Chapter 21

Fetal Thrombotic Vasculopathy

General Considerations

The umbilical vessels insert onto the placental surface, branch, and then at the periphery turn abruptly toward the maternal surface, branching repeatedly to finally become villous capillaries. Blood is returned from the capillary loops to the umbilical cord by veins that merge. In the overwhelming majority of cotyledons, there is *a 1:1 relation between artery and vein* at the periphery and each artery "supplies" a single cotyledon (placentone). It is remarkable that at least *the larger arteries always cross over the veins on the placental surface*. They can thus be readily identified by macroscopic examination, while histologically it is nearly impossible to make this distinction. It is interesting to note that the circumferential architecture of the placental surface vessels is asymmetric. This is the result of hemodynamic thinning in that the pressure buckles and thins the superficial portions of the vessels, whereas the "fixed" portions resist this pressure. This phenomenon of thinning of the superficial aspect of chorionic vessels is also shared with cord vessels.

Thrombosis in the Fetal Circulation

Pathologic Features

Thrombosis: **Mural and occlusive thrombi** occur frequently in the superficial placental vessels and their villous ramifications. They are

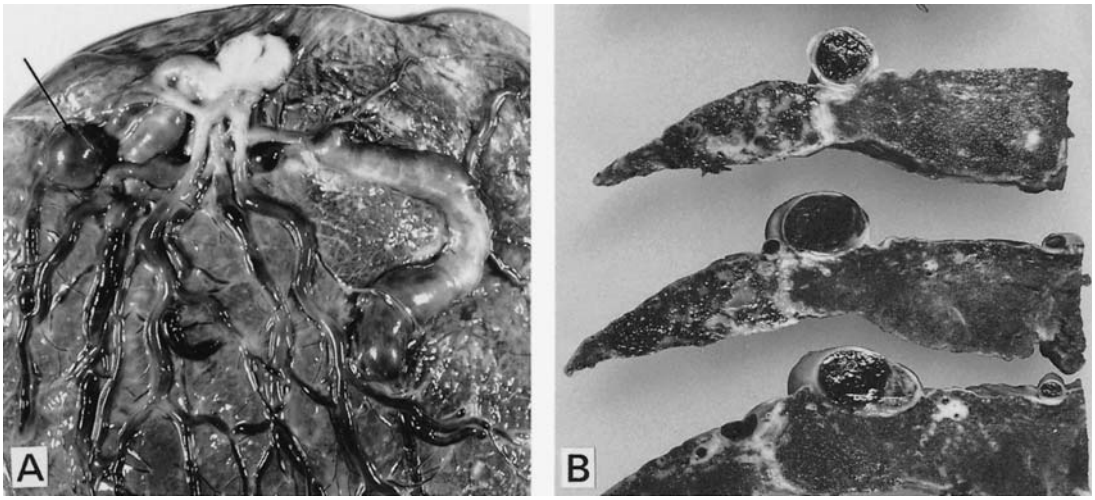

Figure 21.1. (A) Distended surface chorionic vessel (arrow) and a distended and thrombosed vein (at right). (B) Layered thrombi are apparent on cut section of the same placenta.

more commonly present in the veins and are variably located across the fetal surface and within the placenta. They are only occasionally accompanied by thrombi in the umbilical cord. *Surface thrombi can be recognized by careful gross examination.* When the vessel is hugely distended (Figure 21.1), the identification of thrombosis is easy. Much more frequently overlooked are such thrombi as seen in Figure 21.2. When thrombi are fresh, their *gross appearance is that of a slightly enlarged vessel that may have an unusual color, usually tan or white* (Figure 21.3). The vessel is not so shiny and blue as normal vessels. One is also unable to move the blood mechanically in thrombosed vessels.

