Chapter 17

Maternal Diseases Complicating Pregnancy

General Considerations

In certain maternal diseases, placental findings may be confirmatory of the disease, while in others, placental pathology may be the first indication of an abnormality. In many of the diseases complicating pregnancy, the associated placentas are often not examined, or examination is not reported. This is unfortunate because those placentas could aid in diagnosis and knowledge of the pathogenesis of these conditions and the mechanisms by which these conditions affect the fetus.

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For convenience, the diseases covered in this chapter are summarized in Table 17.1, which also includes those disorders in which little information is known or has been reported. Some more common conditions are discussed below. Maternal neoplasms are discussed in Chap. 22.

Connective Tissue Disorders

Systemic lupus erythematosus is a relatively common connective tissue disorder that has a significant affect on pregnancy and the placenta. This disease as well as the associated lupus anticoagulant and antiphospholipid antibody syndrome is discussed in greater detail in the next chapter on placental malperfusion (Chap. 18).

Scleroderma, also called **systemic sclerosis**, is a disease of unknown etiology characterized by the production of autoimmune antibodies and the deposition of fibrous tissue in many organs. It has been reported on many occasions to occur in pregnancy, although the usually late onset of scleroderma makes it an uncommon association. *Stillbirths, abortions, and premature births* are common in women with this disorder and *maternal deaths* have also occurred. Pathologic features of the placenta include *infarcts, decidual vasculopathy, abruptio placentae, extensive fibrinoid deposits, X-cell (extravillous trophoblast) proliferation, and cysts*. These are findings often associated with disorders of placental malperfusion and are seen in other autoimmune disorders (see Chap. 18).

Dermatomyositis, which is an autoimmune disease with primarily cutaneous expression, has been reported during pregnancy uncommonly. Pathologic findings of reported cases include *subamnionic necrosis and hemorrhage, infarcts, and fibrinoid deposition* similar to maternal floor infarction (see Chap. 19).

Ehlers–Danlos syndrome is a heterogeneous disease. It rarely occurs during pregnancy, with an estimated incidence of one in 150,000 pregnancies. *Premature delivery and premature rupture of membranes* have been reported, suggesting that the membranes are exceptionally fragile in these patients. The placentas have otherwise been reported to be normal.

Renal Disease

In general, renal disease, when associated with hypertensive disease in pregnancy, will be associated with decidual vascular lesions and lesions of malperfusion that are seen with preeclampsia (see Chap. 18). Renal disease not associated with hypertension is usually associated with histologically normal placentas, although fetal and placental weights are often diminished.

Specifically patients in **acute renal failure** from any cause usually have normal infants when appropriately managed and in those cases, the placentas are found to be normal. Pregnant women with **chronic renal failure** have a high perinatal mortality rate, and their placentas often are quite abnormal with numerous placental lesions. Most

notable among them is *diminished growth of the placenta*, presumably secondary to maternal decidual vascular disease and hypertension. The histologic findings may be similar to preeclampsia, but tend to be less pronounced. In particular, the *decidual vessels may show nonspecific thickening of the walls* (see Fig. 18.6 in Chap. 18) without overt decidual vasculopathy or atherosis.

Patients with successful **renal transplantation** have a 30% incidence of preeclampsia during pregnancy and suffer occasional rejection of the transplant. Intercurrent infection is a serious hazard, but cyclosporine immunosuppression apparently does not interfere with placentation. The placenta, however, is rarely described.

Liver Disease

Acute fatty liver of pregnancy does not usually affect the placenta directly. It has a dismal prognosis, with a survival rate between 18 and 23%. *Hemolysis, coagulation, and other disturbances occur clinically, and preeclampsia* may result with its complications. It has recently been suggested that this disorder has a similar pathogenesis to preeclampsia and HELLP syndrome (see Chap. 18). When maternal bilirubin is high, *gross examination of the placenta can identify the pigment, particularly in the perivascular connective tissue of the fetal surface* (Fig. 17.1). Microscopically, however, no abnormalities are detected, and visible pigment-laden macrophages are rare. **Cholestasis of pregnancy** has been associated with a high rate of *stillbirth* and other perinatal complications. *Meconium staining, preterm labor, and fetal distress* are common. Other than frequent meconium staining, no specific placental findings have been recorded.

