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Pancreatic Disorders of Pregnancy

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Abstract: The pancreas is an organ with both exocrine and endocrine functions that has a vital role in both digestion as well as glucose metabolism. Although pancreatic dysfunction and disorders are rare in pregnancy, they are becoming increasingly more common. Recognition of these disorders and understanding how they can affect pregnancy is imperative to allow for proper management. We provide an overview of the most common pancreatic disorders that are seen in pregnancy.
Key words: pancreas, acute pancreatitis, chronic pancreatitis

The Pancreas

The pancreas is a retroperitoneal organ, located across the back of the abdomen, behind the stomach. It has both an exocrine and endocrine portion. The exocrine portion, comprising 85% of the mass of the pancreas, consists of acinar cells and a network of pancreatic ductules and ducts. The production of pancreatic enzymes, such as proteases, pancreatic lipase, and amylase occurs in these acinar cells. The epithelial cells lining the pancreatic ducts are responsible for the secretion of bicarbonate and water. These digestive enzymes, water, and sodium bicarbonate are secreted into the duodenum in a coordinated digestive process regulated by neural reflexes, gastrointestinal hormones, and absorbed nutrients.[1] Figure 1 demonstrates this anatomically.[2]

The endocrine pancreas controls the homeostasis of glucose homeostasis in the bloodstream. It consists of small clusters of cells called islets of Langerhans. Pancreatic islets house 3 major cell types: alpha cells, which secrete the hormone glucagon; beta cells, which produce insulin; and delta cells, which secrete the hormone somatostatin.[3]

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The author declare that there is nothing to disclose.

Pancreatic Adaptions to Pregnancy

One of the primary pancreatic adaptations that occur during pregnancy relates to glucose metabolism. The fetus depends on appropriate nutrient flow across the placenta. Glucose is one of the many nutrients that the fetus needs for proper development. Glucose is transported across the placenta in a passive process via facilitative glucose transporters. Glucose delivery to

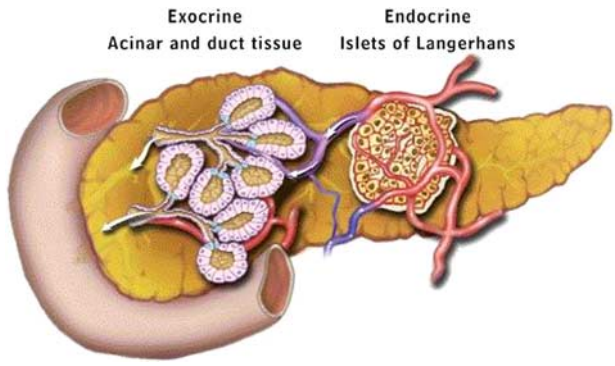

FIGURE 1. A model of the pancreas and its main locations for exocrine and endocrine functions. Pandol.[2] full color online

the fetus depends on the concentration gradient between the fetal and maternal circulations.[4] Early on, the fetal beta cells establish this gradient by maintaining low glucose in the fetal circulation through their high basal insulin secretion and relative glucose insensitivity. As pregnancy progresses, the growing fetus diverts an increasing fraction of maternal glucose across the placenta. To counterbalance this fetal glucose diversion, the placenta secretes hormones, such as human placental lactogen and human placental growth hormone that increase maternal insulin resistance and hepatic glucose production, thus raising glucose levels in the maternal circulation and maintaining the gradient.[5]

Secondary to this increased insulin resistance, there is a compensatory increase in beta-cell mass.[6] Autopsies have shown that maternal beta cells increase during human pregnancy by a factor of 1.4- to 2.4-fold.[7] The exact mechanism for this beta-cell expansion is unclear, however, it has previously been shown that placental lactogens and prolactin facilitate the increased islet mass and beta-cell proliferation.[8] As beta-cell hypertrophy occurs, a lower threshold for glucose-stimulated insulin secretion develops. This will counterbalance the progressive insulin resistance of pregnancy, maintaining normal plasma glucose levels.[9] Several animal studies have shown that when beta-cell expansion or function fails to compensate during pregnancy, gestational diabetes can occur.[10,11]

Unlike the endocrine pancreas, the exocrine pancreatic function does not appear to be significantly altered by pregnancy. Prospective studies of healthy women in pregnancy do not demonstrate any significant alterations in serum amylase or lipase levels when compared with nonpregnant women.[12,13]

Pancreatic Disorders in Pregnancy

Pancreatic disorders are uncommon in most women of reproductive age, and, rare during pregnancy. However, given the trend for increasing maternal age and a higher likelihood of concomitant medical comorbidities, such as diabetes or hypertension, there is an increasing frequency of pancreatic disorders diagnosed in pregnancy, particularly acute pancreatitis (AP).