Mural thrombosis is much more frequent than complete obliteration of the vessel (Figures 21.4, 21.5). Thrombosis may even *calcify* (Figures

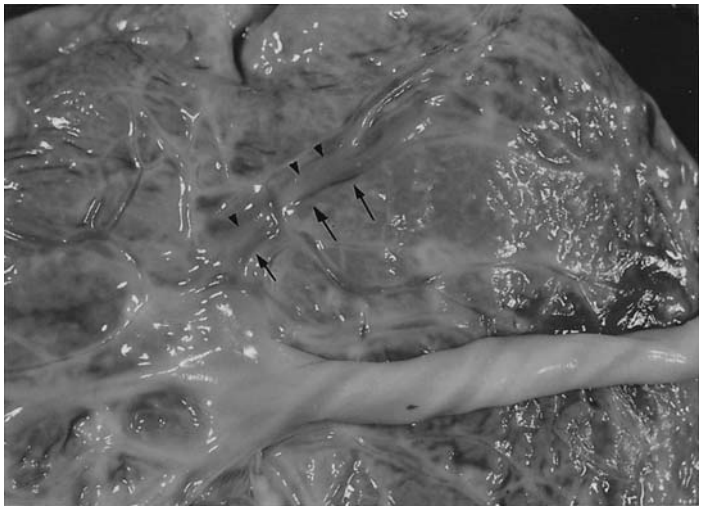

Figure 21.2. Thrombus of an umbilical vein tributary (arrows). The infant developed cerebral palsy.

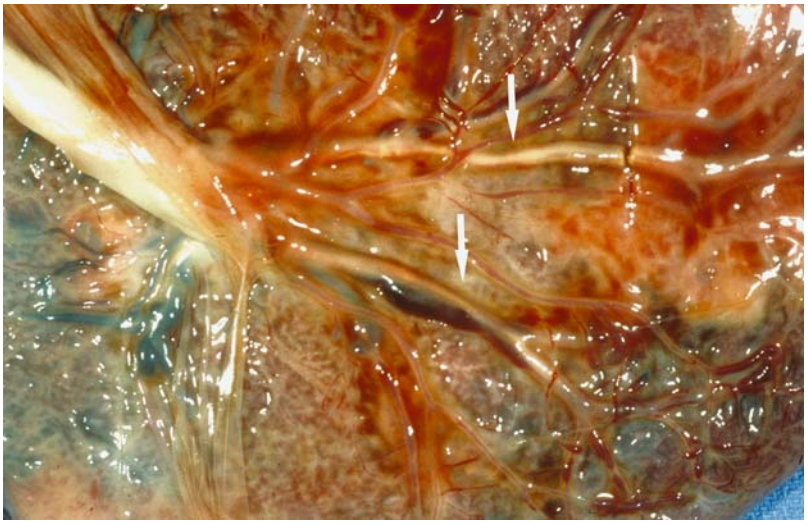

Figure 21.3. Thrombi in chorionic vessels are visible as tan-white streaks (arrows).