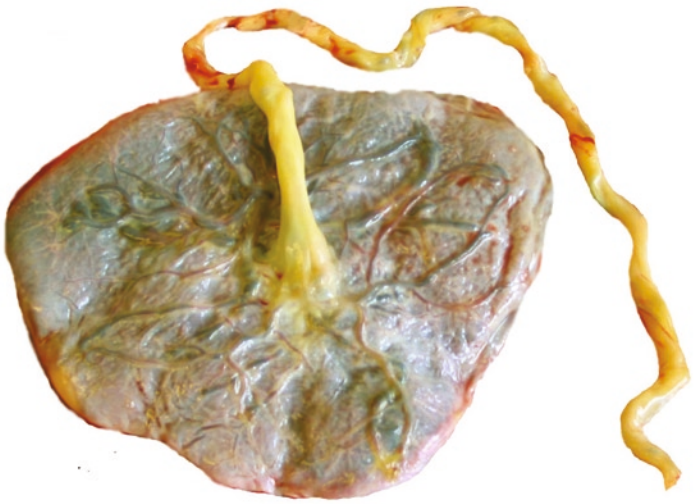

Figure 17.1. "Yellow"-stained placenta due to hyperbilirubinemia in the mother.

Cardiac Disease

The effect maternal **heart disease** has on pregnancy, fetal outcome, and placental development is variable. Patients with valvular disease such as **aortic stenosis**, severe **rheumatic heart disease**, or **cardiomyopathies** may have placentas with *infarcts* and *intervillous thromboses*. *The villous surface may be reduced*, and fetal growth restriction has also been described. Patients with less severe disease often have normal placentas. If there is associated maternal hypoxia, increased villous capillaries may be identified.

Hematologic Disorders

Sickle Cell Anemia

Clinical Features and Implications

Sickle cell anemia occurs predominantly in the African-American population. The heterozygous condition, **sickle cell trait**, occurs with a frequency of 9% in the United States African-American population and is as high as 45% in central Africa. The homozygous condition, **sickle cell anemia** is characterized by the presence of *sickling of red blood cells*, which result from crystallization of the abnormal hemoglobin S into "tactoids," which occurs particularly under conditions of reduced oxygen tension. Pregnant patients with sickle cell disease have many serious problems. *Urinary tract infection (45%), preeclampsia (25%), and puerperal sepsis (20%)* are the main complications. *Increased perinatal mortality, lower birth weights, and fetal growth restriction* have also been reported. In heterozygotes, these complications are significantly less frequent and less severe. Prophylactic transfusion reduces the frequency of painful crises but does not secure a beneficial pregnancy outcome, presumably because the significant placental lesions are present prior to this therapy.

Pathologic Features

Macroscopically, placentas may be *small* and the associated fetuses have *growth restriction*. They may contain grossly visible *infarcts*. Formalin fixation usually allows the microscopic identification of *sickle cells in the intervillous space* in sections (Fig. 17.2). It is thought that the hypoxia of postpartum placental separation induces the sickling of red blood cells in the intervillous space. Of note, Bouin's fixation results in red blood cell lysis and thus may compromise identification of sickle cells, while Zenker's solution causes reversal of the sickling phenomenon. Often, *nucleated red blood cells* can be found as well. *Increased syncytial knots, accelerated villous maturity, infarcts, increased fibrin, abruptios, and villous edema* have also been identified (see Figs. 18.12 and 18.17). Maternal sickle cells traverse the placenta to the fetal side, and in about one-half of placentas, and sickle cells are then found in aspirated cord blood. Doubtless, this is a traumatic feature of delivery of the placenta.

