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CHAPTER 55: Hepatic, Biliary, and Pancreatic Disorders

Pregnancy is comparatively seldom complicated by jaundice. Notwithstanding the fact that in most cases the jaundice disappears without treatment, too favorable a prognosis should not be ventured, for the reason that now and again the condition may represent the initial symptom of acute yellow atrophy of the liver.

—J. Whitridge Williams (1903)

INTRODUCTION

Even though Williams only mentions acute hepatic fatty metamorphosis, in practice, disorders of the liver, gallbladder, and pancreas together comprise a formidable list of complications that may arise in pregnancy. Some stem from preexisting conditions and some are unique to gestation. The relationships of several of these with pregnancy can be fascinating, intriguing, and challenging.

HEPATIC DISORDERS

Customarily, liver diseases complicating pregnancy are placed into three general categories. The first includes those specifically related to pregnancy that resolve either spontaneously or following delivery. Examples are intrahepatic cholestasis and acute fatty liver, both discussed in the next sections. Also, hepatic dysfunction from hyperemesis gravidarum may involve the liver. Mild hyperbilirubinemia with elevated serum transaminase levels is seen in up to half of affected women requiring hospitalization. However, these levels seldom exceed 200 U/L (Table 55-1). Liver biopsy may show minimal fatty changes. Hyperemesis gravidarum is discussed in detail in Chapter 54 (Upper Gastrointestinal Tract Disorders). Another in this first category is hepatocellular damage with preeclampsia—the *HELLP syndrome*—which is characterized by hemolysis, elevated serum liver enzyme levels, and low platelet counts. These changes are discussed in detail in Chapter 40 (Liver).

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TABLE 55-1

Clinical and Laboratory Findings with Acute Liver Diseases in Pregnancy

			Hepatic		Renal	Hematological and Coagulation					
Disorder	**Onset in Pregnancy**	**Clinical Findings**	**AST (U/L)**	**Bili (mg/dL)**	**Cr (mg/dL)**	**Hct**	**Plat**	**Fib**	**DD**	**PT**	**Hemolysis**
Hyperemesis	Early	Severe N&V	NL–300	NL–4	↑	↑↑	NL	NL	NL	NL	No
Cholestasis	Late	Pruritus, jaundice	NL–200	1–5	NL	NL	NL	NL	NL	NL	No
Fatty liver	Late	Moderate N&V, ± HTN, liver failure	200–800	4–10	↑↑↑	↑↑↑	↓↓	↓↓↓	↑	↑↑	↑↑↑
Preeclampsia	Mid to late	HA, HTN	NL–300	1–4	↑	↑	↓↓	NL	↑	NL	↑–↑↑
Hepatitis	Variable	Jaundice	2000+	5–20	NL	↑	↓	NL	NL	↑	No

↑ = increased levels; ↓ = decreased levels; AST = aspartate transaminase; Bili = bilirubin; Cr = creatinine; DD = d-dimers; Fib = fibrinogen; HA = headache; Hct = hematocrit; HTN = hypertension; N&V = nausea and vomiting; NL = normal; Plat = platelets; PT = prothrombin time.

The second category involves acute hepatic disorders that are coincidental to pregnancy, such as acute viral hepatitis. The third category includes chronic liver diseases that predate pregnancy, such as chronic hepatitis, cirrhosis, or esophageal varices.

Importantly, several normal pregnancy-induced physiological changes induce appreciable liver-related clinical and laboratory manifestations (Chap. 4, Gastrointestinal Tract, and Appendix, Serum and Blood Constituents). Findings such as elevated serum alkaline phosphatase levels, palmar erythema, and spider angiomas, which might suggest liver disease, are common during normal pregnancy. Metabolism is also affected, due to altered expression of the cytochrome P450 system. This alteration is mediated by higher levels of estrogen, progesterone, and other pregnancy hormones. For example, hepatic CYP1A2 expression declines, whereas that of CYP2D6 and CYP3A4 rises. Importantly, cytochrome enzymes are expressed in many organs besides the liver, most notably the placenta. The net effect is complex and likely influenced by gestational age and organ of expression (Isoherranen, 2013). Despite all of these functional changes, no major hepatic histological changes are induced by normal pregnancy.

Intrahepatic Cholestasis of Pregnancy

This condition has been called recurrent jaundice of pregnancy, cholestatic hepatosis, and icterus gravidarum and is characterized by pruritus, icterus, or both. It may be more common in multifetal pregnancy, and there is a significant genetic influence (Lausman, 2008; Webb, 2014). Because of this, its incidence varies by population. For example, cholestasis is infrequent in North America, with an overall incidence approximating 1 case in 500 to 1000 pregnancies. But, its rate nears 5.6 percent among Latina women in Los Angeles (Lee, 2006). Historically, indigenous women from Chile and Bolivia also have a relatively high incidence. For unknown reasons, this incidence has declined since the 1970s and is now less than 2 percent (Reyes, 2016). In other countries, for example Sweden, China, and Israel, the incidence varies from 0.25 to 1.5 percent (Glantz, 2004; Luo, 2015; Sheiner, 2006).

Pathogenesis

The cause of obstetrical cholestasis is unclear, but changes in various sex steroid levels are implicated. However, current research focuses on the numerous mutations in the many genes that control hepatocellular transport systems. Examples include mutations of the *ABCB4* gene, which encodes multidrug resistance protein 3 (MDR3) associated with *progressive familial intrahepatic cholestasis,* and errors of the *ABCB11* gene, which encodes a

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bile-salt export pump (Anzivino, 2013; Dixon, 2014). Other potential gene products are the farnesoid X receptor and transporting ATPase encoded by *ATP8B1* (Abu-Hayyeh, 2016; Davit-Spraul, 2012). Some drugs that similarly decrease canalicular transport of bile acids aggravate the disorder. We have encountered impressive cholestatic jaundice in gravidas taking azathioprine following renal transplantation.

Whatever the inciting cause(s), bile acids are cleared incompletely and accumulate in plasma. Hyperbilirubinemia results from retention of conjugated pigment, but total plasma concentrations rarely exceed 4 to 5 mg/dL. Alkaline phosphatase levels are usually elevated even more than in normal pregnancy. Serum transaminase levels are normal to moderately elevated but seldom exceed 250 U/L (see Table 55-1). Liver biopsy shows mild cholestasis with bile plugs in the hepatocytes and canaliculi of the centrilobular regions, but without inflammation or necrosis. These changes disappear after delivery but often recur in subsequent pregnancies or with estrogen-containing contraceptives.

Clinical Presentation

Pruritus develops in late pregnancy, although it occasionally manifests earlier. Constitutional symptoms are absent, and generalized pruritus shows predilection for the soles. Skin changes are limited to excoriations from scratching. Biochemical tests may be abnormal at presentation, but pruritus may precede laboratory findings by several weeks. Approximately 10 percent of women have jaundice.

With normal liver enzymes, the differential diagnosis of pruritus includes other skin disorders (Table 62-1). Findings are unlikely to stem from preeclamptic liver disease if blood pressure elevation or proteinuria is absent. Sonography may be warranted to exclude cholelithiasis and biliary obstruction. Moreover, *acute viral hepatitis* is an unlikely diagnosis because of the usually low serum transaminase levels seen with cholestasis. Conversely, *chronic hepatitis C* is associated with a significantly increased risk of cholestasis, which may be as high as 20-fold among women who test positively for hepatitis C RNA (Marschall, 2013).

Management

Pruritus may be troublesome and is thought to result from elevated serum bile salt concentrations. *Antihistamines* and *topical emollients* may provide some relief. Although cholestyramine is reported to be effective, this compound also lowers absorption of fat-soluble vitamins, which may lead to vitamin K deficiency. Fetal coagulopathy with subsequent intracranial hemorrhage and stillbirth have been reported (Matos, 1997; Sadler, 1995).

A recent metaanalysis suggests that *ursodeoxycholic acid* relieves pruritus, lowers bile acid and serum enzyme levels, and may reduce certain neonatal complications. These include preterm birth, fetal distress, respiratory distress syndrome, and neonatal intensive care unit (NICU) admission (Bacq, 2012). Kondrackiene and associates (2005) randomly assigned 84 symptomatic women to receive either ursodeoxycholic acid (8 to 10 mg/kg/d) or cholestyramine. They reported superior relief with ursodeoxycholic acid—67 versus 19 percent, respectively. Similarly, Glantz and coworkers (2005) found superior benefits to women randomly assigned to ursodeoxycholic acid versus dexamethasone. The American College of Obstetricians and Gynecologists (2015) has concluded that ursodeoxycholic acid relieves pruritus and improves fetal outcomes, although evidence for the latter is not compelling.

Pregnancy Outcomes

Earlier reports describe excessive adverse pregnancy outcomes in women with cholestatic jaundice. That said, data accrued during the past two decades are ambiguous concerning increased perinatal mortality rates and whether close fetal surveillance is preventative. Several studies also illustrate this. In one evaluation of 693 Swedish women, perinatal mortality rates were slightly increased, but only in mothers with severe disease (Glantz, 2004). Sheiner and coworkers (2006) described no differences in perinatal outcomes in 376 affected pregnancies compared with their overall obstetrical population. However, rates of labor induction and cesarean delivery in affected women significantly rose. Lee and associates (2009) described two cases of sudden fetal death not predicted by nonstress testing. In another study of 101 affected women, no term fetuses died, but 87 percent of women underwent labor induction, ostensibly to avoid adverse outcomes (Rook, 2012). Nonetheless, neonatal complications developed in a third of the pregnancies, particularly respiratory distress, fetal distress, and meconium-stained amnionic fluid. These problems were noted more frequently in those with higher total bile acid levels. Herrera and coworkers (2017) reported similar results. Finally, Wikström Shemer and colleagues (2013) reported outcomes in 5477 women with cholestasis from a database of 1,213,668 births. They described novel associations of cholestasis with preeclampsia and gestational diabetes. Although neonates were more likely to have a low 5-minute Apgar score and to be large for gestational age, the stillbirth rate was not increased. This was thought to reflect higher induction and preterm birth rates. Thus, by this time, many had now recommended early labor induction to avoid stillbirth. Reflecting this, at Parkland Hospital, some maternal-fetal specialists offer induction at 38 weeks, whereas

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others suggest 39 weeks.