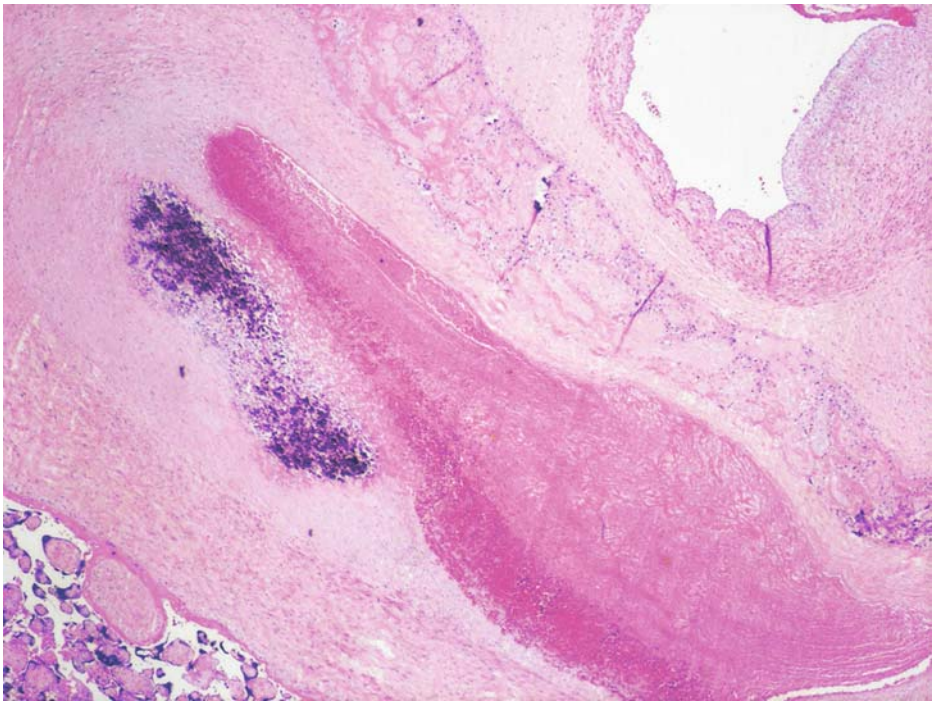

Figure 21.4. Mural thrombi in surface vein with associated calcification. H&E. ×20.

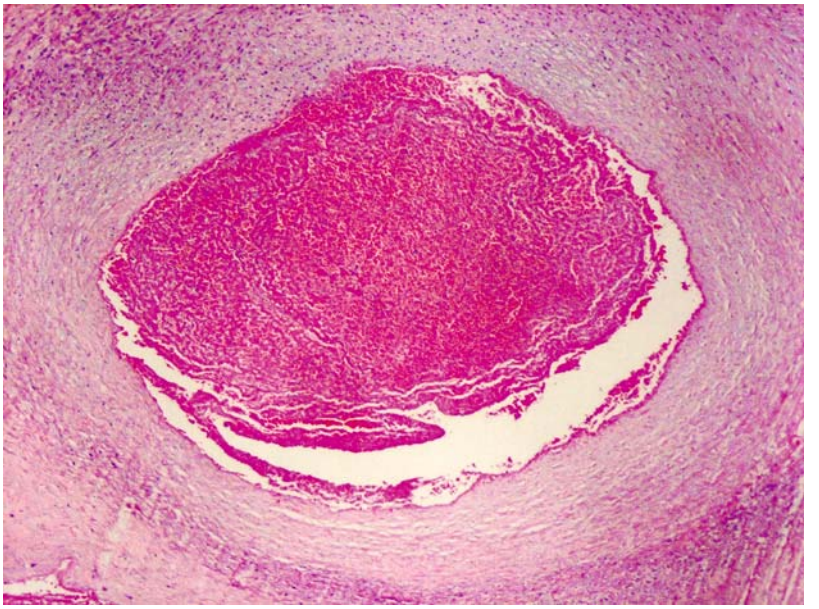

Figure 21.5. Nearly occlusive thrombus in a dilated chorionic vein associated with long cord and stillbirth. H&E. ×20.

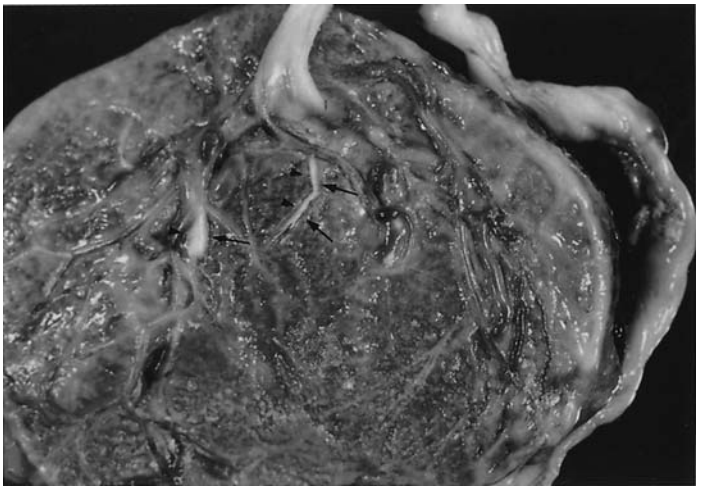

Figure 21.6. Partially calcified thrombi (arrows) associated with a long (77 cm) umbilical cord.