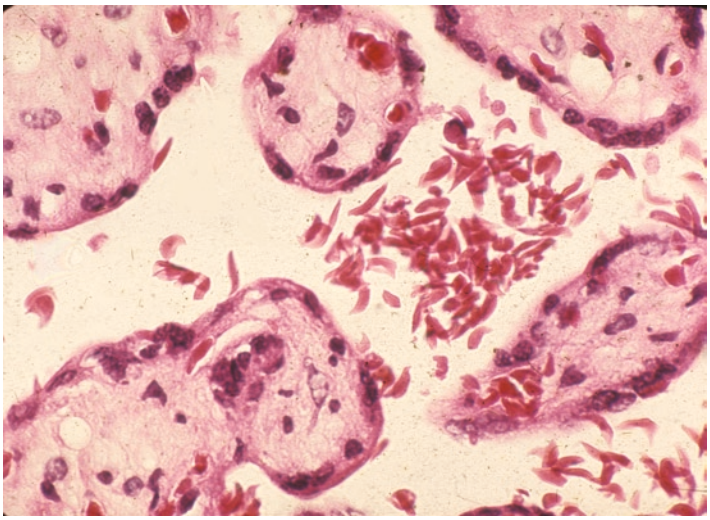

Figure 17.2. Sickled red blood cells in the intervillous space in a case of maternal sickle cell disease. H&E ×400.

Other Hematologic Disorders

Mothers with **β-thalassemia** often have normal infants, but may have *growth restricted infants or spontaneous abortions*. Placentas have not been found to have any associated abnormalities; however, in *infants* with sickle cell thalassemia (**hemoglobin SC disease**), placental infarcts may be found. Maternal **anemia** may cause *significant placental enlargement and in some cases an increase in villous capillaries (see below)*. It seems logical that the anemia leads to inadequate oxygenation of the fetoplacental unit, which, in turn, evokes a physiologic, compensatory placental hypertrophy. However, in severely anemic patients, the placentas are *small with pronounced morphologic changes of decreased uteroplacental perfusion* (see Chap. 18). In **thalassemia trait**, only mild placental enlargement with an increased placental-to-fetal ratio is seen. Simultaneously existing malnutrition is often associated with severe anemia, and this may explain differences in findings in the various studies.

The finding of placental hypertrophy with anemia has raised the question as to what changes may be observed in placentas of chronic oxygen deficiency at **high altitude**. Some studies have shown that the placenta at high altitude is considerably *larger than normal*, while other studies have found the placenta to be of normal size but the infants were smaller. Placentas at high altitude have shown histologic abnormalities such as *an increase in the villous capillaries and a larger capillary volume.* This effect (presumably due to chronic hypoxia), leads to an altered capillary/villous ratio at high altitude. The capillaries are also more closely applied to the trophoblastic surface than is the case at sea level. At times, the increased capillaries are sufficient for a diagnosis of chorangiosis (see Chap. 19).

Idiopathic thrombocytopenia (ITP) is a rare complication of pregnancy. It carries with it the risk of *postpartum hemorrhage and, less commonly, neonatal hemorrhagic complications*. The latter is particularly an issue when obstetricians obtain fetal scalp samples for fetal pH determination or when cordocentesis is performed. On rare occasion, the placenta may have *intervillous thrombi*, *infarcts*, or *decidual vascular lesions*. It is not clear, however, whether these are caused by the ITP or are perhaps the result of preeclampsia.

Thrombotic thrombocytopenic purpura during pregnancy is a serious disease and carries a high mortality rate. *Stillbirth* has also been described. Often the disease is mistaken clinically for severe preeclampsia, perhaps because of the similarity of the vascular lesions. *The decidual arterioles may show hyaline thrombi or fibrin deposition that resembles atherosis*. This has been called the "snowman sign," as it often presents as a sort of segmented thrombus or hyaline deposit looking like several circles connected together.