As discussed, some evidence supports that high serum bile acid levels may contribute to fetal death. Bile acids typically remain <10 µmol/L throughout normal pregnancy (Egan, 2012). Elevated levels have been associated with meconium passage and stillbirth. For example, in the prior study of 693 Swedish women, stillbirths were limited to women with bile acid levels >40 µmol/L (Glantz, 2004). More recent data indicate that adverse outcomes are associated with even higher bile acid levels. For instance, Brouwers and coworkers (2015) reported high rates of spontaneous preterm birth (19 percent), meconium- stained amnionic fluid (48 percent), and perinatal death (10 percent) with bile acids levels >100 µmol/L despite active management leading to earlier delivery. Kawakita and colleagues (2015) found a similar stillbirth link. In particular, among 233 women followed with cholestasis of pregnancy, there were four stillbirths, all of which were among women with bile acid levels >100 µmol/L. Gao and associates (2014) implicated bile acids in cardiac dysfunction. Namely, in an ex-vivo preparation of cardiac myocytes, cholic acid lowered the beating rates in a dose-dependent manner, while increasing intracellular calcium levels. Intriguingly, studies have shown prolongations in the PR interval during fetal echocardiography among affected women (Rodríguez, 2016; Strehlow, 2010).

Acute Fatty Liver of Pregnancy

The most frequent cause of acute liver failure during pregnancy is acute fatty liver—also called *acute fatty metamorphosis* or *acute yellow atrophy*. It is characterized by accumulation of microvesicular fat that literally "crowds out" normal hepatocytic function (Fig. 55-1). Grossly, the liver is small, soft, yellow, and greasy. In its worst form, the incidence approximates 1 case in 10,000 pregnancies (Nelson, 2013). Fatty liver recurring in subsequent pregnancy is rare, but a few cases have been described (Usta, 1994).

FIGURE 55-1

Acute fatty liver of pregnancy. Cross section of the liver from a woman who died as the result of pulmonary aspiration and respiratory failure. The liver has a greasy yellow appearance, which was present throughout the entire specimen. Inset: Electron photomicrograph of one swollen hepatocyte containing numerous microvesicular fat droplets (*). The nuclei (*N*) remain centered within the cell, in contrast to the case with macrovesicular fat deposition. (Used with permission from Dr. Don Wheeler.)

Source: F. Gary Cunningham, Kenneth J. Leveno, Steven L. Bloom, Catherine Y. Spong, Jodi S. Dashe, Barbara L. Hoffman, Brian M. Casey, Jeanne S. Sheffield: Williams Obstetrics, 25th Edition
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Etiopathogenesis

Although much has been learned about this disorder, interpretation of conflicting data has led to incomplete but interesting observations. For example, some if not most cases of maternal fatty liver are associated with recessively inherited mitochondrial abnormalities of fatty acid oxidation. These are similar to those in children with Reye-like syndromes. Several mutations have been described for the mitochondrial trifunctional protein enzyme complex that catalyzes the last oxidative steps in the pathway. The most common are the *G1528C* and *E474Q* mutations of the gene on chromosome 2 that codes for long-chain-3-hydroxyacyl-CoA-dehydrogenase—known as LCHAD. There are other mutations for medium-chain acyl-CoA

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dehydrogenase—MCAD, as well as for carnitine palmitoyltransferase 1 (CPT1) deficiency (Santos, 2007; Ylitalo, 2005).

Sims and coworkers (1995) observed that some *homozygous* LCHAD-deficient children with Reye-like syndromes had *heterozygous* mothers with fatty liver. This was also seen in women with a compound heterozygous fetus. Although some conclude that *only* heterozygous LCHAD-deficient mothers are at risk when their fetus is homozygous, this is not always true (Baskin, 2010).

There is a controversial association between fatty acid β-oxidation enzyme defects and severe preeclampsia—especially in women with HELLP syndrome (Chap. 40, Liver). Most of these observations derive from retrospective study of mothers delivered of a child who later developed Reye-like syndrome. For example, one case-control study compared 50 mothers of children with a fatty-acid oxidation defect and 1250 mothers of matched control infants (Browning, 2006). During their pregnancy, 16 percent of mothers with an affected child developed liver problems compared with only 0.9 percent of control women. Problems included HELLP syndrome in 12 percent and fatty liver in 4 percent. Despite these findings, the clinical, biochemical, and histopathological findings are sufficiently disparate to suggest that severe preeclampsia, with or without HELLP syndrome, and fatty liver are distinct syndromes (American College of Obstetricians and Gynecologists, 2015; Sibai, 2007).

Clinical Findings

Acute fatty liver almost always manifests late in pregnancy. Nelson and colleagues (2013) described 51 affected women at Parkland Hospital with a mean gestational age of 37 weeks (range 31.7 to 40.9). Almost 20 percent were delivered at 34 weeks' gestation or earlier. Of these 51 women, 41 percent were nulliparous, and two thirds carried a male fetus. From other data, 10 to 20 percent of cases are in women with a multifetal gestation (Fesenmeier, 2005; Vigil-De Gracia, 2011).

Fatty liver has a clinical spectrum of severity. In the worst cases, symptoms usually develop over several days. Persistent nausea and vomiting are major complaints, and degrees of malaise, anorexia, epigastric pain, and progressive jaundice vary. Perhaps half of affected women have hypertension, proteinuria, and edema, alone or in combination—signs suggestive of preeclampsia. As shown in Tables 55-1 and 55-2, degrees of moderate to severe liver dysfunction are manifest by hypofibrinogenemia, hypoalbuminemia, hypocholesterolemia, and prolonged clotting times. Serum bilirubin levels usually are <10 mg/dL, and serum transaminase levels are modestly elevated and usually <1000 U/L.

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TABLE 55-2

Laboratory Findings in 215 Women with Acute Fatty Liver of Pregnancy

	Most Abnormal Laboratory Values Mean ± 1 SD (range)[a]				
Series	**No.**	**Fibrinogen (mg/dL)**	**Platelets (10^3/μL)**	**Creatinine (mg/dL)**	**AST (U/L)**
Pereira (1997)	32	ND	123 (26–262)	2.7 (1.1–8.4)	99 (25–911)
Fesenmeier (2005)	16	ND	88 (22–226)	3.3 (0.5–8.6)	692 (122–3195)
Vigil-De Gracia (2011)	35	136 ± 80	86	—	280 ± 236
Nelson (2013)	51	147 ± 96 (27–400)	99 ± 68 (9–385)	2.0 ± 0.8 (0.7–5.0)	449 ± 375 (53–2245)
Xiong (2015)	25	ND	82 (16–242)	2.4 (0.8–5.9)	385 (10–2144)
Zhang (2016)	56	246 ± 186	145 ± 75	1.4 ± 0.9	260 ± 237
Estimated average	215	140	102	2.5	330

[a]Fibrinogen and platelet values listed reflect the nadir for each patient, whereas creatinine and AST values reflect peak values for each patient.

AST = aspartate transaminase; ND = not done.

In almost all severe cases, profound endothelial cell activation with capillary leakage causes hemoconcentration, acute kidney injury, ascites, and sometimes pulmonary permeability edema (Bernal, 2013). With severe hemoconcentration, uteroplacental perfusion is reduced and this, along with maternal acidosis, can cause fetal death even before presentation for care. Both maternal and fetal acidemia are associated with a high incidence of fetal jeopardy and a concordantly high cesarean delivery rate.

Hemolysis can be severe and evidenced by leukocytosis, nucleated red cells, mild to moderate thrombocytopenia, and elevated serum levels of lactic acid dehydrogenase (LDH). Because of hemoconcentration, however, the hematocrit is often within the normal range. The peripheral blood smear demonstrates echinocytosis, and hemolysis is thought to stem from effects of hypocholesterolemia on erythrocyte membranes (Cunningham, 1985).

The degree of clotting dysfunction also varies and can be serious and life threatening, especially if operative delivery is undertaken. Coagulopathy is caused by diminished hepatic procoagulant synthesis, although some evidence supports increased consumption from disseminated intravascular coagulopathy. As shown in Table 55-2, hypofibrinogenemia sometimes is profound. Of 51 women with fatty liver cared for at Parkland Hospital, almost a third had a plasma fibrinogen level nadir to <100 mg/dL (Nelson, 2014). Modest level elevations of serum d-dimers or fibrin-split products indicate an element of consumptive coagulopathy. Although usually modest, occasionally thrombocytopenia is marked (see Table 55-2). Again, among the group from Parkland Hospital, 20 percent had platelet counts <100,000/μL and 10 percent had platelet counts <50,000/μL (Nelson, 2014).