21.6, 21.7) but variations are frequent; and when thrombosis has occurred a *long time before examination, the vessel may obliterate completely. They then appear as a rounded fibromuscular structure without a lumen* (Figure 21.8). True organization of dead tissues, as the pathologist knows it from renal or splenic infarcts, is rare in all placental degenerative lesions. That is, removal of debris by phagocytes and ingrowth of

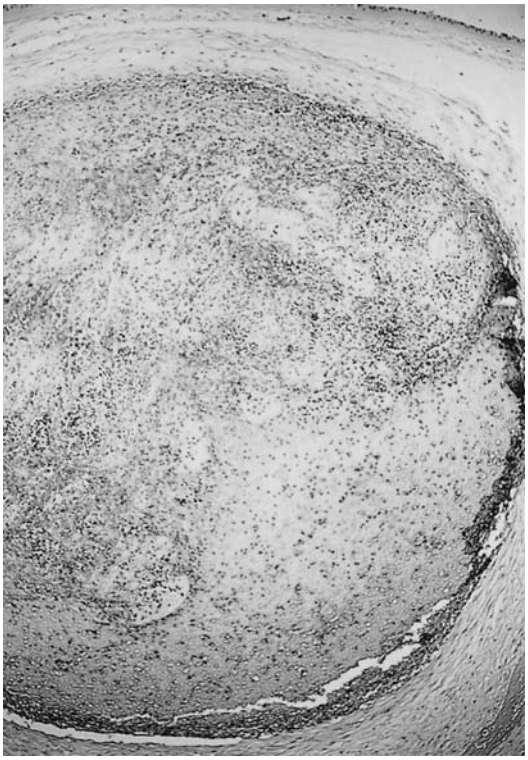

Figure 21.7. Occlusive thrombus with partial calcification (right margin) of surface vein. H&E. ×26.

granulation tissue and fibrous tissue are phenomena not seen in true placental infarcts, nor do these occur in thrombosed placental vessels. Rather, these lesions shrink, and some phagocytes may appear, but eventually they become calcified or the vessel atrophies. It may eventually disappear completely, becoming unrecognizable as a former vessel.

Avascular Villi: If the thrombi have been *occlusive for a prolonged time*, *particularly if the thrombi are present in the arterial circulation*, the villous tree may become avascular and atrophy (Figure 21.9). These villi then become **avascular villi**. Avascular villi are considered direct evidence of thrombosis in the fetal circulation, even without the presence of frank thrombi within vessels. Larger foci of avascular villi may be visible *grossly as a triangular area of pallor with the consistency of villous tissue*. The base is usually at the basal plate, and may be easier to visualize in a fixed specimen. Microscopically, the area is *sharply demarcated* from the surrounding normal villous tissue. Avascular villi differ from true infarction in that the trophoblast is viable because it is still being perfused by the maternal blood in the intervillous space. There may, however, be increased syncytial knotting. The villous vessels and stroma essentially atrophy over time due to loss of the fetal circulation. *The stroma is usually pink and hyalinized without vessels. Occasional hemo-*

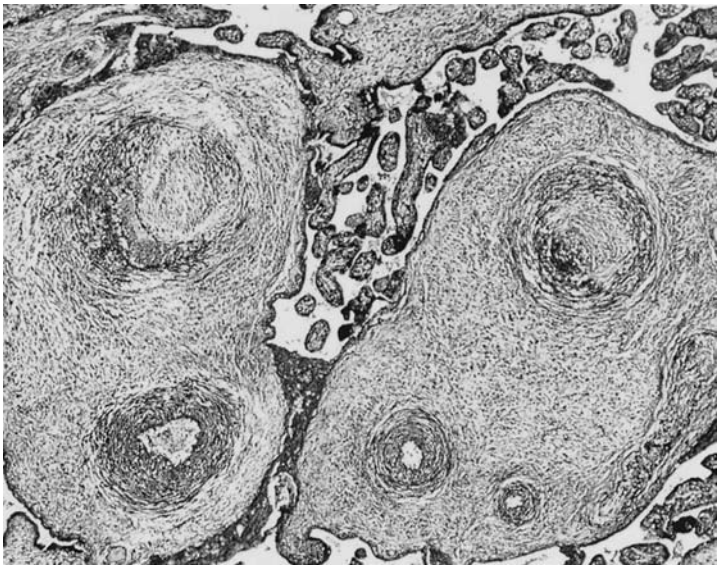

Figure 21.8. Muscular hypertrophy and old occlusions in stem vessels. H&E. ×260.

siderin deposits may be present. At the apex of the lesion, one may occasionally find the supplying artery with thrombosis. In older lesions, the distal stem vessels may show thickening of the vascular walls, ultimately with obliteration of the lumen. Caution must be used in cases of stillbirth, as loss of the entire fetal circulation will cause a similar but diffuse change.