AP

AP during pregnancy is a rare disease with an estimated incidence rate of 1 case per 1000 to 10,000 pregnancies.[14,15] Among AP cases reported in pregnancy, 19% occur in the first trimester, 26% in second trimester, and 53% in third trimester. The increased incidence

TABLE 1. Causes of AP in Pregnancy

Gallstones (65% to 100%)
Alcohol abuse (5% to 10%)
Familial hypertriglyceridemia–induced pancreatitis (5%)
Idiopathic (15%)
Drugs-induced AP (thiazide diuretics) (cases)
Pancreatitis associated with pregnancy-induced hypertension (cases)
Acute fatty liver of pregnancy associated with AP (cases)
Hyperparathyroidism (cases)
Gene mutations (cases)
Cationic trypsinogen (PRSS1)
CFTR

AP indicates acute pancreatitis; CFTR, cystic fibrosis transmembrane conductance regulator.

Ducarme et al.[16]

later in pregnancy parallels the increasing frequency of gallstone disease in pregnancy.[15]

Alcohol-related complications are the most common cause of AP in nonpregnant patients. However, during pregnancy, gallstone pancreatitis is by far the most common etiology. Table 1 is a list of the identified causes of AP and their respective frequency in pregnancy.[16]

Historic reviews on AP report maternal and fetal mortality rates as high as 20% and 50%, respectively.[17,18] However, these studies were published before the more mainstream use of cholecystectomy and endoscopic retrograde cholangiopancreatography (ERCP), as well as the advancing options in abdominal imaging allowing for more timely diagnosis. In addition, advancements in maternal and neonatal intensive care have also drastically improved outcomes. More contemporary studies indicate significantly better maternal and fetal outcomes with maternal mortality ranging from 0% to 3% and fetal loss ranging from 2% to 11%.[19,20] The risk of adverse pregnancy outcomes is also correlated to the severity of AP. Tang and colleagues reported on 54 cases of AP in pregnancy. There were no reported maternal deaths. They found the severity of hyperlipidemic pancreatitis was significantly higher than acute biliary pancreatitis. Overall, 20.4% of cases were complicated by fetal loss, of which 14.8% were stillbirths. The incidence of preterm delivery, fetal distress, and fetal loss also increased with the progression in the severity of AP.[21]

There are also several case studies in which AP presented in the context of concurrent diagnosis of preeclampsia. These clinical reports demonstrate the confusion that can occur in these complicated cases, with overlapping symptoms and laboratory abnormalities for both AP and preeclampsia. It is difficult to identify preeclampsia and/or AP in patients who present with these symptoms. Elevations in transaminases are common in the setting of pancreatitis and can also be identified in case of preeclampsia with severe features. Proteinuria has been documented to occur in upwards of 45% of cases of AP outside of pregnancy, and of these patients, 17% can have identified hypertension.[22] However, abnormalities in amylase or lipase are very uncommon in the setting of preeclampsia.[23]

Fetal complications are most often related to complications of preterm delivery, or first-trimester miscarriage, however, in cases of severe pancreatitis, stillbirths have been reported.[24] Sun and colleagues compared 18 pregnancies complicated by severe AP and 51 pregnancies with mild AP. They reported an overall fetal mortality of 23.2% in patients with AP. They concluded that miscarriages and preterm infants contributed to fetal loss in the 'mild' group, whereas fetal death and stillbirth contributed to the "severe" group.[25]

The typical clinical presentation of AP can often be nonspecific upper abdominal pain, nausea or vomiting, and anorexia. In pregnancy, patients can also present with other clinical symptoms, such as preterm contractions, clouding their diagnosis initially. The differential diagnosis maybe very broad in pregnancy, and

should include any other causes of abdominal pain, including preterm birth, cholecystitis, peptic ulcer disease, intestinal obstruction, and appendicitis. The initial investigation is not altered due to pregnancy and should include a thorough history to review for contributing risk factors such as gallstones, alcohol-related pancreatitis, hypertriglyceridemia, or autoimmune diseases, as well as a thorough examination. Initial laboratory tests should include a complete blood count, urinalysis, liver biochemical testing, triglycerides (although these levels must be interpreted in the context of pregnancy), and serum calcium. These will help determine a possible etiology for AP. Imaging is also necessary, and often abdominal ultrasound (US) is the initial imaging study of choice in pregnancy, as it avoids radiation exposure to the fetus. However, it is not as sensitive at detecting gallstones in the terminal common bile duct or at assessing the pancreas as computed tomography (CT) scan or magnetic resonance imaging (MRI). For patients with idiopathic pancreatitis, and negative right upper quadrant imaging, endoscopic ultrasonography (EUS) is recommended as the first step to assess for occult microlithiasis, neoplasms, and chronic pancreatitis (CP). If EUS is negative, magnetic resonance cholangiopancreatography (MRCP) is advised as a second step to identify other anatomic causes.[26]

Diagnosis of AP requires 2 of the following 3 features: (1) abdominal pain consistent with AP (acute onset of a persistent, severe, epigastric pain often radiating to the back); (2) serum lipase activity (or amylase activity) at least 3 times greater than the upper limit of normal; and (3) characteristic findings of AP on contrast-enhanced computed tomography and less commonly MRI or transabdominal US.[27] These diagnostic criteria are not specific for pregnancy, however, based on our knowledge of the minimal impact pregnancy has on the normal values for pancreatic enzymes, alternative diagnostic criteria are not used.