Neonatal thrombocytopenia has many causes, including the *transfer of maternal human leukocyte antigen (HLA) antibodies, maternal thiazide administration,* and *alloimmunization*. The latter condition has special dangers of fetal intracranial hemorrhage, and is now being treated with prenatal platelet transfusions. Unfortunately, the placenta in these cases has not been well studied, and in the cases that have been described, the placenta was normal.

Thyroid Disease

Thyroid disease has *no known direct impact on placental structure and function*, but many thyroid disorders enhance the probability of preeclampsia. Thus, *placental infarcts, decidual vasculopathy, and abruptio* are more common. Hyperthyroidism during pregnancy may be complicated by *polyhydramnios,* and *hydrops fetalis* has been reported in a number of patients with treated Graves' disease. Infants of hyperthyroid patients may be *growth-restricted or hyperthyroid* and more frequently have *prenatal distress, meconium staining, and fetal demise*. Diabetes is also more frequent in hyperthyroid patients during pregnancy.

Untreated **hypothyroidism** renders most patients anovulatory. It is therefore not often encountered as a complication of pregnancy. *Abortions, congenital anomalies, anemia, preeclampsia, abruptio, and postpartum hemorrhage* are more common in those patients who do become pregnant. *Fetal death* occurs 12% and *growth restriction* in 31%.

Diabetes Mellitus

Clinical Features and Implications

Abnormalities of glucose metabolism, including **gestational diabetes** and **insulin-dependent diabetes**, are among the most common medical complications of pregnancy. These conditions cause *increased fetal wastage, abortion, prematurity, macrosomia, and certain congenital anomalies*. Glucose passes the placenta readily, and the fetus responds to hyperglycemia with hyperplasia of the islets of Langerhans and

increased insulin secretion; the primary reason for macrosomia in maternal diabetes. Periodic hyperglycemia is thought to cause fetal polyuria and resultant polyhydramnios. More severe disease, with vascular complications, may be associated with *fetal growth restriction*.

Pathologic Features

The placentas of diabetic women are often severely abnormal. Placental abnormalities are subject to many variations, mostly due to the degree of diabetic control during gestation. In addition, because of the high fetal mortality during the last 2 weeks of pregnancy, many pregnant diabetic patients are now delivered before term. The placenta of most poorly controlled diabetics is *enlarged, thick, and plethoric* (Fig. 17.3), which is generally thought to be a manifestation of *fetal hypervolemia and maternal hyperglycemia.* There is a decrease in collagen content and mucopolysaccharide in diabetic placentas and they are therefore remarkably *friable*. They may also be edematous. Microscopically, the villous structure of the placenta in maternal diabetes may be focally *dysmature or immature* (Fig. 17.4) with *"persistence" of the cytotrophoblastic layer, increased cytotrophoblastic mitoses, thickening of the trophoblastic basement membrane, and increased perivillous fibrin*. There is frequently some degree of *villous enlargement and hypervascularity, sometimes meeting the criteria for chorangiosis* (see Fig. 19.8), and *nucleated red blood cells* are often present in villous capillaries. In contrast, when diabetes is well controlled during pregnancy, the placental weight does not usually deviate from that of normal organs and the villous tissue is usually microscopically normal.

Figure 17.3. Placenta from a diabetic. The maternal surface shows congestion. Friability of the placental tissue leads to tears and depressions in the surface, as seen here, even with careful handling. The placental disk was also markedly thick.