Various liver imaging techniques have been used to confirm the diagnosis, however, none are particularly reliable. Specifically, Castro and associates (1996) reported poor sensitivity for confirmation by sonography—three of 11 patients, computed tomography (CT)—five of 10, and magnetic resonance (MR) imaging—none of five. Similarly, in a prospective evaluation of the Swansea criteria proposed by Ch'ng and coworkers (2002), only a quarter of women had classic sonographic findings that include maternal ascites or an echogenic hepatic appearance (Knight, 2008). Our experiences are similar (Nelson, 2013).

The syndrome typically continues to worsen after diagnosis. Hypoglycemia is common, and obvious hepatic encephalopathy, severe coagulopathy, and some degree of renal failure each develop in approximately half of women. Fortunately, delivery arrests liver function deterioration.

We have encountered several women with a *forme fruste* of this disorder. Clinical involvement is relatively minor and laboratory aberrations—usually

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only hemolysis and a decreased plasma fibrinogen level—herald the syndrome. Thus, the spectrum of liver involvement varies from milder cases that go unnoticed or are attributed to preeclampsia, to overt hepatic failure with encephalopathy.

Management

Intensive supportive measures and good obstetrical care are essential. In some cases, the fetus may already be dead when the diagnosis is made, and the route of delivery is less problematic. Often, living fetuses tolerate labor poorly. Because significant procrastination in effecting delivery may increase maternal and fetal risks, we prefer a trial of labor induction with close fetal surveillance. Although some recommend cesarean delivery to hasten hepatic healing, this increases maternal risk when coagulopathy is severe. Nonetheless, cesarean delivery is common, and rates approach 90 percent. Transfusions with whole blood or packed red cells, along with fresh-frozen plasma, cryoprecipitate, and platelets, are usually necessary if surgery is performed or if obstetrical lacerations complicate vaginal delivery (Chap. 41, Hypovolemic Shock).

Hepatic dysfunction resolves postpartum. It usually normalizes within a week, and in the interim, intensive medical support may be required. Two associated conditions can be seen around this time. Perhaps a fourth of women have evidence for *transient diabetes insipidus.* This presumably stems from elevated vasopressinase concentrations caused by diminished hepatic production of its inactivating enzyme. Finally, *acute pancreatitis* develops in approximately 20 percent.

With supportive care, recovery usually is complete. Maternal deaths are caused by sepsis, hemorrhage, aspiration, renal failure, pancreatitis, and gastrointestinal bleeding. Two women died in the series from Parkland Hospital. One was an encephalopathic woman who aspirated before intubation during transfer to our care. The other was in a woman with massive liver failure and nonresponsive hypotension (Nelson, 2013). In some centers, other measures have included plasma exchange and even liver transplantation (Fesenmeier, 2005; Franco, 2000; Martin, 2008).

Maternal and Perinatal Outcomes

Although maternal mortality rates with acute fatty liver of pregnancy have approached 75 percent in the past, the contemporaneous outlook is much better. From his review, Sibai (2007) cites an average mortality rate of 7 percent. He also cited a 70-percent preterm delivery rate and a perinatal mortality rate of 15 percent, which in the past was nearly 90 percent. At Parkland Hospital, the maternal and perinatal mortality rates during the past four decades have been 4 percent and 12 percent, respectively (Nelson, 2013).

Acute Viral Hepatitis

Although most viral hepatitis syndromes are asymptomatic, during the past 30 years, acute symptomatic infections have become even less common in the United States (Daniels, 2009). There are at least five distinct types of viral hepatitis: A (HAV), B (HBV), D (HDV) caused by the hepatitis B-associated delta agent, C (HCV), and E (HEV). The clinical presentation is similar in all, and although the viruses themselves probably are not hepatotoxic, the immunological response to them causes hepatocellular necrosis (Dienstag, 2015a,b).

Acute infections are most often subclinical and *anicteric*. When they are clinically apparent, nausea and vomiting, headache, and malaise may precede jaundice by 1 to 2 weeks. Low-grade fever is more common with hepatitis A. By the time jaundice develops, symptoms are usually improving. Serum transaminase levels vary, and their peaks do not correspond with disease severity (see Table 55-1). Peak levels that range from 400 to 4000 U/L are usually reached by the time jaundice develops. Serum bilirubin values typically continue to rise, despite falling serum transaminase levels, and peak at 5 to 20 mg/dL.

Any evidence for severe disease should prompt hospitalization. These include persistent nausea and vomiting, prolonged prothrombin time, low serum albumin level, hypoglycemia, high serum bilirubin level, or central nervous system symptoms. In most cases, however, clinical and biochemical recovery is complete within 1 to 2 months in all cases of hepatitis A, in most cases of hepatitis B, but in only a small proportion of cases of hepatitis C.

When patients are hospitalized, their feces, secretions, bedpans, and other articles in contact with the intestinal tract should be handled with glove-protected hands. Extra precautions, such as double gloving during delivery and surgical procedures, are recommended. Due to significant exposure of health-care personnel to hepatitis B, the Centers for Disease Control and Prevention (CDC) (2016a) recommend active and passive vaccination, described later. There is no vaccine for hepatitis C, so recommendations are for postexposure serosurveillance only.

Acute hepatitis has a case-fatality rate of 0.1 percent. For patients ill enough to be hospitalized, it may reach 1 percent. Most fatalities are due to

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fulminant hepatic necrosis, which in later pregnancy may resemble acute fatty liver. In these cases, hepatic encephalopathy is the usual presentation, and the mortality rate is 80 percent. Approximately half of patients with fulminant disease have hepatitis B infection, and co-infection with the delta agent is common.

Chronic Viral Hepatitis

The CDC (2016b) estimated that more than 4 million Americans were living with chronic viral hepatitis. Although most chronically infected persons are asymptomatic, approximately 20 percent develop cirrhosis within 10 to 20 years (Dienstag, 2015b). When present, symptoms are nonspecific and usually include fatigue. In some patients, cirrhosis with liver failure or bleeding varices may be the presenting finding. Indeed, asymptomatic chronic viral hepatitis as a group remains the leading cause of liver cancer and the most frequent reason for liver transplantation.

Chronic viral hepatitis is usually diagnosed serologically (Table 55-3). With persistently abnormal biochemical tests, liver biopsy usually discloses active inflammation, continuing necrosis, and fibrosis that may lead to cirrhosis. Chronic hepatitis is classified by cause; by grade, defined by histological activity; and by stage, which is the degree of progression (Dienstag, 2015b).

TABLE 55-3

Simplified Diagnostic Approach in Patients with Hepatitis

	Serological Test			
Diagnosis	**HBsAg**	**IgM Anti-HAV**	**IgM Anti-HBc**	**Anti-HCV**
Acute hepatitis A	–	+	–	–
Acute hepatitis B	+	–	+	–
Chronic hepatitis B	+	–	–	–
Acute hepatitis A with chronic B	+	+	+	–
Acute hepatitis A and B	+	+	+	
Acute hepatitis C	–	–	–	+

HAV = hepatitis A virus; HBc = hepatitis B core; HBsAg = hepatitis B surface antigen; HCV = hepatitis C virus.

Compiled from the Centers for Disease Control and Prevention, 2016b; Dienstag, 2015a.

Most young women with chronic viral hepatitis either are asymptomatic or have only mild liver disease. For seropositive asymptomatic women, there usually are no problems with pregnancy. With *symptomatic* chronic active hepatitis, pregnancy outcome depends primarily on disease and fibrosis severity, and especially on the presence of portal hypertension. The few women whom we have managed have done well, but their long-term prognosis is poor. Accordingly, they should be counseled regarding possible liver transplantation as well as abortion and sterilization options.

Hepatitis A

Vaccination has reduced the incidence of hepatitis by 95 percent since 1995. In 2014, the rate was 0.4 per 100,000 individuals (Centers for Disease Control and Prevention, 2016b). This 27-nm RNA picornavirus is transmitted by the fecal–oral route, usually by ingestion of contaminated food or water. The incubation period is approximately 4 weeks. Individuals shed virus in their feces, and during the relatively brief period of viremia, their blood is also infectious. Signs and symptoms are often nonspecific and usually mild, although jaundice develops in most patients. Symptoms usually last less than 2 months, although 10 to 15 percent of patients may remain symptomatic or relapse for up to 6 months (Dienstag, 2015a). Early serological testing identifies IgM anti-HAV antibody, which may persist for several months. During convalescence, IgG antibody predominates, and it

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persists and provides subsequent immunity. There is no chronic stage of hepatitis A.

Management of hepatitis A in pregnancy includes a balanced diet and diminished physical activity. Women with less severe illness may be managed as outpatients. In developed countries, the effects of hepatitis A on pregnancy outcomes are not dramatic (American College of Obstetricians and Gynecologists, 2015, 2016). Both perinatal and maternal mortality rates, however, are substantively increased in resource-poor countries. Hepatitis A virus is not teratogenic, and transmission to the fetus is negligible. Preterm birth rates may be increased, and neonatal cholestasis has been reported (Urganci, 2003). Although hepatitis A RNA has been isolated in breast milk, no cases of neonatal hepatitis A have been reported secondary to breastfeeding (Daudi, 2012).

Preventatively, vaccination during childhood with formalin- inactivated hepatitis viral vaccine is more than 90-percent effective. HAV vaccination is recommended by the American College of Obstetricians and Gynecologists (2016) and the Advisory Committee on Immunization (Kim, 2015a) for high-risk adults. This category includes behavioral and occupational populations and travelers to high-risk countries. These countries are listed in the CDC (2016c) Health Information for International Travel "yellow book," which is available on the CDC website. Passive immunization for the pregnant woman recently exposed by close personal or sexual contact with a person with hepatitis A is provided by a 0.02 mL/kg dose of immune globulin (Kim, 2015a). Victor and colleagues (2007) reported that a single dose of HAV vaccine given in the usual dosage within 2 weeks of contact with an affected person was as effective as immune serum globulin to prevent hepatitis A. In both groups, HAV developed in 3 to 4 percent.