According to the revised Atlanta Classification, there are 2 subtypes of AP: interstitial edematous and necrotizing.[27] Interstitial edematous pancreatitis involves inflammation of the parenchyma of the pancreas, with CT findings demonstrating homogeneous enhancement of the parenchyma, along with mild stranding of the peripancreatic fat. Clinical symptoms of interstitial edematous pancreatitis typically resolve within 1 week. About 5% to 10% of the patients develop pancreatic necrosis. This most commonly manifests as necrosis involving both the pancreas and peripancreatic tissue. The impairment of pancreatic perfusion and signs of peripancreatic necrosis evolve over several days. CT findings typically demonstrate nonenhancing areas of the parenchyma or necrotic areas in the peripancreatic tissue.[28,29]

The revised Atlanta Classification further subdivides AP based on the severity. Mild pancreatitis is defined by the absence of organ failure, local, or systemic complications. Moderately severe AP is characterized by either transient organ failure, <48 hours, or local or systemic complications in the absence of persistent organ failure. These complications include pancreatic pseudocysts, peripancreatic fluid collection, and walled-off necrosis (WON). Severe AP is defined by the presence of persistent organ failure. In this classification system, the presence of organ failure is assessed by the modified Marshall scoring system (Table 2).[27]

In addition to the above-noted classification system, numerous scoring systems designed to predict the severity of AP exists. Early and accurate prediction of prognosis enables patients with or at risk of developing severe AP to be identified and thus has implications for management and timely intervention. Current scoring systems assess a combination of physiological, biochemical, and/or imaging

TABLE 2. Modified Marshall Scoring System for Organ Dysfunction

Organ System	Score 0	Score 1	Score 2	Score 3	Score 4
Respiratory (PaO_2/FiO_2)	> 400	301-400	201-300	101-200	≤ 101
Renal (serum creatinine	< 1.4	1.4-1.8	1.9-3.6	3.6-4.9	> 4.9
Cardiovascular (systolic blood pressure)	> 90	< 90 Fluid responsive	< 90 Fluid nonresponsive	< 90 pH < 7.3	< 90 pH < 7.2

A score of ≥ 2 in any 1 organ system defines "organ failure."

FiO_2 indicates fraction of inspired oxygen; PaO_2, partial pressure of oxygen.

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features and include such systems as Ranson criteria (Table 3), the BISAP score, and the modified Glasgow score.[31] However, none of these tests has high accuracy in predicting the true severity of AP, and none of these tests has been validated in the pregnant population.[30]

Gallstone Pancreatitis

As noted, gallstone pancreatitis is the most common etiology for pancreatitis in pregnancy. Certain physiological changes that occur in pregnancy heighten the risk of gallstone formation in pregnancy. Progesterone triggers the relaxation of smooth muscle with subsequent bile stasis along with a reduction in gallbladder ejection fraction. Estrogen induces increase in cholesterol content in bile and its supersaturation.[32] The incidence of gallbladder disease in pregnancy is low, about 1% to 8%. Ko and colleagues conducted a prospective study of over 3000 patients who had serial US examinations throughout the pregnancy. They found that in early pregnancy, the incidence of sludge or gallstones was 10.2%, and gallstones was 2.8%. Symptomatic biliary complication occurred in 1.2% of pregnant women.[33]

TABLE 3. Ranson Criteria

Present on Admission	Develop During First 48 Hours
Age >55 y	Hematocrit fall >10%
WBC >16,000/μl	BUN increase >5 mg/dL despite fluid
Blood glucose >200 mg/dL	Serum calcium <8 mg/dL
Serum LDH >350 U/L	Arterial oxygen saturation <60 mm Hg
AST >250 U/L	Base deficit >4 mEq/L
	Estimated fluid sequestration >6000 mL
Score 0-2: minimal mortality	
Score 3-5: 10%-20% mortality	
Score >5: >40% mortality	

Calculated on admission, and at 48 hours, to estimate mortality from pancreatitis. One point is given for each positive parameter for a maximum score of 11.

