Fetal Vascular Malperfusion

Amer Heider, MD

Fetal vascular malperfusion, also known as fetal thrombotic vasculopathy, remains an underrecognized pathologic finding and should be noted during placental evaluation.

Objective.—To review histologic findings, gain familiarity with the updated terminology, and to recognize important clinical associations with this entity.

Data Sources.—University of Michigan cases, PubMed search, multiple review articles including recent placental workshop group consensus statement, and selected book chapters.

Conclusions.—Multiple histologic patterns of fetal vascular malperfusion have been described including thrombosis, avascular villi, villous stromal-vascular karyorrhexis, intramural fibrin thrombi, and stem villous vascular obliteration. Various underlying etiologies can be involved in fetal vascular malperfusion. Cord lesions including abnormal insertion, length, and coiling are important causes. Maternal vascular malperfusion such as preeclampsia, hypercoagulable states, lupus anticoagulant, and sometimes diabetes have been associated with this condition. Fetal cardiac dysfunction/ malformations and severe fetal inflammatory response in the setting of ascending intrauterine infection have also been attributed to this important finding. Fetal vascular malperfusion has been implicated in several significant and sometimes devastating clinical associations; these include intrauterine growth restriction, poor perinatal outcome, fetal demise, and neurodevelopmental sequelae. A diagnostic challenge may be encountered in cases with prior intrauterine fetal death, since degenerative changes post demise result in a similar histomorphologic picture. The diffuse versus the focal nature of the lesions may help in the distinction.


Although fetal thrombotic vasculopathy diagnosis has been emphasized recently,\textsuperscript{1–4} it is still an underrecognized, clinically important entity that should be identified during placental examination. Fetal vascular malperfusion (FVM) is the recommended new terminology for fetal thrombotic vasculopathy by the Amsterdam Placental Workshop Consensus Statement.\textsuperscript{5} Any location in the vascular tree can be involved starting from umbilical vessels through chorionic vessels and stem villi ending with the terminal villi.\textsuperscript{6,7}

Multiple histologic findings are encompassed under the umbrella of fetal vascular malperfusion.\textsuperscript{1–7} These patterns include thrombosis of the fetal chorionic plate or umbilical cord vessels, which can be observed with careful gross examination. Mural organizing thrombosis with lamination may be seen along with vascular muscular degeneration and ectasia (Figures 1 and 2). Older thrombi are associated with calcifications (Figure 3), and remote thrombotic lesions reveal complete luminal obliteration. Stem villous or arterial occlusion is typically associated with changes in its villous downstream ramifications (Figure 4). Venous obstruction appears more frequently. However, the difference and clinical implication of distinguishing arterial versus venous thrombosis are not well elucidated.

Stem villous obliteration (fibromuscular sclerosis) is characterized by remarkable thickening of vascular walls with luminal obliteration. It is probably one of the more difficult lesions to precisely recognize but appears more frequently in histologic sections adjacent to the cord insertion site (Figure 5). Intramural fibrin deposit (intimal fibrin cushion) may be the easiest manifestation to recognize. Laminated fibrin in the intima or in the muscular wall is seen, typically nonocclusive (Figure 6). Older lesions are associated with dystrophic calcifications. Thrombi and intramural fibrin are most common in chorionic plate surface veins and in major villous stem vessels. The endothelial cells degenerate and thrombosis subsequently develops.

Another histologic feature of FVM, associated with prolonged occlusion, is the presence of avascular villi. Grossly pale triangular foci may be noted, especially post fixation. Microscopically, the terminal villi demonstrate loss of villous capillaries with stromal fibrosis. The syncytiotrophoblasts are preserved as the intervillous maternal circulation is maintained ( Figures 7 and 8). The initial criteria were defined as the presence of foci of more than 5 terminal villi showing total loss of capillaries.\textsuperscript{1} Subsequently, the term fetal thrombotic vasculopathy (FTV) was reserved for groups with 15 or more affected terminal villi per section (at least 2), revealing avascular villous morphology or villous stromal karyorrhexis.\textsuperscript{7} The recent proposed criteria include the presence of at least 3 or more foci of 2 to 4 terminal villi
Figure 1. Fetal vascular malperfusion with grossly recognized tan fixed thrombus in fetal chorionic plate vessels. A case associated with 38 weeks’ gestation stillbirth.

Figure 2. Organized thrombosis with vascular ectasia indicating a premortem process; same case as above (hematoxylin-eosin, original magnification ×2).

Figure 3. Older thrombotic lesions can be calcified and acute chronic thrombosis would be suggested (hematoxylin-eosin, original magnification ×2).

Figure 4. Stem villous arterial occlusion with avascular villi distributed in its ramification (hematoxylin-eosin, original magnification ×4).

Figure 5. Stem villous vascular luminal obliteration with markedly thickened muscular wall; fibromuscular sclerosis (hematoxylin-eosin, original magnification ×4).

