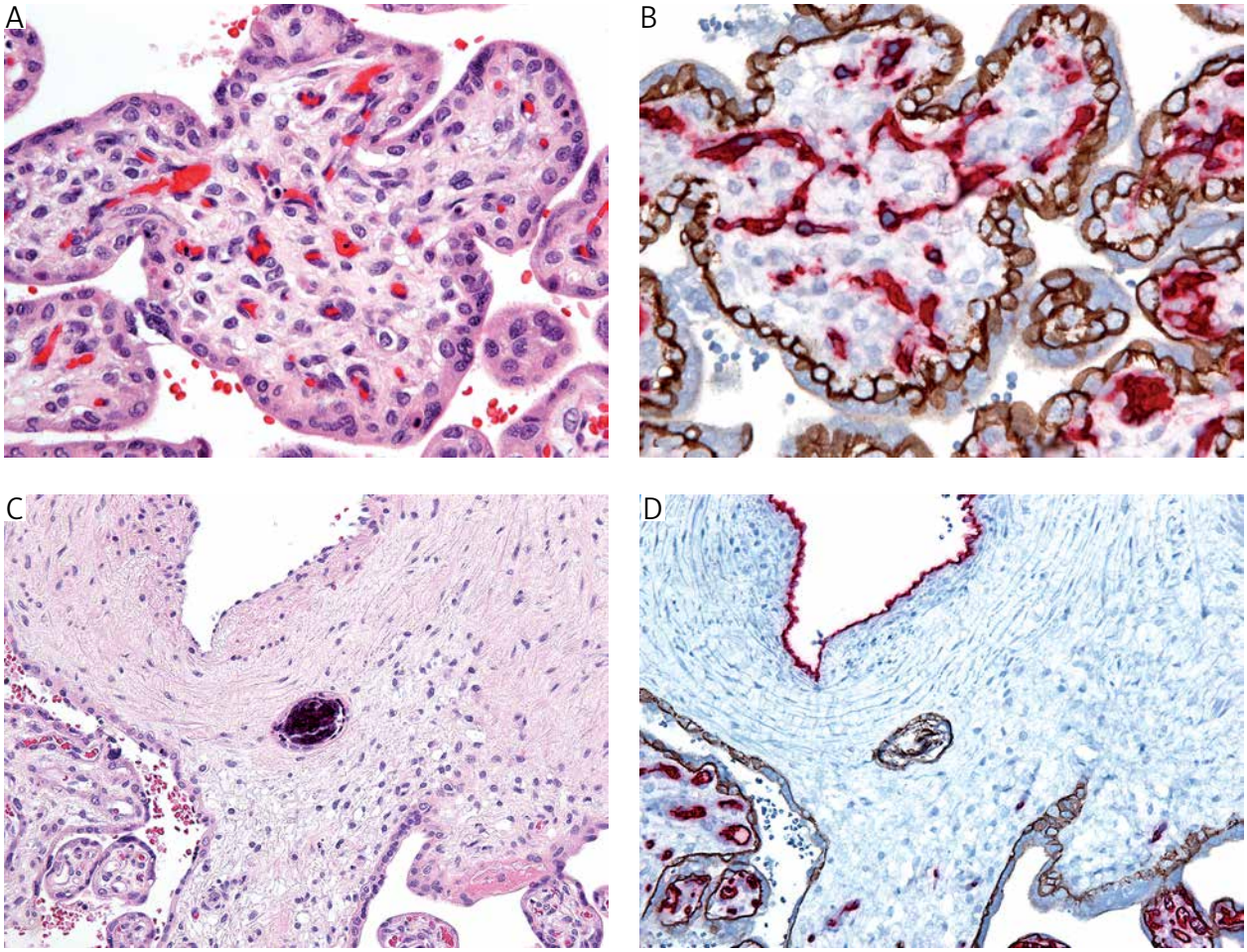
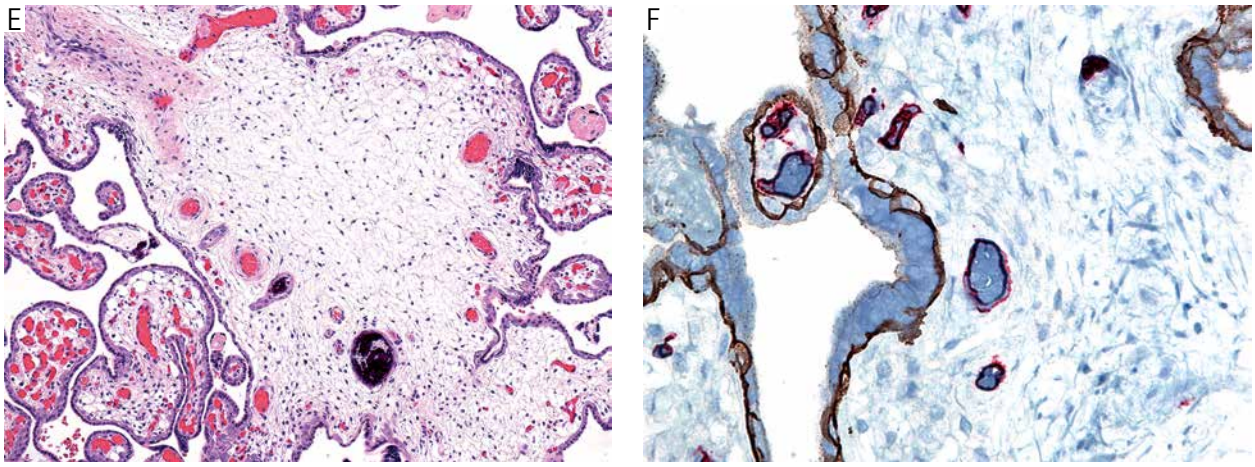