Score interpretation: 0 to 2 points: mortality 0% to 3%, 3 to 4 points: 15%, 5 to 6 points: 40%, 7 to 11: nearly 100%.

AST indicates aspartate transaminase; BUN, blood urea nitrogen; LDH, lactate dehydrogenase; WBC, white blood cell.

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Gallstone pancreatitis is initially treated with conservative measures including supportive care, in vitro fertilization replacement, pain control, and if necessary, nutritional support. Administration of total parenteral nutrition can be performed in pregnancy, however, there are known increased risks due to central line insertion in pregnancy compared with nonpregnant women.[34] Many experts prefer the use of a nasojejunal tube, with tube feeds rather than total parenteral nutrition through a central line. Tube feeds are associated with less risk of infection and allow for continued physiological use of the gut.[35] Unless there is an obvious infection, prophylactic antibiotics, are not standard treatment for AP.

Conservative measures will often suffice for most patients with gallstone pancreatitis,

due to spontaneous passage of the bile stone into the duodenum. Conservative management has not been shown to increase the risk of preterm birth or neonatal mortality.[36] However, studies have demonstrated upwards of a 50% risk of recurrence of AP during pregnancy, with further passage of gallstones.[37] For patients with cholangitis or common bile duct obstruction, conservative measures are much less successful.

The decision for surgery is never made without careful thought and planning. Two very important considerations are which procedure to use for treatment, and when treatment should be performed. These decisions are influenced by the trimester of pregnancy, the severity of AP, as well as the presence or absence of common bile duct dilation or cholangitis. The second trimester is the preferred gestational age for surgery as organogenesis is complete and the uterus is not big enough to obliterate the surgical view in a laparoscopic approach.

Cholecystectomy, for many experts, is the procedure of choice for definitive treatment of gallstone pancreatitis. Patients with mild pancreatitis can safely have a cholecystectomy within 7 days of recovery. Those with more severe AP, surgery should be delayed until the patient is stable, all peripancreatic fluid collections resolve, and evidence of resolution of acute inflammation.[38] Often, if performed in the second trimester, laparoscopic cholecystectomy is feasible. A recent systematic review of open versus laparoscopic cholecystectomy in pregnancy included 11 studies and over 10,000 patients. They found that the laparoscopic approach was associated with a lower risk of fetal and maternal complications. Overall, 90% of those treated were in the first or second trimester.[39]

For those patients with evidence of cholangitis or common bile duct obstruction, ERCP is often required. ERCP is not indicated otherwise. When indicated, it is ideally performed within 24 hours of admission, as this has been shown to decrease the severity of AP. If there are overt signs of gallbladder disease, a cholecystectomy is still indicated. As treatment by ERCP alone maybe associated with a higher risk of biliary complications during follow-up compared with cholecystectomy, these patients may require close surveillance.[40] Although the performance of ERCP requires fluoroscopy, it can be performed in pregnancy, often with techniques to minimize radiation exposure. Smith and colleagues demonstrated that with modified fluoroscopic techniques, the estimated fetal radiation exposure ranged from 0.1 to 0.5 mGy. They, along with others, have demonstrated the safety of performing ERCP in pregnancy.[41]

Polydorou and colleagues published a report in 2012 on a multimodal approach to the treatment of AP in pregnancy. They reported 7 pregnant women managed by using MRCP, ERCP, and sphincterotomy followed by laparoscopic cholecystectomy. They concluded that active management of gallstone pancreatitis provides definite treatment and does not appear to increase the risk of adverse events.[42] Other studies have shown similar findings. As such, some experts propose a treatment strategy based on gestational age. In the first trimester: conservative treatment and delayed laparoscopic cholecystectomy during second trimester. In the second trimester: laparoscopic cholecystectomy. And, in the third trimester: conservative treatment or ERCP with biliary endoscopic sphincterotomy, and laparoscopic cholecystectomy in the early postpartum period.

Postprocedural Pancreatitis

ERCP is a procedure where a special endoscope is utilized to examine the pancreatic and bile ducts. The endoscope is guided into the duodenum, allowing visualization and instrumentation of the bile and pancreatic ducts. The contrast medium is injected and allows radiographic imaging of the ducts.

It historically was used for diagnostic purposes, but given the advancements in MRCP, ERCP is typically reserved for therapeutic purposes. Postprocedural pancreatitis is the most common adverse event after an ERCP, occurring in roughly 1% to 10% of cases. Transient elevations in serum amylase can occur in upwards of 75% of cases and does not constitute a diagnosis of pancreatitis.[43] The mechanism for pancreatitis is thought to be related to either mechanical trauma to the pancreatic ducts or hydrostatic injury from forceful injection into the pancreatic ducts.[44]

The consensus definition of post-ERCP pancreatitis consists of the following criteria: serum amylase at least 3 times above the upper limit of normal 24 hours postprocedure level accompanied by new abdominal pain consistent with pancreatitis and symptoms severe enough to require a hospital stay or to extend the length of stay of already hospitalized patients, and/or abdominal CT consistent with the diagnosis of AP.[45] The cases are further subdivided into mild, moderate, and severe cases, as listed in Table 4.