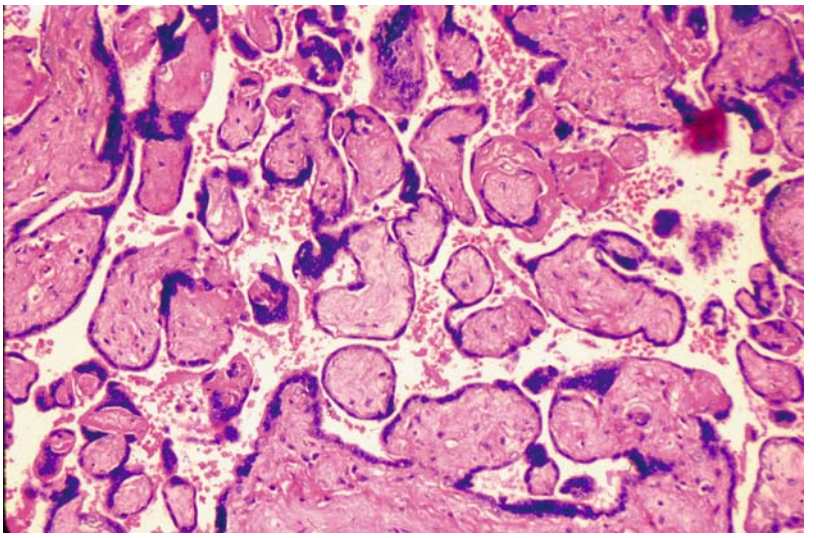

Figure 21.9. Avascular villi demonstrating hyaline quality of villous stroma, which is devoid of vessels. Extensive thrombosis was also present in surface vessels. H&E. ×100.

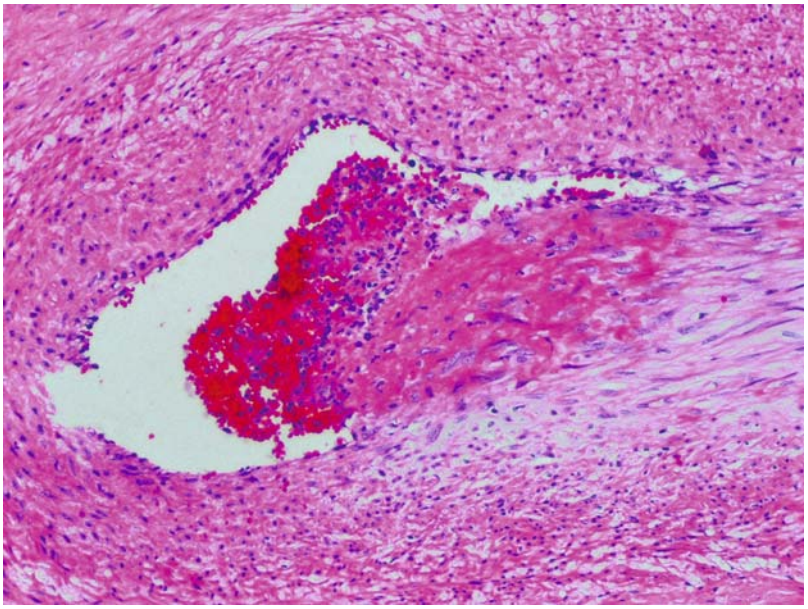

Figure 21.10. Intimal fibrin cushion. H&E. ×100.

Intimal Fibrin Cushions: **Intimal fibrin cushions** or intimal vascular cushions are microscopically similar to those that pathologists find in the pulmonary vessels of patients with pulmonary hypertension. *Laminated fibrin is deposited in the intima of the vessel and bulges out into the lumen like a "cushion"* (Figure 21.10). The lumen is often not obstructed to a significant degree. At times, one may see *accumulation of what appears to be mucopolysaccharide or ground substance within the intima as well*. This appears as pale, blue material separating the vascular smooth muscle from the endothelium. Calcifications may occur in older lesions (Figure 21.11).