Hepatitis B

This double-stranded DNA virus is found worldwide. It is endemic in Africa, Central and Southeast Asia, China, Eastern Europe, the Middle East, and certain areas of South America, where prevalence rates reach 5 to 20 percent. The World Health Organization (WHO) (2009) estimates that more than 2 billion people worldwide are infected with HBV, and of these, 370 million have chronic infection. The CDC (2016b) estimated nearly 18,100 cases of acute hepatitis B in the United States in 2014. This is a substantial decline since vaccination was introduced in the 1980s.

The hepatitis B virus is transmitted by exposure to blood or body fluids from infected individuals. In endemic countries, vertical transmission, that is, from mother to fetus or newborn, accounts for at least 35 to 50 percent of chronic HBV infections. In low-prevalence countries such as the United States, which has a prevalence <2 percent, the more frequent mode of HBV transmission is by sexual transmission or by sharing contaminated needles. HBV can be transmitted in any body fluid, but exposure to virus-laden serum is the most efficient.

Acute hepatitis B develops after an incubation period of 30 to 180 days with a mean of 8 to 12 weeks. At least half of acute infections are asymptomatic. If symptoms are present, they are usually mild and include anorexia, nausea, vomiting, fever, abdominal pain, and jaundice. Acute HBV accounts for half of cases of fulminant hepatitis. Symptoms completely resolve within 3 to 4 months in more than 90 percent of patients.

Figure 55-2 details the sequence of the various HBV antigens and antibodies in acute infection. The first serological marker to be detected is the hepatitis B surface antigen (HBsAg), often preceding the increase in transaminase levels. As HBsAg disappears, antibodies to the surface antigen develop (anti-HBs), marking complete resolution of disease. Hepatitis B core antigen is an intracellular antigen and not detectable in serum. However, anti-HBc is detectable within weeks of HBsAg appearance. The hepatitis Be antigen (HBeAg) is present during times of high viral replication and often correlates with detectable HBV DNA. After acute hepatitis, approximately 90 percent of adults recover completely. The 10 percent who remain chronically infected are considered to have chronic hepatitis B.

FIGURE 55-2

Sequence of various antigens and antibodies in acute hepatitis B. ALT = alanine transaminase; anti-HBc = antibody to hepatitis B core antigen; anti-HBe = antibody to hepatitis B e antigen; anti-HBs = antibody to hepatitis B surface antigen; HBeAg = hepatitis B e antigen; HBsAg = hepatitis B surface antigen. (Reproduced with permission from Dienstag JL: Acute viral hepatitis. In Kasper DL, Fauci AS, Hauser SL, et al (eds): Harrison's Principles of Internal Medicine, 19th ed. New York, McGraw-Hill Education, 2015).

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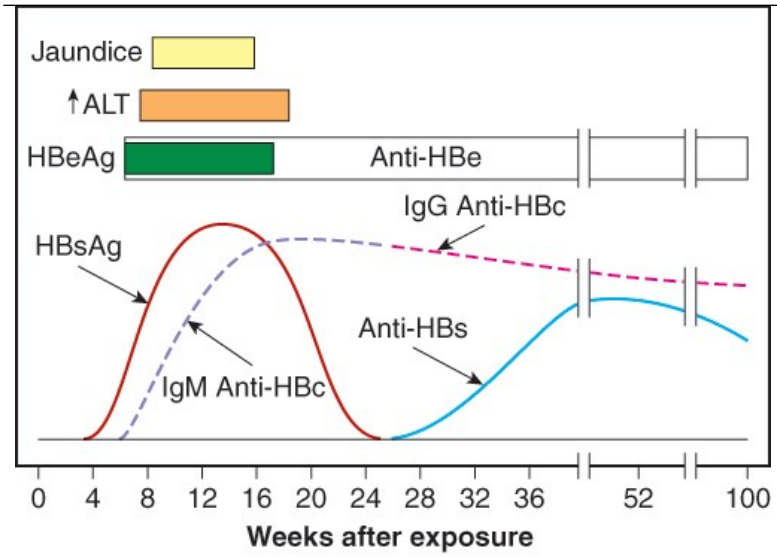

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Chronic HBV infection is often asymptomatic but may be clinically suggested by persistent anorexia, weight loss, fatigue, and hepatosplenomegaly. Extrahepatic manifestations may include arthritis, generalized vasculitis, glomerulonephritis, pericarditis, myocarditis, transverse myelitis, and peripheral neuropathy. One risk factor for chronic disease is age at acquisition. It is more than 90 percent in newborns, 50 percent in young children, and less than 10 percent in immunocompetent adults. Another risk is an immunocompromised state such as those with human immunodeficiency virus (HIV) infection, transplant recipients, or persons receiving chemotherapy. Chronically infected persons may be asymptomatic carriers or have chronic disease with or without cirrhosis. Patients with chronic disease have persistent HBsAg serum positivity. The patients with evidence of high viral replication—HBV DNA with or without HBeAg—have the highest likelihood of developing cirrhosis and hepatocellular carcinoma. The WHO considers hepatitis B to be second only to tobacco among human carcinogens. HBV DNA has been found to be the best correlate of liver injury and disease progression risk.

Pregnancy and Hepatitis B

Hepatitis B infection is not a cause of excessive maternal morbidity and mortality. It is often asymptomatic and found only on routine prenatal screening (Stewart, 2013). A review of data from the National Inpatient Sample reported a modest increase in preterm birth rates in HBV-positive mothers but no effect on fetal growth restriction or preeclampsia rates (Reddick, 2011). Others have shown similar results (Chen, 2015). Transplacental viral infection is uncommon, and Towers and associates (2001) reported that viral DNA is rarely found in amnionic fluid or cord blood. Interestingly, HBV DNA has been found in the ovaries of HBV-positive pregnant women, although this may not be a significant factor in perinatal transmission (Jin, 2016b). The highest HBV DNA levels were found in women who transmitted the virus to their fetuses (Dunkelberg, 2015; Society for Maternal-Fetal Medicine, 2016).

In the absence of HBV immunoprophylaxis, 10 to 20 percent of women positive for HBsAg transmit viral infection to their infant. This rate increases to almost 90 percent if the mother is HBsAg and HBeAg positive. Immunoprophylaxis and hepatitis B vaccine given to newborns of HBV-infected mothers has decreased transmission dramatically and prevented approximately 90 percent of infections (Smith, 2012). But, women with high HBV viral loads—10^6 to 10^8 copies/mL—or those who are HBeAg positive still have approximately a 10-percent vertical transmission rate, regardless of immunoprophylaxis (Yi, 2016).

The Society for Maternal–Fetal Medicine (2016) recommends antiviral therapy to decrease vertical transmission in women at highest risk because of high HBV DNA levels. Although lamivudine, a cytidine nucleoside analogue, significantly lowers the risk of fetal HBV infection in women with high HBV viral loads, recent data indicate that lamivudine may be less effective in the third trimester. Moreover, it is associated with the development of resistant mutations and is no longer recommended at a first-line agent. Newer drugs include the adenosine nucleoside analogue tenofovir and the thymidine analogue telbivudine. Both are associated with a lower risk of resistance than lamivudine (Ayres, 2014; Yi, 2016). Tenofovir has been recommended as the first-line agent during pregnancy by the Society for Maternal-Fetal Medicine (2016). These antiviral medications appear safe in pregnancy and are not associated with higher rates of congenital malformations or adverse obstetrical outcomes (Brown, 2016). Hepatitis B immunoglobulin (HBIG) given

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antepartum to women at highest risk of transmission is also cost-effective (Fan, 2016).

Newborns of seropositive mothers are given HBIG very soon after birth. This is accompanied by the first of a three-dose hepatitis B recombinant vaccine. Hill and colleagues (2002) applied this strategy in 369 infants and reported that the 2.4-percent transmission rate was not increased with breastfeeding if vaccination was completed. Although virus is present in breast milk, the incidence of transmission is not lowered by formula feeding (Shi, 2011). The American Academy of Pediatrics and the American College of Obstetricians and Gynecologists (2017) does not consider maternal HBV infection a contraindication to breastfeeding.

For high-risk mothers who are seronegative, hepatitis B vaccine can be given during pregnancy. The efficacy is similar to that for nonpregnant adults, and overall seroconversion rates approach 95 percent after three doses (Stewart, 2013). The traditional vaccination schedule of 0, 1, and 6 months may be difficult to complete during pregnancy, and compliance rates decline after delivery. Sheffield and coworkers (2011) reported that the three-dose regimen given prenatally—initially and at 1 and 4 months—resulted in seroconversion rates of 56, 77, and 90 percent, respectively. This regimen was easily completed during routine prenatal care.

Hepatitis D

Also called *delta hepatitis*, this is a defective RNA virus that is a hybrid particle with an HBsAg coat and a delta core. The virus must co-infect with hepatitis B either simultaneously or secondarily. It cannot persist in serum longer than hepatitis B virus. Transmission is similar to hepatitis B. Chronic co-infection with B and D hepatitis is more severe and accelerated than with HBV alone, and up to 75 percent of affected patients develop cirrhosis. HDV infection is detected by the presence of anti-HDV and HDV DNA. Neonatal transmission is unusual, as neonatal HBV vaccination usually prevents delta hepatitis.