As discussed above, ERCP is a procedure that can safely be performed in pregnancy. There are very few studies specifically addressing the risk of post-ERCP pancreatitis in pregnant women. Inamdar and colleagues performed a retrospective matched cohort study comparing 907 pregnant women who underwent ERCP to 2721 nonpregnant women who underwent ERCP. This is one of the largest studies looking at this topic. They found that post-ERCP pancreatitis occurred in 12% of pregnant women and in 5% of controls ($P < 0.001$). Interestingly, the rate of postprocedural pancreatitis was lower when the procedure was performed at teaching hospitals (9.6%) compared with nonteaching hospitals (14.6%). This may suggest there is some potential benefit to transferring pregnant women to a tertiary care center if an ERCP is necessary.[46]

TABLE 4. Classification of Post-ERCP Pancreatitis

Mild	Moderate	Severe
Clinical pancreatitis AND	Pancreatitis requiring hospitalization of 4-10 d	Hospitalization for > 10 d OR
Amylase at least 3 times normal at > 24 h after the procedure AND		Development of hemorrhagic pancreatitis, phlegmon, pseudocyst, or infection OR
Requiring admission or prolongation of planned admission to 2-3 d		Need for percutaneous drainage or surgery

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Postprocedural pancreatitis is treated in a similar fashion to AP, regardless of pregnancy.

Hypertriglyceridemia-induced Pancreatitis

One of the known metabolic changes that ensue in pregnancy, is the alteration of cholesterol levels. The concentration of plasma cholesterol increases by 50% and triglycerides by 2 to 3 times, in an effort to supply the fetus needed cholesterol.[47] Triglyceride concentration rises gradually over prepregnancy levels, reaching a peak during the third trimester. In the first 2 trimesters, the primary changes noted are directing lipids toward storage depots for use in later gestation. In the third trimester, estrogen stimulates the production of hepatic very-low-density lipoprotein, reduces removal of triglycerides by lipoprotein lipase (LPL) in the liver and adipose tissue. After pregnancy, lipid levels have been shown to decrease by as much as 15% within 24 hours of delivery and return to near normal by 6 weeks postpartum.[48]

During a normal pregnancy, elevations in triglyceride and cholesterol levels usually do

not exceed 332 and 337 mg/dL. For the vast majority of women, these temporary increases in cholesterol and triglycerides do not pose a serious risk to maternal health. However, for a small percentage of women, primarily those with familial hypertriglyceridemia, this increasing production of triglycerides, can increase the risk for complications in pregnancy, including hyperviscosity syndrome and AP.[49] Hyperviscosity syndrome classically presents with the triad of neurological deficits, visual changes, and mucosal bleeding. Elevated blood viscosity is the result of either red blood cell shape deformity or a pathologic increase in serum proteins, red blood cells, white blood cells, or platelets.

Women with familial hypertriglyceridemia require careful monitoring in pregnancy. There is no clear threshold at which hypertriglyceridemia triggers AP, however, triglyceride level >1000 mg/dL is a known risk factor for the development of AP. Scherer et al[50] reported that the risk of developing AP is ~5% with serum triglycerides >1000 mg/dL and 10% to 20% with triglycerides >2000 mg/dL.

The exact mechanism by which hypertriglyceridemia induces AP in the unknown, however, several theories exist. The most common theory put forward by Havel and colleagues, suggests that very large triglyceride lipoproteins impair pancreatic microcirculation, leading to ischemia and hydrolytic release of free fatty acids. The high concentration of free fatty acids overwhelm the binding capacity of albumin and induce acinar cell and pancreatic capillary injury.[51] Although hypertriglyceridemia is not the most common etiology for AP in pregnancy, several studies have suggested that it accounts for a large percentage of cases of severe AP, in some instances up to 50%.[52]

There are no specific guidelines on how to treat hypertriglyceridemia in pregnancy. Some experts propose a goal of trying to keep triglyceride levels <500 mg/dL.[53] Primary treatment options include low-fat diet, strict avoidance of alcohol, and consideration for lipid-lowering agents. Dietary modification typically includes reduction of dietary fat content to ~15% of caloric intake. However, care must be taken to avoid significant weight loss in pregnancy, as it can be associated with intrauterine growth restriction. In addition to low fat diet, supplementation with omega-3 fatty acids are recommended as they have been shown to reduce serum triglycerides.[54] Fibrate therapy is typically the initial lipid-lowering treatment chosen for nonpregnant patients who are not responding to dietary and lifestyle modifications. There is minimal data on fibrates in pregnancy and it is unknown if they cross the placenta, therefore, fibrates are typically avoided in the first trimester. However, a few small studies have not demonstrated any increased risk of congenital birth defects with exposure in the first trimester. Its use must, therefore, be weighed in the context of potential benefits versus unknown risks.[55]