Fibromuscular Sclerosis: A vascular lesion of small vessels called **fibromuscular sclerosis** has been found to be associated with abnormal Doppler flow. It is often seen in conjunction with terminal villus deficiency. In this lesion, there is *an increase in the smooth muscle and fibrous tissue of the stem arteries leading to narrowed lumens*. Occasionally, complete occlusion may occur.

Hemorrhagic Endovasculitis: Finally, a group of lesions referred to as **hemorrhagic endovasculitis** or **HEV** have been described. The lesions are divided into two groups, bland and active lesions. **Bland lesions** consist of *extravasated red blood cells in the stroma, karyorrhexis of the nuclei of endothelial and blood cells, and septation* (Figure 21.12). The integrity of the vascular walls is lost, and they may be hard to identify on histologic section. Similar to avascular villi, some of the bland lesions may be present in the setting of fetal demise. In the latter case, they tend to be more diffuse, but the differences are often subtle. **Active lesions** are those with *evidence of inflammatory infiltrates in the villi, which is called*

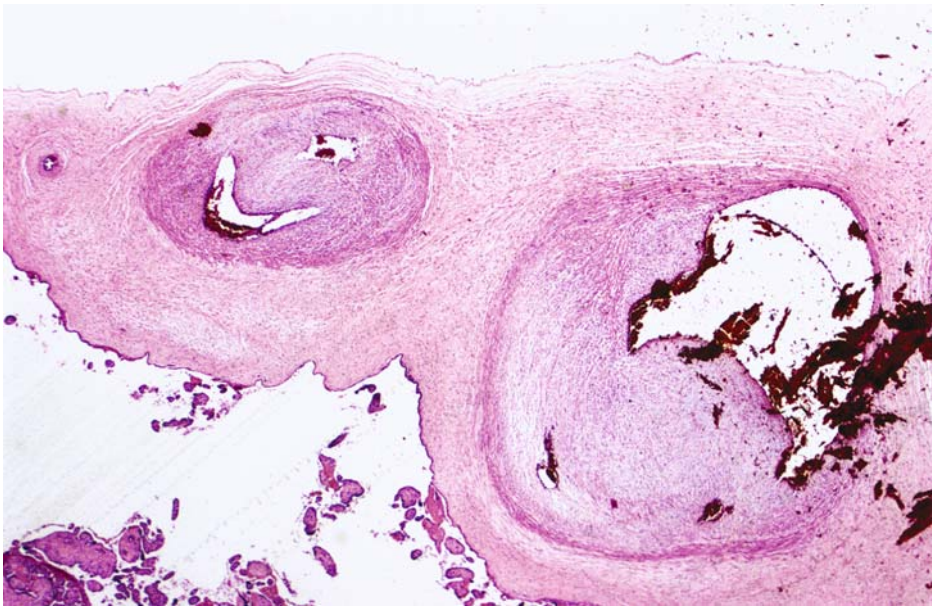

Figure 21.11. Intimal fibrin cushion from same case with calcification in the vessel wall. H&E. ×20.