Hepatitis C

This is a single-stranded RNA virus, and transmission occurs via blood and body fluids, although sexual transmission is inefficient. Up to a third of anti-HCV positive persons have no identifiable risk factors (Dienstag, 2015b). Screening for HCV is recommended for HIV-infected individuals, persons with injection drug use, hemodialysis patients, children born to mothers with HCV, persons exposed to HCV-positive blood or body fluids, persons with unexplained elevations in transaminase values, and recipients of blood or transplants before July 1992. Prenatal screening is recommended for high-risk women, and in the United States, seroprevalence rates reach 1 to 2.4 percent (American College of Obstetricians and Gynecologists, 2016; Arshad, 2011). It is higher in women who are infected with HIV. Santiago-Munoz and associates (2005) found that 6.3 percent of HIV-infected pregnant women at Parkland Hospital were co-infected with hepatitis B or C.

Acute HCV infection is usually asymptomatic or yields mild symptoms. Only 10 to 15 percent develop jaundice. The incubation period ranges from 15 to 160 days with a mean of 7 weeks. Transaminase levels are elevated episodically during the acute infection. Hepatitis C RNA testing is now preferred for HCV diagnosis. RNA levels may be found even before elevations of transaminase and anti-HCV levels. Specifically, anti-HCV antibody is not detected for an average of 15 weeks and in some cases up to a year (Dienstag, 2015a).

Nearly 80 to 90 percent of patients with acute HCV will be chronically infected. Although most remain asymptomatic, approximately 20 to 30 percent progress to cirrhosis within 20 to 30 years. Transaminase values fluctuate, and HCV RNA levels vary over time. Liver biopsy reveals chronic disease and fibrosis in up to 50 percent, however, these findings are often mild. Overall, the long-term prognosis for most patients is excellent.

Pregnancy and Hepatitis C

As expected, most pregnant women diagnosed with HCV have chronic disease. HCV infection was initially thought to have limited pregnancy effects. However, more recent reports have chronicled modestly increased fetal risks for low birthweight, NICU admission, preterm delivery, and mechanical ventilation (Berkley, 2008; Pergam, 2008; Reddick, 2011). In some women, these adverse outcomes may have been influenced by concurrent high-risk behaviors associated with HCV infection.

The primary adverse perinatal outcome is vertical transmission of HCV infection to the fetus-infant. This is higher in mothers with viremia (Indolfi, 2014; Joshi, 2010). Airoldi and Berghella (2006) cited a rate of 1 to 3 percent in HCV-positive, RNA-negative women compared with 4 to 6 percent in those who were RNA-positive. In a report from Dublin, the vertical transmission rate in 545 HCV-infected women was 7.1-percent in RNA-positive women compared with none in those who were RNA-negative (McMenamin, 2008). Some have found an even greater risk when the mother is co-

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infected with HIV (Snidjewind, 2015; Tovo, 2016). Invasive prenatal diagnostic procedures have not been reported to increase transmission to the fetus. However, Rac and Sheffield (2014) note that few studies have addressed this possibility, and they recommend avoiding traversing the placenta during amniocentesis. Approximately two thirds of prenatal transmission cases occur peripartum. HCV genotype, invasive prenatal procedures, breastfeeding, and delivery mode are not associated with mother-to-child transmission. That said, invasive procedures such as internal electronic fetal heart rate monitoring are avoided. HCV infection is not a contraindication to breastfeeding.

No licensed vaccine is available for HCV prevention. The chronic HCV infection treatment has traditionally included alpha interferon (standard and pegylated), alone or in combination with ribavirin. This regimen is contraindicated in pregnancy because of the teratogenic potential of ribavirin in animals (Joshi, 2010). The initial 5-year review of the Ribavirin Pregnancy Registry found no evidence for human teratogenicity. However, the registry has enrolled fewer than half of the necessary numbers to allow a conclusive statement to be made (Roberts, 2010). The development and study of direct-acting and host-targeted antiviral drugs in the past decade shows great promise for chronic hepatitis C management (Liang, 2013; Lok, 2012; Poordad, 2013). Current interferon-free, ribavirin-free regimens are being evaluated, although no data are available for pregnant women.

Hepatitis E

This water-borne RNA virus usually is enterically transmitted by contaminated water supplies. Hepatitis E is probably the most common cause of acute hepatitis (Hoofnagle, 2012). It causes epidemic outbreaks in third-world countries with substantial morbidity and mortality rates. Pregnant women have a higher case-fatality rate than nonpregnant individuals. In a metaanalysis of nearly 4000 subjects from Asia and Africa, Jin and coworkers (2016a) reported maternal and fetal case-fatality rates of 21 and 34 percent, respectively. Fulminant hepatitis, although rare overall, is more common in gravidas and contributes to the increased mortality rates. An altered innate immune response to incipient hepatitis E infection during pregnancy, affecting macrophage function and toll-like receptor signaling, may be a factor in the development of fulminant hepatitis (Sehgal, 2015).

A recombinant HEV vaccine has been developed and licensed in China. It is >95 percent effective for 12 months after vaccination. Long-term efficacy is 87 percent, and protective titers are maintained for up to 4.5 years (Zhang, 2015). Preliminary data from inadvertently vaccinated pregnant women show no adverse maternal or fetal events (Wu, 2012). At this time, it is unclear if this Chinese-licensed vaccine is effective in other areas of the world where other genotypes predominate. Genotype 4 is most common in China, and types 2 and 3 are more common in the Americas. A Food and Drug Administration (FDA) approved vaccine is not available at this time.

Hepatitis E is found worldwide, and although the highest prevalence is in east Asia, the CDC (2015) lists Mexico as a highly endemic country. Seroprevalence rates vary by age and geography, but overall seroprevalence rates of 10 percent have been reported. Durango State has the highest rate (37 percent) (Fierro, 2016).

Hepatitis G

Hepatitis G is the former name of an RNA flavivirus now known as HPvG or human pegivirus. This blood-borne infection of the liver, spleen, bone marrow, and mononuclear cells of the peripheral blood does not actually cause hepatitis (Chivero, 2015). It is thought to infect 750 million people worldwide, with up to two times that many with evidence of past infection. It may modulate the immune response, particularly during co-infection with HIV. Currently, no treatment aside from basic blood and body fluid precautions is recommended. Vertical transmission (to the fetus/infant) and horizontal transmission (to peers) has been described (Trinks, 2014).

Autoimmune Hepatitis

This is a generally progressive chronic hepatitis that is important to distinguish from other forms. Autoimmune hepatitis is more common in women and frequently coexists with other types of autoimmune disease, particularly autoimmune thyroid disease and Sjögren syndrome. Symptoms are typical of acute and chronic hepatitis, but one quarter may be asymptomatic. Rates of cirrhosis vary worldwide, but in western countries autoimmune hepatitis is more common and is characterized by multiple autoimmune antibodies such as antinuclear antibodies (ANA) and anti–smooth muscle antibody. Type 2 autoimmune hepatitis has an even higher prevalence in females and typically a more aggressive presentation. The incidence peaks in childhood and adolescence, before peak reproductive years. Treatment employs corticosteroids, alone or combined with azathioprine. Failure to respond to these two agents is more frequent in those with type 2 disease, and nearly all women with type 2 disease require more intensive therapy that is sustained long term (Vierling, 2015). In some patients with progressive disease and cirrhosis, hepatocellular carcinoma develops. In general, autoimmune hepatitis—especially when severe—increases the risk of adverse pregnancy outcomes.

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Westbrook and coworkers (2012) reported the outcomes of 81 pregnancies in 53 women. A third had a flare, and these were more common in those not taking medication and those with active disease in the year before conception. Maternal and fetal complications were higher among women with cirrhosis, particularly with respect to the risks of death or need for liver transplantation during the pregnancy or within 12 months postpartum. From one Swedish national database analysis, frequencies of preterm birth, low birthweight, and diabetes were higher, but not those of preeclampsia or cesarean delivery (Stokkeland, 2016). Danielsson Borssén (2016) reported stable or mild disease in 84 percent of 58 women who delivered 100 newborns. Nearly a fourth of cases were delivered before 38 weeks, and a postpartum flare developed in a third. Cirrhosis was present in 40 percent, and these women experienced more complications during pregnancy.

Iron and Copper Overload

Chronic hepatitis and cirrhosis can result from iron and copper overload. Iron overload may stem from a primary cause that is generally inherited, such as hereditary hemochromatosis, or originates secondary to complications of certain hemoglobinopathies. Many of the gene mutations underlying hereditary hemochromatosis involve hepcidin and result in dysregulated iron transport (Chap. 4, Iron Metabolism). Some of these mutations are more common in certain populations originating from northern Europe (Pietrangelo, 2016; Salgia, 2015). Cardiomyopathy, diabetes, joint disease, and skin changes can coexist with liver disease. Pregnancy outcomes associated with iron overload in hereditary hemochromatosis are driven by the degree of liver dysfunction, although higher iron levels may affect birthweight (Dorak, 2009).

A form of neonatal hemochromatosis that does not affect the mother is now thought to be alloimmune and is called *gestational alloimmune liver disease* (Anastasio, 2016). With this, maternal autoantibodies cross to the fetus and mediate dysfunction of iron homeostasis, although the antigenic target of these alloantibodies remains unclear. It is associated with significant neonatal morbidity and mortality, and frequently recurs in subsequent pregnancies. In these cases, antepartum treatment with intravenous immunoglobulin (IVIG) may improve outcomes (Feldman, 2013; Roumiantsev, 2015).

