proteinuria. It occurs in about 3% to 5% of pregnant women, usually in the last trimester and more commonly in primiparas (women pregnant for the first time). Some of these women become more seriously ill, developing convulsions; this more severe form of the disorder is termed *eclampsia*. Other complications stemming from systemic endothelial dysfunction include hypercoagulability, acute renal failure, and pulmonary edema. Approximately 10% of women with severe preeclampsia develop microangiopathic hemolytic anemia, elevated liver enzymes, and low platelets, referred to as the HELLP syndrome (Chapter 17). Preeclampsia should be distinguished from gestational hypertension that can develop in pregnancy without proteinuria.

Pathogenesis. **While the exact mechanisms leading to development of preeclampsia are still being investigated, it is clear that the placenta plays a central role in the pathogenesis of the syndrome, since the symptoms disappear rapidly after delivery of the placenta.** The critical abnormalities in preeclampsia are diffuse endothelial dysfunction, vasoconstriction (leading to hypertension), and increased vascular permeability (resulting in proteinuria and edema). Recent work has demonstrated that these effects are most likely mediated by placenta-derived factor(s) released into the maternal circulation. Although the release of these factors and the clinical syndrome develop late in gestation, the pathogenesis of the disease appears to be closely tied to the earliest events of pregnancy and placentation. The principal pathophysiologic aberrations appear to be the following:

- *Abnormal placental vasculature.* The precipitating events in the pathogenesis of preeclampsia are abnormal trophoblastic implantation and a failure of physiologic remodeling of the maternal vessels, which is required for adequate perfusion of the placental bed. In normal pregnancy, fetal extravillous trophoblastic cells (trophoblastic cells not associated with chorionic villi) at the implantation site invade the maternal decidua and decidual vessels, destroy the vascular smooth muscle, and replace the maternal endothelial cells with fetal trophoblastic cells (forming hybrid fetomaternal blood vessels). This process converts the decidual spiral arteries from small-caliber resistance vessels to large capacity uteroplacental vessels lacking a smooth muscle coat (Fig. 22-50). In preeclampsia, this remodeling fails to occur, leaving the placenta ill equipped to meet the increased circulatory demands of late gestation and setting the stage for the development of placental ischemia.
- *Endothelial dysfunction and imbalance of angiogenic and antiangiogenic factors.* Although not formally proven, it is postulated that in response to hypoxia, the ischemic placenta releases factors into the maternal circulation that cause an imbalance in circulating angiogenic and anti-angiogenic factors; this in turn leads to systemic maternal endothelial dysfunction and the clinical symptoms of the disease. In support of this, the blood levels of two placenta-derived antiangiogenic factors, soluble FMS-like tyrosine kinase (sFltl) and endoglin, which antagonize the effects of VEGF and TGFβ , respectively, are several orders of magnitude higher in women with preeclampsia than in healthy controls. In preeclampsia, high levels of sFlt1 and soluble endoglin bring about a decrease in angiogenesis much earlier than in normal pregnancy. The result is defective vascular development in the placenta. Furthermore, TGFβ induces endothelial production of NO, a potent vasodilator; thus, inhibition of TGFβ by endoglin may directly contribute to systemic vasoconstriction, hypertension, and tissue hypoperfusion.

  Studies in animal models also implicate sFltl and soluble endoglin in the pathogenesis of endothelial dysfunction. When sFlt and endoglin are overexpressed together, rats develop nephrotic-range proteinuria, severe hypertension, and fetal growth restriction, the hallmarks of severe preeclampsia, as well as features of the HELLP syndrome, including elevated liver enzymes, decreased platelet counts, and hemolysis. Thus, it seems that sFlt1 and soluble endoglin are key mediators that link the placenta to the characteristic maternal endothelial dysfunction of preeclampsia.
- *Coagulation abnormalities.* Preeclampsia is associated with a hypercoagulable state that may lead to the

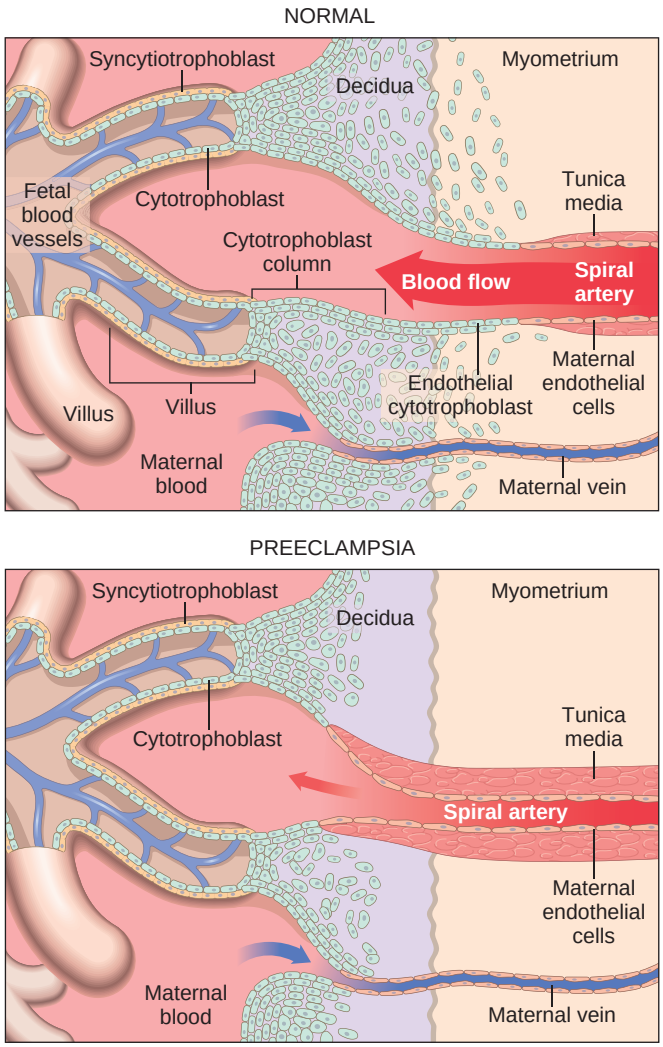

Figure 22-50 The physiologic alterations in the uterine spiral arteries and the failure of their remodeling in preeclampsia. (Modified from Maynard S, et al: Preeclampsia and angiogenic imbalance. Ann Rev Med 59:61, 2008.)

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