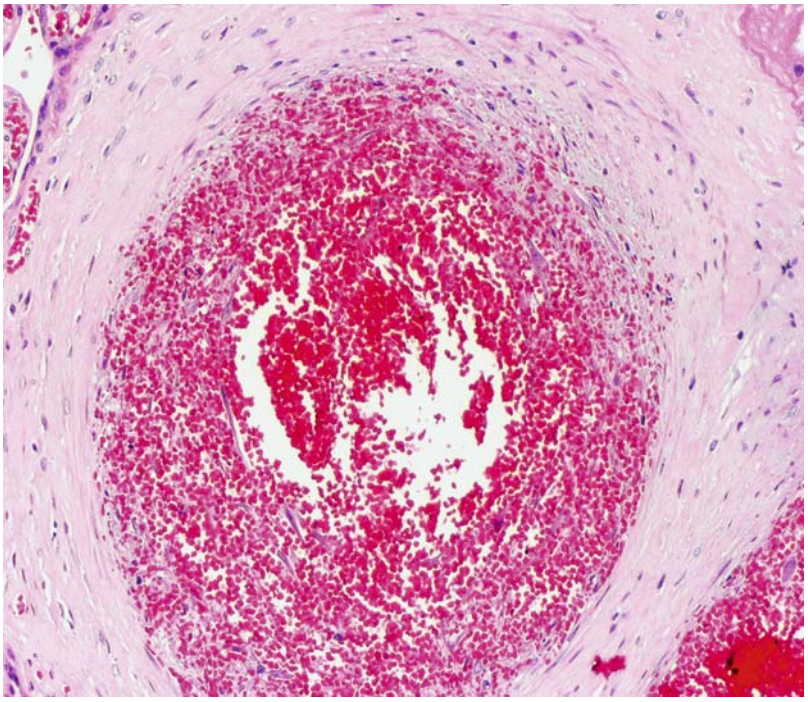

Figure 21.12. Bland hemorrhagic endovasculitis (HEV). Extravasated blood cells are present around this vessel in a stem villus. H&E. ×100.

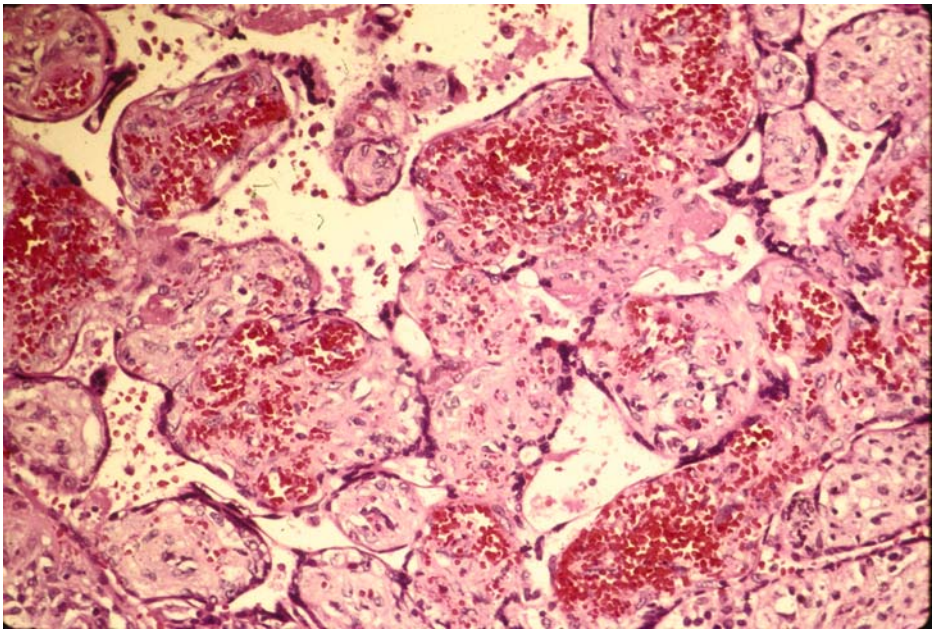

Figure 21.13. Active HEV demonstrating hemorrhagic villitis. There is destruction and necrosis of the vessel wall and karyorrhexis. H&E. ×200.

hemorrhagic villitis, *or necrosis and destruction of the vascular walls* (Figure 21.13). Active lesions may involve all types of vessels, from the large stem vessels down to the villous capillaries. Associations with poor neonatal outcome are stronger with active lesions. HEV also has a recurrence rate of 28% in subsequent pregnancies.

Pathogenesis

Thrombosis clearly bespeaks a pathologic prenatal environment. Thrombotic lesions may form in the venous or arterial circulation and may involve umbilical vessels (see Figure 15.24, page 271), chorionic vessels, large and small stem vessels, and villous capillaries. Arterial thrombosis is much less common than thrombosis in the venous circulation. *Significant obstruction in the arterial circulation* will rob the "downstream" villi of their vascular supply. Whenever the fetal circulation is lost but the maternal circulation is maintained, there will be loss of the fetal vasculature but the trophoblastic cells will be left intact. The villi then become sclerotic or **avascular** (see Figure 21.9). The presence of avascular villi can be considered direct evidence of the presence of thrombosis.