Fig. 6. Combined E-cadherin and CD34 evaluation. A, B) 35 weeks, diabetes mellitus on diet, chronic hypertension, polyhydramnios, omphalocele 40×, dysmaturity/hypomaturity (delayed villous maturation) with widening of vasculosyncytial membranes. A) Haematoxylin and eosin (HE). B) E-cadherin/CD34. C, D) 37 weeks, gestational diabetes mellitus on diet, polyhydramnios, cleft lip and palate, calcified stem trophoblastic pseudo inclusions, 20×. C) HE. D) E-cadherin CD34. E, F) 37 weeks, early amnion rupture sequence, calcified stem vascular thrombi. E) HE, 10×. F) E-cadherin CD34 20×



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Conclusions

The current review shares our experience with the double E-cadherin/CD34 immunostaining in histological placental diagnosis. We routinely perform the stain on a grossly unremarkable placental section in our population of predominantly foetal congenital malformations, which is at high risk for FVM (particularly the mass-forming anomalies) and foetal aneuploidies. It helps us to diagnose the FVM, particularly early, with endothelial fragmentation, the lesion that is not visible grossly or on routine HE-stained sections. In selected cases, it is useful for revealing the temporal heterogeneity of FVM lesions, solely or in conjunction with other placental lesions and patterns, to establish the cause of foetal death or poor neonatal condition. However, it must be understood that the endothelial fragmentation may be seen in association with other placental lesions, particularly chronic villitis of unknown aetiology and the lesions of MVM, which, because of a different pattern of the distal villous involvement, should not produce any confusion. Also, the double immunostain is invaluable in diagnosis of villous hypomaturity/dysmaturity with widening of vasculosyncytial membranes.

Disclosures

1. This study was presented at the Society for Pediatric Pathology Spring Meeting, Baltimore, Maryland, U.S.A., 23 March 2024.
2. Assistance with the article: None.
3. Financial support and sponsorship: None
4. Conflicts of interest: None.

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