In nonpregnant patients, heparin and insulin have been used in the management of hypertriglyceridemia-induced AP. Both have been shown to decreases serum triglyceride levels.[56] LPL is a pivotal enzyme required for the removal of triglycerides from the plasma. Insulin promotes synthesis and activation of LPL, thereby accelerating chylomicron degradation. Heparan sulfate proteoglycan has also been shown to release LPL into plasma increasing TG metabolism. This effect is likely transient because chronic depletion of LPL can cause the TG level to increase once again. The safety and efficacy of heparin and insulin in the treatment of hypertriglyceridemia-associated AP have not been well established yet as most of our understanding of their use comes from isolated cases.[57] These modalities are also not well studied in the pregnant population. The risks

need to be weighed for either therapy. Insulin can, of course, induce hypoglycemia in patients without known diabetes. As such, it is typically avoided in pregnancy unless a patient has diabetes.

Therapeutic plasma exchange (TPE) is used in nonpregnant patients with hypertriglyceridemia-induced AP for a rapid reduction in triglyceride levels. TPE used for lowering triglycerides levels was first reported in 1978 by Betteridge et al.[58] It involves removal of patient plasma and replacement with colloid or crystalloid solutions. Triglyceride levels have been shown to decrease by as much as 70% after a single session of TPE.[59] Numerous, mainly retrospective, case reports or small series have reported on the use of TPE in patients with hypertriglyceride induced AP, however, due to variability between studies, and lack of larger prospective or randomized trials. The role of TPE is still not well defined. TPE is categorized as a grade 1c recommendation for severe AP by the American Society for Apheresis guidelines.[60] The data on use of TPE for hypertriglyceridemia in pregnancy is even more lacking. Huang and colleagues recently performed a review of 21 patients with AP. Ten of these patients included had hypertriglyceridemia-induced AP, of these, 5 patients had TPE. TPE decreased the incidence of systemic inflammatory response syndrome from 100% to 28.6% and the triglyceride level from 20.36 ± 7.41 to 5.23 ± 3.62 mmol/L. This report, and several others appear to suggest the safety and effectiveness of TPE use during pregnancy.[61]

CP

CP is an inflammatory syndrome of the pancreas in individuals with genetic, environmental and/or other risk factors who develop persistent pathologic responses to parenchymal injury or stress.[62] The progressive changes that occur cause irreversible damage, resulting in loss of exocrine and endocrine function. The pathophysiology of CP is complex and includes acinar cell injury, duct dysfunction, persistent inflammation and fibrosis of the pancreas, but the mechanisms for these are not completely understood. The overall incidence of CP ranges from 4.4 to 11.9 per 100,000 per year, with the incidence being higher in men than women by a factor of 1.5 to 3.[63]

Patients with CP most often present with abdominal pain, and those with long-standing CP often have evidence of pancreatic insufficiency. This pancreatic insufficiency includes issues with fat malabsorption (steatorrhea) and/or glucose intolerance or overt diabetes.[64] Initial symptoms of abdominal pain can make it difficult to differentiate between CP and AP. The 2 diseases can often be distinguished by careful history and evaluation of symptoms as well as laboratory values. CP often has long periods where patients are asymptomatic, and often evidence of pancreatic insufficiency without pain, whereas AP most often presents with abdominal pain. Patients with CP often have normal amylase and lipase values, while these laboratory values are consistently elevated in AP.

The etiology of CP has traditionally been classified as alcohol, hereditary, obstructive, hyperlipidemia, and idiopathic. Alcohol and smoking contribute greatly to the development of CP; however, alcohol is the greatest contributor, accounting for 44% to 65% of cases.[65] There are several different classification systems that have been developed for the etiologies of CP. One of the more commonly used is the TIGAR-O risk factor classification, proposed as follows: toxic-metabolic, idiopathic, genetic, autoimmune, recurrent and severe AP associated CP, and obstructive etiologic factors (Table 5). This classification system was developed with the premise that the risk of developing CP in an individual is

TABLE 5. TIGAR-O Classification

Toxic-metabolic	Alcohol, tobacco, smoking, hypercalcemia, hyperlipidemia, chronic renal failure, medications, toxins
Idiopathic	Early-onset, late-onset, tropical
Genetic mutations	PRSS1, CFTR, SPINK1, other
Autoimmune	Isolated, syndromic
Recurrent and severe acute pancreatitis associated chronic pancreatitis	Postnecrotic (severe acute pancreatitis), vascular disease/ischemic, postirradiation
Obstructive	Pancreas divisum, sphincter of Oddi disorders, duct obstruction (eg, tumor), posttraumatic pancreatic duct scars