Figure 6. Nonocclusive intramural fibrin with developing thrombosis (hematoxylin-eosin, original magnification ×10).
Figure 7. Large focus of avascular villi with stem villous calcifications. Patchy pattern with preserved villi on the right lower portion (hematoxylin-eosin, original magnification \( \times 4 \)).

Figure 8. More advanced fetal vascular malperfusion lesion overlaps with postdemise degenerative changes (hematoxylin-eosin, original magnification \( \times 10 \)).

Figure 9. Villous stromal-vascular karyorrhexis (hematoxylin-eosin, original magnification \( \times 20 \)).

Figure 10. Villous stromal-vascular karyorrhexis. Loss of integrity of the vascular wall; fragmentation and extravasation of red blood cells in the stroma with early septation (hematoxylin-eosin, original magnification \( \times 20 \)).

Figure 11. Long and hypercoiled cords with deep indentations are associated with fetal vascular malperfusion and increased risk of cord compression with demise.

Figure 12. Abnormal umbilical cord marginal insertion.
demonstrating total capillary loss in the small foci category, whereas involvement of more than 10 villi is suggested to represent the large foci category.3

Villus stromal-vascular karyorrhexis, previously described as hemorrhagic endovasculitis, is another manifestation of FVM.1,6 It is characterized by villous endothelial karyorrhexis with congestion, red blood cell extravasation, stromal apoptosis, and septation of the endothelial lumens (Figures 9 and 10). Three or more foci of 2 to 4 terminal villi demonstrating karyorrhexis of fetal cells (nucleated erythrocytes, leukocytes, endothelial cells, and/or stromal cells) with preservation of surrounding trophoblast has been the proposed criteria.25 Earlier publications suggested that veno-occlusive disease is implicated in the development of this lesion, which was initially identified as playing an important role in perinatal adverse poor outcome.5,10–12 Nonetheless, it represents a form of microangiopathy, similar to glomerulopathy associated with hemolytic uremic syndrome, subsequent to vasodestructive mechanism and endothelial injury leading to thrombosis.6,13 Villous stromal karyorrhexis appears to be an earlier stage of the same process and underlying etiology within the spectrum of avascular villi.1,2 Earlier phases have more pronounced congestion and hemorrhage, and later stages will progress toward completely obliterated and avascular villi. Villitis of unknown etiology can also be seen in the setting of vascular damage and is commonly associated with stem villous obliteration or foci of avascular villi.1,2,5

Multiple placental, maternal, and fetal underlying etiologies can result in FVM. Umbilical cord pathology with compromise to blood flow and thrombosis of umbilical vessels are important and major causes.4,14–21 Obliteration of the venous circulation is the main concern, as the umbilical vein is more prone to compression compared to the arteries. Congestion and venous stasis lead to endothelial injury, subsequent fibrosis, thrombosis, FVM, and vascular ectasia. Vasospasm can occur and may augment the circulatory compromise. Abnormal length with extra long (more than 80 cm) and short cords (less than 35 cm) is important to note. Hypercoiled cords (more than 3 coils per 10 cm) with deep grooves in the Wharton jelly are antecedents to blood flow abnormalities. It has been suggested that certain gross patterns of coiling with most significant indentation, including segmented and linked (Figure 11), are significantly correlated with histologic evidence of chronic fetal circulatory obstruction, FVM/FTV, and stillbirth.19 Hypocoiled and thin cords are also more prone to compression of the vessels. In addition, abnormal insertion, particularly velamentous and marginal (Figure 12), harbors a higher risk of umbilical cord compression, entanglement, vascular compromise, fetal growth restriction, and adverse perinatal outcome. True knots, especially tight ones, are also associated with cord accidents and FVM.

Abnormalities in maternal circulation (maternal vascular malperfusion) can lead to fetoplacental unit underperfusion and FVM.22–27 Preeclampsia hypertension, hypercoagulable states such as antiphospholipid antibodies, lupus anticoagulant, factor V Leiden mutation, protein S deficiency, and protein C deficiency have been documented in FVM cases. Maternal diabetes is sometimes associated with FVM.28,29 A recent study30 demonstrated a 2.6-fold increased risk but it was not statistically significant. It is possible that better management with well-controlled cases may account for changes in prevalence and association. *Maternal vascular malperfusion* is the new preferred terminology for decidual vasculopathy.5,27–31 The morphologic features include placental infarcts, decidual arteriopathy with foamy histiocytes, fibrinoid necrosis, retroplacental hemorrhage (abruption clinically), accelerated (advanced) villous maturation with distal villous hypoplasia, and lack of physiologic remodeling of the spiral arterioles (Figures 13 and 14).