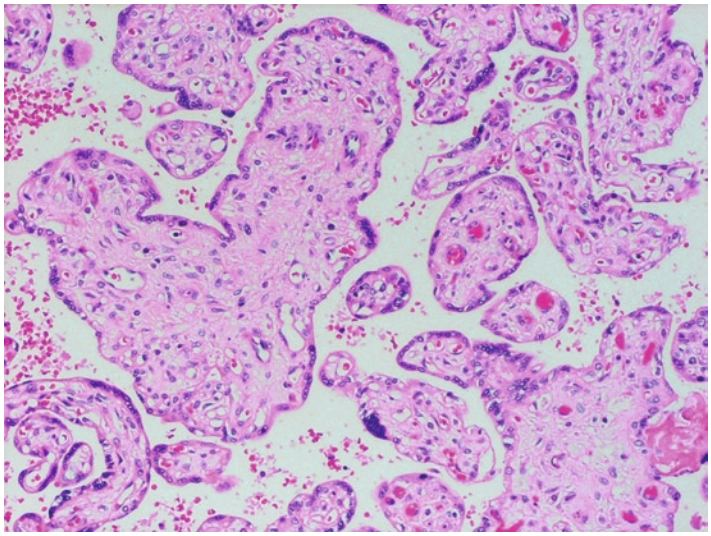

Figure 17.4. Villous dysmaturity in a diabetic placenta showing enlarged and immature appearing villi and increased villous vascularity. H&E ×100.

Fetal and placental vascular thrombosis is more common in the infants of diabetic mothers. This problem is occasionally reflected in *fetal renal and adrenal vein thrombosis*. There is a slight increase in the frequency of *single umbilical artery* (3–5% in diabetic progeny compared to a <1% average incidence). The umbilical cord is usually more "edematous" or, more accurately, it contains more Wharton's jelly. **Sacral agenesis** (caudal regression syndrome) is a highly characteristic fetal anomaly associated with maternal diabetes, but no specific placental lesions have been associated with this congenital anomaly.

When the pregnancy is complicated by **nephropathy (class F diabetes)**, fetal *growth restriction and placental infarcts* are found with increased frequency. *The decidua is also often unusually thick.* Infarcts are otherwise uncommon in diabetic mothers' placentas. In this situation, the placenta may even be smaller than expected for that gestational age.

Miscellaneous Conditions

Pregnancy complicated by **hypercholesterolemia** or **hypobetalipoproteinemia** has resulted in entirely normal placentas but may be associated with fetal growth restriction. In one reported case, *numerous lipid-laden macrophages were present in the intervillous space*, concentrated in the maternal floor, but not within the placental villi. The infant was normal and the placenta had a normal gross appearance.

Pheochromocytoma complicating pregnancy has serious implications for the fetus and mother. It is estimated that pheochromocytoma is associated with fetal death in 45% of cases, abortions in 12%, and maternal mortality in 25%. *Thrombosis of the umbilical cord* has been found in one case and *abruptio placentae* in four cases. The disease is often mistaken for preeclampsia because of the hypertension and albuminuria.

Maternal Drug Use

Tobacco

Clinical Features and Implications
Smoking during pregnancy has been the topic of numerous studies, which unfortunately have yielded contradictory results. Smoking is often considered the cause of an increased frequency of *low birth weight infants.* It has also been associated with *abortions, premature rupture of membranes, preterm delivery, placenta previa, perinatal death, and abruptions*. *Passive smoking* may also have a similar deleterious effect on fetal development.

Pathogenesis
The adverse effects of smoking may be mediated through reduced blood flow to placenta and fetus. When umbilical and uterine blood flow velocities have been studied, the effect on fetal growth appears to result from a significant rise in fetal placental vascular resistance. The relative hypoxia has been incriminated as the cause of the significant elevation of fetal erythropoietin levels with maternal smoking.

Pathologic Features
There is an increase in the placental to fetal weight ratio in smokers, which is due to the lower fetal weights, rather than to larger placentas. An increased frequency of *single umbilical artery* (SUA) and *abnormal cord insertions* is seen in smokers. Smokers' placentas have *more calcifications, increased perivillous fibrin,* and an increased incidence of *abruptions,* although the latter association is often overstated. *Chorangiosis* has also been seen with increased frequency in the placentas of smokers. **Electron microscopy** of the placenta has also yielded significant changes induced by smoking. Alterations and damage to the endothelium of the umbilical arteries and vein have been identified as well as a reduction in the microvillous surface of the syncytial cells and other changes, which adversely affect oxygen exchange from mother to fetus.