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determined by the presence of ≥ 1 risk factor.[66,67]

The diagnosis of CP is made based on a patient's history, clinical presentation, and imaging findings. There is no single test that is diagnostic of CP, especially in the early stages. If CP is suspected based on history and physical examination, a diagnostic workup should be initiated. Imaging studies, such as CT scan, US, or MRI, demonstrating pancreatic calcifications strongly support the diagnosis. It is very important that during any workup that pancreatic cancer is considered in the differential, as it has a very similar presentation to CP. A diagnostic algorithm has been proposed by the American Pancreatic Association, as shown in Figure 2.[68]

There is very limited data on CP in pregnancy. The small studies that do exist are often confounded by the inclusion of cases of AP as well as CP. Eddy and colleagues reported on 101 cases of pancreatitis in pregnancy over 10 years. Of these 101 cases, 12 women had CP. Alcohol-related complications were the underlying etiology in 58% of these cases of CP. Their retrospective study found that CP was associated with a 45% risk of preterm delivery, however, they did not differentiate iatrogenic preterm birth from spontaneous. There were no associated cases of maternal or fetal death.[52]

Pancreatic Fluid Collections

Pancreatic fluid collections are a frequent complication of pancreatitis. According to the revised Atlanta Criteria, fluid collections are classified as either acute (<4 wk after the pancreatitis episode) or chronic (>4 wk after the pancreatitis episode). Acute and chronic collections are further subdivided based on the presence of necrosis within the collection. Acute collections are divided into acute peripancreatic fluid collections and acute necrotic collections (ANCs); chronic fluid collections are divided into pseudocysts or WON. Approximately 5% to 15% of pancreatitis cases are complicated by the development of pseudocysts, whereas 15% of cases are complicated by pancreatic necrosis, of which 33% are complicated by infected necrosis.[69]

Acute peripancreatic fluid collections have been shown to complicate acute interstitial edematous pancreatitis and can be evident in up to 30% to 50% cases. These collections develop early after the onset of pancreatitis due to the extravasation of fluid secondary to pancreatic injury. These appear on imaging as poorly defined, homogenous fluid collections adjacent to the pancreas that lack a wall. These typically resolve spontaneously within 2 weeks. Approximately 7% worsen to form pseudocysts.[70]

ANCs result from acute necrotizing pancreatitis. Early on during acute necrotizing pancreatitis acinar cell death can lead to injury of the microvasculature. This, in turn, can lead to