Copper overload leading to chronic hepatitis and cirrhosis is Wilson disease. This systematic condition can also manifest with cardiomyopathy, renal disease, neuropsychiatric symptoms, and certain endocrine abnormalities. A Kayser-Fleischer ring surrounding the iris is highly specific, but a suspected diagnosis generally requires genetic analysis. Autosomal recessive mutations of the *ATP7B* gene underlie this disorder. This gene codes for the P-type ATPase involved in copper transport to ceruloplasmin and bile (Bandman, 2015).

With Wilson disease, infertility may be present, but pregnancy outcomes among affected women who do conceive are influenced by disease severity. Malik and colleagues (2013) reported four cases in pregnancy, and three had associated gestational hypertension or preeclampsia. Maternal and neonatal outcomes were good, and the authors review chelation therapy with penicillamine and zinc sulfate in pregnancy. The American College of Gastroenterology states that few data guide which of the various chelating agents is best (Tran, 2016). These include penicillamine, zinc, and trientine, and any theoretical risks are outweighed by the risks of discontinuing therapy. The latter include not only hepatic decompensation, but also injury to the placenta and fetal liver. Accordingly, the American College of Gastroenterology recommends that pregnant women should continue their chelation therapy, although a dose reduction of 25 to 50 percent should be considered to promote wound healing in the event of a surgical delivery. As a reminder, copper ions regulate the activity of proteins essential to wound repair.

Nonalcoholic Fatty Liver Disease

This condition is frequently comorbid with obesity and is the most common chronic liver disease in the United States (Diehl, 2017). Its most severe form—*nonalcoholic steatohepatitis (NASH)*—is an increasingly recognized condition that may occasionally progress to hepatic cirrhosis. Nonalcoholic fatty liver disease (NAFLD) is a macrovesicular fatty liver condition that resembles alcohol-induced liver injury but is seen without this substance abuse. Obesity, type 2 diabetes, and hyperlipidemia—*syndrome X*—frequently coexist (Chap. 48, Pregnancy and Obesity). The current hypothesis suggests that these conditions may interact with other unknown etiological agents to cause multiple insults or “hits” leading to hepatic injury. For example, half of persons with type 2 diabetes have NAFLD, and insulin resistance has been postulated to act as one possible “hit” (Buzzetti, 2016). Browning and associates (2004) used MR spectroscopy to determine the prevalence of NAFLD in Dallas County and found that approximately a third of adults were affected. This varied by ethnicity, with 45 percent of Hispanics, 33 percent of whites, and 24 percent of blacks being affected. Most people—80 percent—found to have steatosis had normal liver enzymes. In a study of obese adolescents undergoing bariatric surgery, more than a third had fatty liver without hepatitis, whereas an additional 20 percent had borderline or definite NASH (Xanthakos, 2015).

Liver damage follows a progressive continuum from NAFLD to NASH and then to hepatic fibrosis that may progress to cirrhosis (Goh, 2016). Still, in

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most persons, the disease is usually asymptomatic, and it is a frequent explanation for elevated serum transaminase levels found in blood donors and during other routine screening. Indeed, NAFLD is the cause of elevated asymptomatic transaminase levels in up to 90 percent of cases in which other liver disease is ultimately excluded. It also is the most common cause of abnormal liver tests among adults in this country. Currently, weight loss along with control of diabetes and dyslipidemia is the only recommended treatment.

Fatty liver infiltration is probably much more common than realized in obese and diabetic gravidas. During the past decade, we encountered an increasing number of pregnant women with these disorders. Once severe liver injury, that is, acute fatty liver of pregnancy, is excluded, gravidas with fatty liver infiltration have no greater rates of adverse outcomes relative to liver involvement compared with pregnant women of similar weight. That said, some emerging data indicate that this condition may portend adverse pregnancy outcomes. In 110 pregnancies with NAFLD from the Swedish Medical Birth and the National Patient Registries, risks of gestational diabetes, preeclampsia, preterm birth, and low-birthweight newborns were two- to threefold greater than in unaffected women (Hagström, 2016). Yarrington and associates (2016) reported a high rate of gestational diabetes among nonobese women without liver disease, alcohol use, or diabetes, and who had elevated alanine transaminase levels in the first trimester. As the obesity endemic worsens, adverse effects of this liver disorder on pregnancy will be clarified.

Cirrhosis

Irreversible chronic liver injury with extensive fibrosis and regenerative nodules is the final common pathway for several disorders. *Laënnec cirrhosis* from chronic alcohol exposure is the most frequent cause in the general population. But in young women—including pregnant women—most cases are caused by *postnecrotic cirrhosis* from chronic hepatitis B and C. Many cases of *cryptogenic cirrhosis* are now known to be caused by NAFLD (Goh, 2016). Clinical manifestations of cirrhosis include jaundice, edema, coagulopathy, metabolic abnormalities, and portal hypertension with gastroesophageal varices and with splenomegaly that may cause thrombocytopenia. The incidence of deep-vein thromboembolism is increased (Søgaard, 2009). The prognosis is poor, and 75 percent have progressive disease that leads to death in 1 to 5 years.

Women with symptomatic cirrhosis frequently are infertile. Those who become pregnant generally have poor outcomes. Common complications include transient hepatic failure, variceal hemorrhage, preterm delivery, fetal growth restriction, and maternal death (Tan, 2008). Outcomes are generally worse if esophageal varices coexist.

Another potentially fatal complication of cirrhosis arises from associated splenic artery aneurysms. Up to 20 percent of ruptures occur during pregnancy, and 70 percent of these rupture in the third trimester (Palatnik, 2017; Tan, 2008). In a review of 32 gravidas with aneurysm rupture, the mean aneurysm diameter was 2.25 cm, and in half of cases, the diameter was <2 cm (Ha, 2009). The 22-percent maternal mortality rate was likely related to the emergent presentation of these events. Parrish and colleagues (2015) described embolization of a 13 × 9 mm aneurysm in the third trimester leading to a splenic abscess and sepsis 3 weeks later.

Portal Hypertension and Esophageal Varices

In pregnant women, approximately half of cases of esophageal varices originate from cirrhosis or extrahepatic portal vein obstruction, which leads to portal system hypertension. Some cases of extrahepatic hypertension develop following portal vein thrombosis associated with one of the *thrombophilia syndromes* (Chap. 52, Thrombophilias). Others follow thrombosis from umbilical vein catheterization when the woman was a neonate, especially if she was born preterm.

With either intrahepatic or extrahepatic resistance to flow, portal vein pressure rises from its normal range of 5 to 10 mm Hg, and values may exceed 30 mm Hg. Collateral circulation develops that carries portal blood to the systemic circulation. Blood drains into the gastric, intercostal, and other veins to the esophageal system, where varices develop. Bleeding is usually from varices near the gastroesophageal junction, and hemorrhage can be torrential. Bleeding during pregnancy from varices occurs in a third to half of affected women and is the major cause of maternal mortality within this group (Tan, 2008).

Maternal prognosis with esophageal varices largely depends on whether these rupture. Mortality rates are higher if varices are associated with cirrhosis compared with rates for varices without cirrhosis—18 versus 2 percent, respectively. Perinatal mortality rates are high in women with varices and are worse if cirrhosis caused the varices. Increased rates of neonatal demise, preterm birth, low birthweight, preeclampsia, and postpartum hemorrhage have been reported (Puljic, 2016).

Treatment is the same as for nonpregnant patients. Preventatively, all patients with cirrhosis, including pregnant women, should undergo endoscopic

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screening for identification of variceal dilatation (Bacon, 2015). Beta-blocking drugs such as propranolol are given to reduce portal pressure and hence the bleeding risk (Bissonnette, 2015; Tran, 2016).

For acute bleeding and for prophylaxis, endoscopic band ligation is preferred to sclerotherapy as it avoids any potential risks of injecting sclerotherapeutic chemicals (Bissonnette, 2015; Tan, 2008). Acute medical management for bleeding varices verified endoscopically includes the intravenous (IV) vasoconstrictors octreotide or somatostatin along with endoscopic banding. Vasopressin is less often used (Bacon, 2015). *Balloon tamponade* using a triple-lumen tube placed into the esophagus and stomach to compress bleeding varices can be lifesaving if endoscopy is not available. An interventional radiology procedure—*transjugular intrahepatic portosystemic stent shunting (TIPSS)*—can also control bleeding from gastric varices that is unresponsive to other measures (Bissonnette, 2015; Tan, 2008). This procedure can be done electively in patients with prior variceal hemorrhage.

Acetaminophen Overdose Hepatotoxicity

This drug is the most common cause of acute liver failure in the United States (Lee, 2013). Acetaminophen is often used during pregnancy, and overdose–either accidentally or by attempted suicide–may lead to hepatocellular necrosis and acute liver failure (Bunchorntavakul, 2013). Massive necrosis causes a cytokine storm and multiorgan dysfunction. Early symptoms of overdose are nausea, vomiting, diaphoresis, malaise, and pallor. With an acute overdose, after a latent period of 24 to 48 hours, liver failure ensues and usually begins to resolve in 5 days. In a prospective Danish study, only 35 percent of patients who were treated for fulminant hepatic failure spontaneously recovered before being listed for liver transplantation (Schmidt, 2007).