Alcohol

A direct effect of **alcohol** on the placenta is disputed, although fetal growth restriction and other consequences of the fetal alcohol syndrome are well delineated in the offspring of patients with alcohol abuse during pregnancy. Several studies have shown that the placenta is smaller than that of controls, and there is an *increased incidence of chorioamnionitis, chronic villitis, meconium staining, chorangiomas, abruptio placentae, and embryologic remnants in the umbilical cords*. The significance of the increase in these lesions is unknown.

Cocaine

The use of **cocaine** (benzoylmethylecgonine) and "**crack**" (the free-base smokable form of cocaine) during pregnancy has increased appreciably. Consuming cocaine in pregnancy has been linked to *abruptio placentae, prematurity, preeclampsia, fetal growth restriction, transient*

hypertension, and severe placental vasoconstriction. Much of the effect of cocaine, at least during pregnancy, seems to be mediated through its known hypertensive and vasoconstrictive activity. Following cocaine exposure, there is a rise of maternal arterial pressure combined with a reduction of uterine blood flow. The frequency of abruptio placentae is, in our experience, not as excessive as given in the many reports. It must be admitted that cocaine abuse is often combined with alcohol and other drug abuse and with maternal cigarette smoking, which may confound the issue. The vasoconstriction caused by these agents may be transmitted to the fetus, in which *cerebral infarction* has occasionally been observed.

Miscellaneous Therapeutic Medications

Few other drugs have shown well-recorded effects on placental structure, the notable exception being **methotrexate** in which there is *severe trophoblast toxicity*. This is apparently the reason it is used successfully in the eradication of early ectopic pregnancies and in gestational trophoblastic disease. A number of other chemotherapeutic agents have been used on pregnant women in the treatment of malignancies, generally with little ill effect on the fetus or placenta. Severe fetal growth restriction occurred with a patient who attempted to cause abortion by taking **aminopterin**; the placenta was not described. **Cyclophosphamide** is considered teratogenic and therefore is generally not used in the first trimester. The data on **6-mercaptopurine** and **azathioprine** suggest that the risk for congenital anomalies early in pregnancy is low. **Alkylating agents** have been used successfully and have been attended without ill effect. Neither fetal toxicity nor placental abnormalities have been described with use of a variety of cytotoxic drugs. In general, malignancy and the need for administration of chemotherapy are not considered an indication for termination of pregnancy.

Irradiation during pregnancy is usually avoided because of the known deleterious effects it has on the fetus. Occasional reports of the effect of therapeutic irradiation on fetuses have shown variable findings including *fetal anomalies (such as hydronephrosis)* and placental abnormalities, including *decidual inflammation and necrosis, necrosis of the fetal membranes, and nonspecific degenerative changes*.

Suggestions for Examination and Report
(Maternal diseases and conditions)

Gross Examination: In the setting of maternal disease, gross examination is relatively routine. Specific attention should be given to any gross lesions that are associated with the specific maternal condition present. As usual, any gross lesions identified should be sampled.

Comment: Correlation of findings with those typical for the specific maternal disease should be attempted, however, diagnosis of maternal disease from placental pathology can only be suggested.

Table 17.1. Reported features of maternal disorders.