Fetal causes of FVM include cardiac malformation, cardiac dysfunction, polycythemia, and large vascular anomalies.32 It is debatable whether fetal thrombophilia is linked to FVM; some authors showed a significant association while others did not.33–35

Severe cases of ascending intrauterine infection (acute chorioamnionitis) can be associated with FVM.2 Thrombosis of fetal chorionic plate vessels, especially in the presence of severe fetal inflammatory response or funisitis, is observed (Figure 15). The mechanism is caused by damage to the endothelium and vascular walls secondary to the inflammatory changes and cytokines.2,3,6,14 Cytomegalovirus infection is reported in cases with FVM.30,36 Cytomegalovirus is known to have vascular endothelial affinity, which causes endothelial cell damage and can lead to FVM.

The clinical complications associated with FVM/FTV have been largely studied, in part owing to medical litigation and stillbirth settings.8 Fetal vascular malperfusion has been strongly associated with adverse perinatal outcomes, fetal growth restriction, intraterine fetal demise, thromboembolic events/necrosis of multiple fetal organs, and increased obstetric and maternal complications. Central nervous system complications were recognized earlier, as the brain parenchyma has higher susceptibility to vascular alterations. Prenatal/neonatal stroke with intracranial hemorrhages, infarcts, neonatal encephalopathy, cerebral degenerative changes, cerebral palsy, and long-term neurologic impairments have been reported in various studies. In addition, systemic thrombosis with necrosis and infarctions in multiple neonatal and fetal organs including liver, renal vessels, pulmonary circulation, and myocardium are also identified. Disruption sequences with limb deficiencies and intestinal atresia have been linked to FVM. Furthermore, obstetric complications with nonreassuring fetal heart tracing, need for emergency delivery procedures, cesarean deliveries, and poor immediate ex utero adaptation are noted.

The initial criteria for classification and grading of FVM/FTV concluded that poor clinical outcome was correlated with the severe cases, harboring extensive avascular villi or at least 2 foci consisting of more than 15 distal contiguous villous vascular karyorrhectic/avascular villi.4 A more recent study1 has confirmed the importance and the utility of the Society of Pediatric Pathology grading in regard to the association with poor outcomes, intracranial hemorrhage, neonatal coagulopathy, neurologic and developmental delay, and cerebral palsy. It also assessed the significance of large vessel lesions and designated the severe category as occlusive or nonocclusive cord thrombi and/or 2 or more thrombi in the chorionic plate and/or stem villous vessels. Large vessel lesions were associated with significant cognitive delay and developmental issues, intraterine growth restriction, and nonreassuring fetal indications. On the other hand, nonsevere lesions did not have a significant difference from control in regard to morbidity or neurologic

References 1, 3, 7, 8, 11, 30, 31, 33, 37–48.
A 2-tier, semiquantitative grading system is suggested by the Amsterdam group. The low-grade pattern likely represents a segmental form of FVM, referring to occlusion of chorionic or stem villous vessels, or stem vessel obliteration. The severe form (high grade) is a global form of FVM, indicating a partial or intermittent obstruction in umbilical blood flow with venous ectasia, intramural fibrin deposition in large vessels, and/or foci of avascular or karyorrhectic villi. The application of this system may have a better prediction for subsequent clinical outcome and complications. Nonetheless, larger clinicopathologic studies are needed to further investigate and accurately assess its utility and practical application.

Placenta cases associated with prolonged intrauterine fetal demise pose a challenge in establishing the diagnosis of FVM with certainty. Cessation of blood circulation post demise results in a similar histologic picture including villous stromal karyorrhexis, avascular villi, fibromuscular sclerosis, vascular luminal obliterations, and degenerative changes. The causal relationship of FVM to demise can be difficult to reliably establish and would be easily debatable, particularly given that umbilical cord compression and FVM are common causes for third-trimester stillbirth and perinatal morbidity. Proposed criteria for cord accident connection to stillbirth include morphologic features of FVM in a regional distribution, which should be independent of other placental lesions. Subsequent study revealed high specificity for cord compression relationship to demise when the “complete criteria” were met. However, the sensitivity was very low. Two morphologic observations can help in distinguishing between maceration stillbirth changes and predemise FVM. Contrary to the regional distribution in true predemise FVM and relatively greater stromal fibrosis, postdemise changes tend to be diffuse and reflect somewhat similar stages of degeneration. Sometimes an alternating pattern with discrete avascular villi and more clearly viable ones may also be helpful in the distinction. Additionally, the presence of intravascular fetal thrombi with organizing fibrin layering and calcifications is another supportive feature to suggest premortem pathology.

In summary, FVM is a very important finding to recognize during placental examination. Albeit not common, it has been associated with adverse fetal/perinatal outcome, stillbirth, and multiple obstetric and fetal complications and neurologic impairment. Once standardized diagnostic criteria and unified terminology are adopted, larger long-term prospective studies may be of interest for further risk stratification of complications associated with this entity. Caution is warranted in cases with remote stillbirth, and gaining familiarity and experience is crucial in these situations.

The author would like to thank Brian Soles, MD, for obtaining some selected references.