Thrombi may develop when blood flow through the umbilical cord is compromised, and here the problem is *primarily in the venous circulation*. Cord accidents such as *excessively long cords*, *excessive spiraling*, *true umbilical cord knots*, *cord entanglement*, *and velamentous cord insertion* are common antecedents. Mechanical obstruction of the cord will initially lead to compression of the umbilical vein, as it is more pliable than the umbilical arteries. *Occlusion of blood flow in the venous circula-*

tion leads to congestion, *venous stasis*, and increased intraluminal pressure, which in turn results in endothelial injury and subsequent thrombosis. Venous stasis also may lead to vasospasm, further compromising the circulation. Thrombosis may also be seen in the arterial circulation, and in this case it is more likely to be associated with abnormal coagulative states in the mother or the fetus.

The origin of **intimal fibrin cushions** is not completely clear, but it is thought that they either are "*organized*" *mural thrombi or are an early stage of thrombosis*. The fact that they may be associated with calcifications suggests an older lesion, at least in those cases. They are also often associated with venous hypertension. Thrombi and cushions are most common in placental surface veins and in major villous stem vessels (see Figure 21.10). They often have mural thrombi overlying them. It may be that the cushions form first and then, after much distension and elevated pressure, their endothelial surface degenerates and mural thrombosis develops.

Venoocclusive disease has also been implicated in the development of **hemorrhagic endovasculitis (HEV)**. This entity has aroused much controversy. It was initially identified in the study of many placentas from perinatal deaths and infants with perinatal problems, and it was hypothesized that HEV played an important role in the etiology of these tragedies. HEV is, in effect, a *microangiopathy that etiologically and pathologically resembles the glomerulopathy of the hemolytic uremic syndrome* and is often referred to as a *vasodisruptive* process. It is postulated that, as in frank thrombosis, there is *endothelial injury and vessel necrosis*, *which leads to fragmentation of RBCs and extravasation of these fragments into the villous stroma*. It is strongly associated with thrombosis as well. The etiology of HEV has been hotly debated and this is, in part, because the histologic picture is often seen in placentas of stillborns and that some of the features can be directly related to loss of fetal circulation to the villous tissue.

Clinical Features and Implications

Venous thrombosis is associated with *compromise of blood flow through the umbilical cord* secondary to cord entanglement, abnormal insertion, and abnormal length or coiling. Thrombosis may also be seen associated with *maternal or fetal thrombophilias* such as the Factor V Leiden mutation, activated protein C resistance, protein S deficiency, protein C deficiency, lupus anticoagulant, and antiphospholipid antibodies (see Chapter 18). *Maternal diabetes* is occasionally associated with thrombosis in the placenta or neonate or both, but there are no other morphologic or clinical features to explain the cause of this fetal vascular coagulation. *Severe chorioamnionitis*, particularly when there is a fetal response, may be associated with thrombosis in fetal vessels. This occurs secondary to damage to the endothelium and vessel wall from the inflammatory changes. Finally, thrombosis has also been associated with *vascular anomalies and various forms of trauma*.

Fetal thrombotic vasculopathy as a whole has been strongly associated with *preeclampsia*, *intrauterine growth restriction* (*IUGR*), *intrauterine fetal demise* (*IUFD*), *seizures*, *and amputation necrosis*. Prenatal and

neonatal thrombosis has been described in the central nervous system (CNS), pulmonary circulation, and renal vessels. *Neonatal stroke*, *cerebral degenerative changes*, *abnormalities in brain imaging*, *cerebral palsy*, *and poor long-term neurologic outcome* have also been described.

Suggestions for Examination and Report: Fetal Thrombotic Vasculopathy

Gross Examination: When gross thrombi are noted or there is a clinical history of cord problem or thrombosis, additional sections of fetal surface vessels should be submitted.

Comment: Specific lesions should be listed. Thrombosis may explain poor perinatal outcome, and findings should be correlated with clinical history of coagulopathy, diabetes, or cord problems.

Selected References

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Section VI

Neoplasms and Gestational Trophoblastic Disease

This section covers primary and metastatic tumors of the placenta and trophoblastic disease. It starts in Chapter 22 with a discussion of the primary tumors seen in the placenta as well as tumors that may metastasize from the mother or the fetus. Gestational trophoblastic disease is discussed in the following chapters. Hydatidiform moles are covered in Chapter 23, choriocarcinoma in Chapter 24, and lesions of extravillous trophoblast in Chapter 25.