Disorder	Clinical prenatal features	Pathology
Connective tissue disorders		
Dermatomyositis	–	Subamnionic necrosis, infarcts, ↑fibrinoid
Ehlers–Danlos	PM, PROM	?Fragile membranes
Myositis ossificans	PROM	–
Periarteritis nodosa	–	NL
Rheumatoid arthritis	IUGR	Small infarcts, calcification
Scleroderma	IUFD, Ab, PM, abruptio, maternal death	Infarcts, DV, ↑fibrinoid
Takayasu's arteritis	–	–
Renal and liver disease		
Chronic renal disease	–	Small, abnormal decidual vessels
Acute fatty liver of pregnancy	PEC, coagulation abnormalities	Gross bilirubin staining
Cholestasis of pregnancy	IUFD, PM	Meconium macrophages
Hyperlipidemia	IUGR	Rare foam cells in intervillous space
Miscellaneous inherited disorders		
Cystic fibrosis	–	–
Cystinosis	–	Vacuolization of decidual cells
Cystinuria	IUGR	–
Gaucher's disease	Thrombocytopenia	NL
Gordon's syndrome	–	NL
Impetigo herpetiformis	IUFD	"Placental insufficiency"
Niemann–Pick disease	–	NL
Phenylketonuria	–	NL
Pruritus gravidarum	Cholestasis, PM, IUFD	Meconium macrophages
Sarcoidosis	–	Granulomas
Smith–Lemli–Opitz	–	NL
Wilson's disease	–	NL
Hematologic disorders		
Heart disease	↓fetal/placental weight ratio, IUGR	Infarcts, intervillous thrombi
β-Thalassemia	Ab, IUFD	Occasional infarcts
Factor VII deficiency	–	–
Folate deficiency	Ab, abruption	Retroplacental hematoma

(continued)

Table 17.1. (continued)

Disorder	Clinical prenatal features	Pathology
Hematologic disorders		
Hemorrhagic hereditary telangiectasia	–	–
High altitude	–	Placentomegaly, increased syncytial knots, chorangiosis
ITP	Postpartum hemorrhage	Intervillous thrombus, infarcts, decidual vasculopathy
Leukoagglutinins	–	–
Maternal anemia	–	Placentomegaly or small placenta with increased syncytial knots
SC disease (sickle thalassemia)	Ab, IUFD	Infarcts
Sickle cell disease	PEC, sepsis, perinatal mortality, IUGR, abruptio	Small placenta, sickle cells in intervillous space, increased syncytial knots, infarcts, increased fibrin, villous edema, retroplacental hematoma
Sickle cell trait	Similar to disease but less severe	Similar to sickle cell disease but less severe
TTP	IUFD, high mortality	Hyaline thrombi in decidual vessels
Von Willebrand's disease	–	–
Endocrine disorders		
Cushing's disease	Ab, IUFD, PM	NL
Diabetes insipidus	Severe oligohydramnios	–
Diabetes mellitus	Macrosomia, PM, Ab, IUGR, congenital anomalies, fetal vascular thrombopathy	Placentomegaly, dysmature villi, hypervascular villi, NRBCs, thrombosis
Thyroid disease (general)	PEC, abruptio, IUGR, IUFD	Infarcts
Thyroid-hyperthyroidism	Polyhydramnios, fetal distress	Meconium macrophages
Thyroid-hypothyroidism	Ab, congenital anomalies, postpartum hemorrhage	–
Zollinger–Ellison	–	NL

(continued)

Table 17.1. (continued)

Disorder	Clinical prenatal features	Pathology
Maternal drug use		
Alcohol	IUGR, fetal alcohol syndrome, abruptio	Acute chorioamnionitis, meconium macrophages, chorangioma, umbilical cord remnants
Cocaine	Abruptio, IUGR, maternal hypertension, PM, PEC	Retroplacental hematoma
Heroin	IUGR	Acute chorioamnionitis, meconium macrophages
LSD	Ab, chromosome breakage	NL
Tobacco	IUGR, Ab, PROM, IUFD, abruptio	Single umbilical artery, abnormal cord insertions, calcifications
Marijuana	–	–

"–" Not been reported; *Ab* abortion; *IUFD* intrauterine fetal demise; *IUGR* intrauterine growth restriction; *NL* normal; *NRBC* nucleated red blood cell; *PEC* preeclampsia; *PM* prematurity; *PROM* premature rupture of membranes

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