The antidote is *N-acetylcysteine*, which must be given promptly. The drug is thought to increase glutathione levels, which aid metabolism of the toxic metabolite, *N*-acetyl-*p*- benzoquinoneimine. The need for treatment is based on projections of possible plasma hepatotoxic levels as a function of the time from acute ingestion. For this, many poison control centers use the nomogram established by Rumack and Matthew (1975). A plasma level is measured 4 hours after ingestion, and if the level is >150 µg/mL, treatment is given (Smilkstein, 1988). If plasma determinations are not available, empirical treatment is given if the ingested amount exceeded 7.5 g. An oral loading dose of 140 mg/kg of N-acetylcysteine is followed by 17 maintenance doses of 70 mg/kg every 4 hours for 72 hours of total treatment time. Both the oral and an equally efficacious IV dosing regimen have been reviewed by Hodgman and Garrard (2012). The drug has been reported to reach therapeutic concentrations in the fetus (Wiest, 2014).

After 14 weeks' gestation, the fetus has some cytochrome P450 activity necessary for metabolism of acetaminophen to the toxic metabolite. Riggs and colleagues (1989) reported follow-up data from the Rocky Mountain Poison and Drug Center in 60 women suffering overdose. The likelihood of maternal and fetal survival was better if the antidote was given soon after overdose. At least one 33-week fetus appears to have died as a direct result of hepatotoxicity 2 days after maternal ingestion. In another case, Crowell and associates (2008) reported a case of acetaminophen overdose at 32 weeks' gestation. The woman had taken 9.75 grams of acetaminophen approximately 1.5 hours prior to arrival. With treatment, the patient survived and went on to deliver a healthy term neonate.

Focal Nodular Hyperplasia

This benign lesion of the liver is characterized in most cases by a well-delineated accumulation of normal but disordered hepatocytes that surround a central stellate scar. These usually can be differentiated from hepatic adenomas by magnetic resonance (MR) or computed tomographic (CT) imaging. Except in the rare situation of unremitting pain, surgery is rarely indicated, and most women remain asymptomatic during pregnancy. In one review of 20 cases in Germany, no woman had related complications during pregnancy (Rifai, 2013). Three women showed 20-percent tumor growth; in 10 patients, the tumor decreased in size; and the remaining seven were unchanged across pregnancy. Ramírez-Fuentes and associates (2013) studied 44 lesions with MR imaging in 30 women. Of the lesions, 80 percent were unchanged in size, and most of the remainder decreased in size. They concluded that size changes were unrelated to pregnancy, combination oral contraceptive (COC) use, or menopause. Notably, this lesion is not a contraindication to estrogen-containing contraceptives (Chap. 38, Transdermal Patch).

Hepatic Adenoma

This is an uncommon benign neoplasm but has a 5-percent risk of malignant transformation and a significant risk of rupture-associated hemorrhage, particularly in pregnancy. As just discussed, adenomas can usually be differentiated from focal nodular hyperplasia by MR or CT imaging. Adenomas have a 9:1 predominance among women and are strongly linked with COC use. The rupture risk progresses with lesion size, and surgery is generally

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recommended for tumors measuring >5 cm (Agrawal, 2015). Tran and colleagues (2016) recommend sonographic surveillance of hepatic adenomas during pregnancy. In one review of 27 cases in pregnancy, 23 became apparent in the third trimester and puerperium (Cobey, 2004). Bleeding complicated no tumors measuring <6.5 cm. However, 16 of 27 women (60 percent) with an adenoma presented with tumor rupture that resulted in seven maternal deaths and six fetal deaths. Of note, 13 of 27 women presented within 2 months postpartum, and in half, hemorrhage heralded rupture. Wilson and coworkers (2011) described two cases of bleeding hepatic adenoma during pregnancy. One was managed by laparoscopic segmental resection, and another, which followed liver biopsy, required open surgery. The authors discourage biopsy during pregnancy for suspected hepatic adenomas, and emphasize the feasibility of resection for problematic lesions.

Liver Transplantation

In 2013 in the United States, 5921 adult liver transplants were performed, and 34 percent of patients were women (Kim, 2015b). Currently, more than 65,000 recipients of liver transplant are living, and one literature review cited 450 pregnancies in 3026 women who had undergone transplantation (Deshpande, 2012). Although their live-birth rate of 80 percent and miscarriage rate compare favorably with those of the general population, risks of preeclampsia, cesarean delivery, and preterm birth are significantly elevated. A fourth of pregnancies were complicated by hypertension, approximately a third resulted in preterm birth, and in 10 percent, there was one or more rejection episodes (Table 55-4). Importantly, 4 percent of mothers had died within a year after delivery, but this rate is comparable to that in nonpregnant liver transplantation patients. Ghazali and associates (2016) analyzed the National Inpatient Sample database and found 2.1 liver transplants per 100,000 deliveries. Pregnancies after liver transplant had significantly greater risks of maternal and fetal complications, including hypertensive disorders, gestational diabetes, and postpartum hemorrhage. Rates of preterm birth, fetal growth restriction, and congenital anomalies were also increased. Mattila and colleagues (2017) found that half of the women they cared for had maternal complications.

TABLE 55-4

Pregnancy Complications (%) in 558 Pregnancies after Liver Transplantation

Series	No.	Preeclampsia/Hypertension	Cesarean Delivery	Rejection	Live Birth
Jain (2003)	49	2–8	45	24	100
Nagy (2003)	38	21	46	17	63
Christopher (2006)	71	13–28	28	17	70
Coscia (2010)	281	22–33	32	6	75
Jabiry-Zieniewicz (2011)	39	8–26	79	8	100
Blume (2013)	62	6	30	13	77
Weighted Average:	540	16–28	38	10	78

GALLBLADDER DISORDERS

Cholelithiasis and Cholecystitis

In the United States, 20 percent of women older than 40 years have gallstones. Most stones contain cholesterol, and its oversecretion into bile is thought to be a major factor in stone formation. The cumulative risk of all patients with silent gallstones to require surgery for symptoms or complications is 10 percent at 5 years, 15 percent at 10 years, and 18 percent at 15 years (Greenberger, 2015). For these reasons, prophylactic cholecystectomy is not warranted for *asymptomatic* stones. For *symptomatic* gallstone disease, nonsurgical approaches have been used and include oral bile acid therapy with ursodeoxycholic acid and extracorporeal shock wave lithotripsy. Experience with these during pregnancy is lacking.

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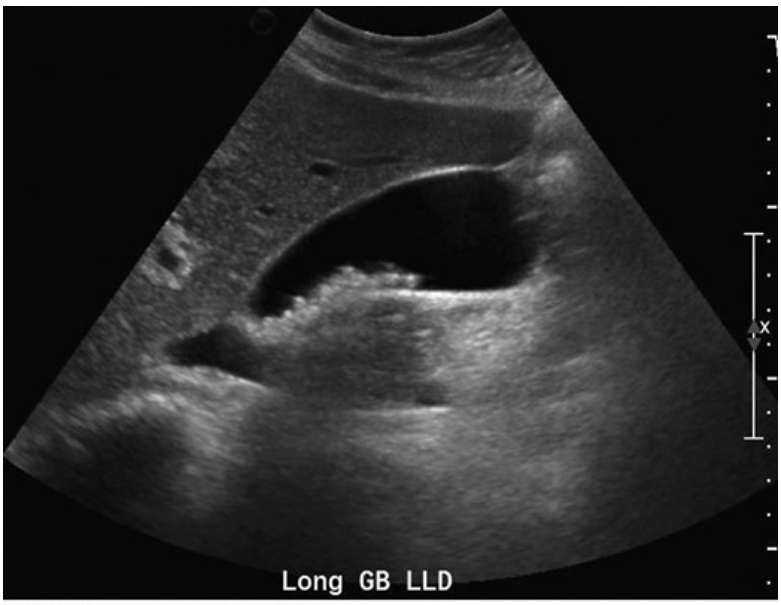
Acute cholecystitis usually develops when the cystic duct is obstructed. Bacterial infection plays a role in 50 to 85 percent of cases. In more than half of patients with acute cholecystitis, a history of prior right upper quadrant pain from cholelithiasis is elicited. With acute disease, pain is accompanied by anorexia, nausea and vomiting, low-grade fever, and mild leukocytosis. As shown in Figure 55-3, sonography can help visualize stones, and both false-positive and false-negative rates range from 2 to 4 percent (Greenberger, 2015). In acute cases, medical therapy consists of IV fluids, antimicrobials, analgesics, and in some instances, nasogastric suction, before surgical therapy. Laparoscopic cholecystectomy is the preferred treatment for most patients.

FIGURE 55-3

This sonogram shows multiple hyperechoic gallstones filling an anechoic gallbladder.



Source: F. Gary Cunningham, Kenneth J. Leveno, Steven L. Bloom, Catherine Y. Spong, Jodi S. Dashe, Barbara L. Hoffman, Brian M. Casey, Jeanne S. Sheffield: Williams Obstetrics, 25th Edition
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Gallbladder Disease During Pregnancy

After the first trimester, the gallbladder fasting volume and the residual volume after postprandial emptying are doubled. Incomplete emptying may result in retention of cholesterol crystals, a prerequisite for cholesterol gallstones. Maringhini and colleagues (1993) showed that the incidence of biliary sludge—which can be a forerunner to gallstones—and gallstones in pregnancy are 31 and 2 percent, respectively. Ko and colleagues (2014), however, cited a combined incidence of <5 percent. Others have identified asymptomatic gallstones in 2.5 to 10 percent of more than 1500 pregnant or postpartum women (Maringhini, 1993; Valdivieso, 1993).

Postpartum, sludge frequently regresses, and occasionally gallstones will resorb. Still, within a year after delivery, hospitalization for gallbladder disease remains relatively common, particularly for women managed conservatively in pregnancy. Jorge and coworkers (2015) reported that half of 53 women with symptomatic gallstones in pregnancy underwent postpartum cholecystectomy. In 80 percent of these women, recurrent symptoms developed prior to surgery, requiring readmission in half.

Medical versus Surgical Management

Acute cholecystitis during pregnancy or the puerperium is common and usually associated with gallstones or biliary sludge. Symptomatic cholecystitis is initially managed in a manner similar to that for nonpregnant women. In the past, most favored medical therapy. However, the recurrence rate during the same pregnancy is high, and 25 to 50 percent of women ultimately required cholecystectomy for persistent symptoms. Moreover, if cholecystitis recurs later in gestation, preterm labor is more likely and cholecystectomy is technically more difficult.

For these reasons, operative and endoscopic interventions are increasingly favored over conservative measures. Othman and coworkers (2012)

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showed that women managed conservatively had more pain, more recurrent visits to the emergency department, more hospitalizations, and a higher rate of cesarean delivery. Dhupar and associates (2010) reported more complications with conservative management of gallbladder disease compared with laparoscopic cholecystectomy in pregnancy. These included multiple admissions, prolonged total parenteral nutrition, and unplanned labor induction for worsening gallbladder symptoms. Cholecystectomy was performed safely in all trimesters. Only one of 19 patients who underwent laparoscopic cholecystectomy had a complication, which did not require further surgery. A metaanalysis found that cholecystectomy does not increase the risk of preterm labor or of maternal or fetal mortality (Athwal, 2016). Management at Parkland Hospital has evolved to a more aggressive surgical approach, especially if there is concomitant biliary pancreatitis as subsequently discussed. During the past two decades, laparoscopic cholecystectomy has evolved as the favored surgical approach and is discussed in Chapter 46 (Medications and Surgeries).

Endoscopic Retrograde Cholangiopancreatography

Relief from symptomatic biliary duct gallstones during pregnancy has been greatly aided by use of endoscopic retrograde cholangiopancreatography (ERCP) (Fogel, 2014; Menees, 2006). The procedure is performed if common duct obstruction is suspected or proven. Approximately 10 percent of patients with symptomatic stone disease have common duct stones (Stinton, 2012). ERCP can be modified in many cases so that radiation exposure from fluoroscopy is avoided (Sethi, 2015).

Tang and associates (2009) reported results from 68 ERCP procedures performed in 65 pregnant women at Parkland Hospital. All but two women had gallstones, and sphincterotomy was performed in all but one woman. Common duct stones were identified in half of these 65 women, and in all but one, the stones were successfully removed. A biliary stent was placed in 22 percent of cases and removed after delivery. Complications were minimal, and post-ERCP pancreatitis developed in 16 percent. Pregnancy outcomes were not different than for the general obstetrical population. As a less invasive approach, MR cholangiopancreatography (MRCP) has been reported to have utility in pregnancy in small, retrospective case series. Wu and colleagues (2014) caution against its use in pregnancy, particularly for seriously ill women. Also, MRCP is not readily available, and this may lead to delayed definitive management.

Ascending cholangitis can complicate acute biliary obstruction. Nearly 70 percent of affected patients develop *Charcot triad*—jaundice, abdominal pain, and fever. The diagnosis is aided by sonography, and treatment is broad-spectrum antibiotics and biliary drainage by ERCP (Greenberger, 2015).

PANCREATIC DISORDERS

Pancreatitis

Acute pancreatic inflammation is triggered by factors that cause activation of pancreatic trypsinogen followed by autodigestion. It is characterized by cell-membrane disruption and proteolysis, edema, hemorrhage, and necrosis (Conwell, 2015; Fogel, 2014). Up to 10 percent of women develop necrotizing pancreatitis, which carries a mortality risk of 15 percent. This rate rises if infection develops (Cain, 2015).

In nonpregnant patients, acute pancreatitis is almost equally associated with gallstones and alcohol abuse. During pregnancy, however, cholelithiasis is almost always the predisposing condition. Other causes are hyperlipidemias, usually hypertriglyceridemia; hyperparathyroidism; congenital ductal anomalies; ERCP; some drugs; and rarely autoimmune pancreatitis (Cain, 2015; Ducarme, 2014). Nonbiliary pancreatitis occasionally develops postoperatively, or it is associated with trauma, drugs, or some viral infections. Certain metabolic conditions, including acute fatty liver of pregnancy and familial hypertriglyceridemia, also predispose to pancreatitis (Nelson, 2013). Cases of acute and chronic pancreatitis have been linked to numerous mutations of the cystic fibrosis transmembrane conductance regulator gene (Chang, 2015).

The incidence of pancreatitis varies with the population studied. At Parkland Hospital, with a predominant Mexican American population, acute pancreatitis complicated approximately 1 in 3300 pregnancies (Ramin, 1995). At Brigham and Women's Hospital, with a more diversely ethnic population, Hernandez and colleagues (2007) reported an incidence of 1 in 4450. In a multiple-institution Midwestern three-state review, the incidence of acute pancreatitis was 1 in 3450 (Eddy, 2008). In contrast, from California birth certificate data, the incidence approximated only 1 case in 6000 pregnancies (Hacker, 2015).

Diagnosis

Acute pancreatitis is characterized by mild to incapacitating epigastric pain, nausea and vomiting, and abdominal distention. Patients are usually distressed and have low-grade fever, tachycardia, hypotension, and abdominal tenderness. As many as 10 percent have systemic inflammatory

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response syndrome (SIRS), which causes endothelial activation and can lead to acute respiratory distress syndrome (Chap. 47, Sepsis Syndrome).

Of laboratory tests, serum amylase levels usually measure three times values considered the upper limit of normal. In 173 pregnant women with pancreatitis, the mean amylase value approximated 2000 IU/L, and the mean lipase value approached 3000 IU/L (Table 55-5). *Importantly, the degree of enzyme elevation and disease severity do not reliably correlate.* Indeed, by 48 to 72 hours, amylase levels may return to normal despite other evidence for continuing pancreatitis. Serum lipase activity is also increased and usually remains elevated with continued inflammation. Leukocytosis is usually found, and 25 percent of patients have hypocalcemia. Elevated serum bilirubin and aspartate transaminase levels may signify gallstone disease.

TABLE 55-5

Laboratory Values in 173 Pregnant Women with Acute Pancreatitis

Analyte	Mean	Range	Normal
Serum amylase (IU/L)	1980	111–8917	28–100
Serum lipase (IU/L)	3076	36–41,824	7–59
Total bilirubin (mg/dL)	1.7	0.1–8.71	0.2–1.3
Aspartate transferase (U/L)	115	11–1113	10–35
Leukocytes (per µL)	10,700	1000–27,200	3900–10,700

From Ramin, 1995; Tang, 2010; Turhan, 2010.

Several prognostic scoring systems have been used to classify pancreatitis severity, but not all of these are useful in pregnancy. For instance, two of the five Ranson criteria determined at admission include variables specific to nonpregnant patients. Similarly, certain criteria for the Apache II scoring system do not account for the changes in pregnancy physiology. In contrast, the Atlanta Classification incorporates the degree of organ failure as a measure of severity and may be more applicable in pregnancy (Banks, 2013; Cain, 2015).

Management

Medical treatment mirrors that for nonpregnant patients. This includes analgesics, IV hydration, and measures to decrease pancreatic secretion by interdiction of oral intake. Other than supportive therapy, antibiotics when appropriate, and targeted surgical interventions in the case of gallstone pancreatitis, no particular treatment schemes have improved outcomes. In a series by Ramin and colleagues (1995), all 43 affected pregnant women responded to conservative treatment and were hospitalized for a mean of 8.5 days. Nasogastric suction does not improve outcomes of mild to moderate disease, but enteral feeding may be helpful once pain improves and associated ileus resolves. For women with more severe pancreatitis and a prolonged disease course, total enteral nutrition using nasojejunal feeding is superior to total parenteral nutrition (Cain, 2015; Conwell, 2015). If there is bacterial superinfection of necrotizing pancreatitis, sepsis, or cholangitis, then broad-spectrum antimicrobials are administered. If common duct stones are found, then ERCP is indicated (Fogel, 2014; Tang, 2010). Cholecystectomy is considered after inflammation subsides because women with gallstonic pancreatitis carry an increased risk of recurrent pancreatitis (Cain, 2015).

Pregnancy outcomes are affected by acute pancreatitis severity. Eddy and associates (2008) reported a 30-percent preterm delivery rate, and 11 percent were delivered before 35 weeks' gestation. There were two pancreatitis-related maternal deaths. Importantly, almost a third of 73 women had recurrent pancreatitis during pregnancy. Of the 342 pregnancies complicated by pancreatitis in the California study, preterm delivery and fetal mortality rates were increased (Hacker, 2015). Also, preeclampsia risk was increased fourfold.

Pancreatic Transplantation

Few reports describe pregnancy following pancreas transplantation. Of 44 pregnancies in 73 women following pancreas-kidney transplantation,

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outcomes are encouraging, and vaginal delivery has been described (Mastrobattista, 2008). Although the incidence of hypertension, preeclampsia, preterm delivery, and fetal-growth restriction are high, there was only one perinatal death. Four rejection episodes developed during pregnancy and were treated successfully. Pancreatic islet autotransplantation may be performed to prevent diabetes following pancreatectomy, and at least three successful pregnancies have been reported (Jung, 2007).

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