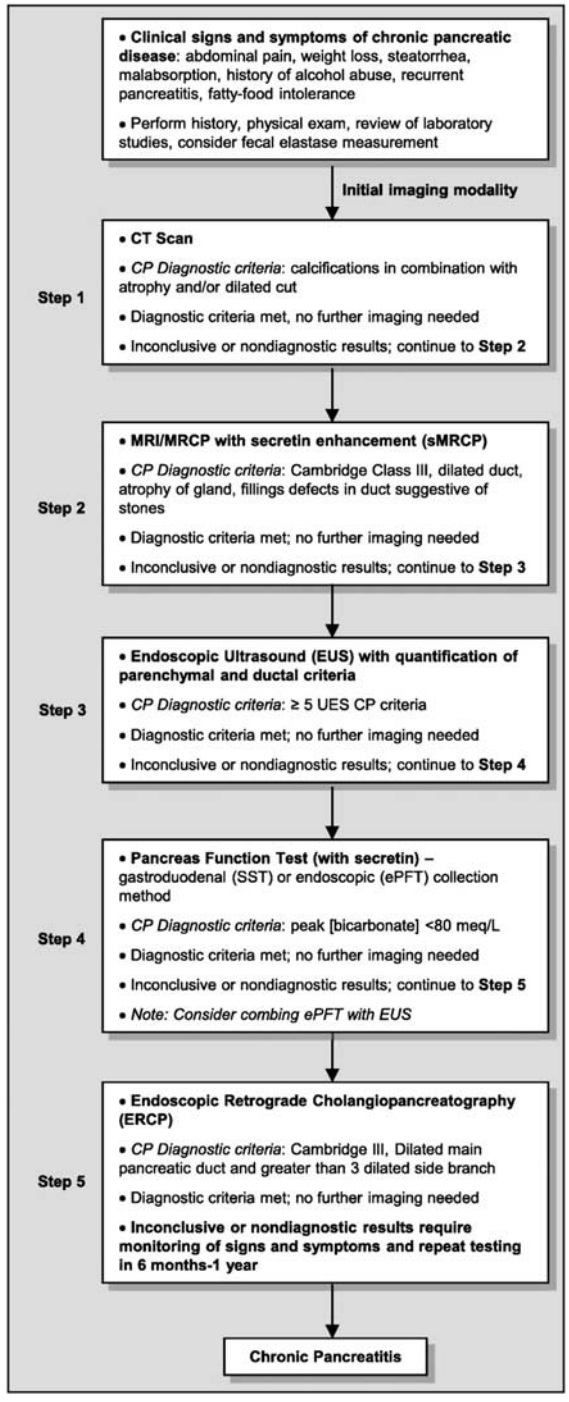

FIGURE 2. Diagnostic guidelines for chronic pancreatitis. Reprinted with permission from Conwell et al.[68] CP indicates chronic pancreatitis; CT, computed tomography; EUS, endoscopic ultrasonography; MRCP, magnetic resonance cholangiopancreatography; MRI, magnetic resonance imaging; PFT, pulmonary function test; SST, secretin stimulation test.

inappropriate emission of pancreatic enzymes as well as cytokines to the surrounding peripancreatic tissue, which can cause necrosis. After the first several days of AP, ACNs can begin to form and appear as heterogenous areas with no defined wall, both within and outside the pancreatic parenchyma. They can consist of both solid and liquid components representative of areas of necrosis. Over time, the liquid component increases further as the process of liquefaction necrosis evolves. As the ANCs mature, the body tends to wall of the reactive tissues and the ANC then becomes encapsulated. At that stage, the collection is termed WON.[71] WON typically takes about 3 to 4 weeks from the initial episode of AP to develop. On imaging, WON appears heterogenous with liquid and nonliquid density with varying degrees of loculations and a well-defined wall. Both ANC and WON are initially sterile, but over time can develop infection. Approximately 30% of patients with pancreatic necrosis develop infected necrosis. Infected necrosis is initially treated with empiric antibiotic therapy directed at the most common offending pathogens (*Escherichia coli*, *Pseudomonas*, *Klebsiella*, and *Enterococcus*).[72] If the patient remains stable, antibiotics are typically utilized for a minimum of 4 weeks. If a patient's clinical status is worsening, debridement is likely necessary. If they remain stable, attempts are made to delay debridement for at least 4 weeks to allow for a less invasive technique of drainage or debridement.[73]

Pancreatic pseudocysts complicate 5% of cases of pancreatitis and are defined as a fluid collection in the peripancreatic tissues surrounded by a well-defined wall with essentially no solid material and no recognizable necrosis. Pseudocysts are thought to arise from disruption of pancreatic ducts, allowing leakage of pancreatic secretions into a localized fluid collection. Pseudocysts most often occur in the setting of AP but can also occur in the setting of pancreatic trauma or CP.[74] They typically occur at least 4 weeks after the onset of interstitial edematous pancreatitis. During this time, upwards of 30% of pseudocysts will spontaneously resolve. Those that do not resolve will require treatment due to the risk of infection, hemorrhage or rupture.[75]

Management of most pancreatic pseudocysts is contingent upon the clinical status of the patient. Patients with minimal to no symptoms can be managed expectantly. Pseudocysts that rapidly expand, become infected or cause progressively worsening symptoms, are drained. Endoscopic drainage is the preferred method for drainage, with a 90% success rate and a 10% rate of recurrence.[76]

There is limited data on pancreatic fluid collections in pregnancy with <15 reported cases in the literature. Eddy and colleagues performed a review of available case reports. They found that hyperlipidemia induced AP accounted for almost half the cases of pseudocysts. The natural history of pseudocysts in pregnant patients seems to be like that of their nonpregnant counterparts. Therefore, management of pseudocyst in pregnancy is similar to the nonpregnant population. Complications that arise in pregnancy, are likely related more to the underlying severity of the patient's pancreatitis or pancreatic insult. It is impossible to differentiate from the literature if pancreatic pseudocysts alone increase the risk further for adverse outcomes in pregnancy. Eddy et al[77] also report on successful vaginal delivery in women with pseudocysts, however, there is also a reported case of a pseudocyst rupturing during vaginal delivery requiring patient admission to the intensive care unit. This raises the question of a theoretical concern over Valsalva for women at the time of delivery in the presence of a pseudocyst, however, with such limited data, no recommendations can be made.

Pancreatic Cystic Neoplasms (PCNs)

PCNs are a type of cystic lesion in the pancreas, most often identified incidentally during imaging performed for other reasons. PCN's account for 50% of identified pancreatic cysts (with the remainder being non-neoplastic cysts). There are 4 subtypes of PCN: serous cystic tumors, mucinous cystic neoplasms, intraductal papillary mucinous neoplasm, and solid pseudopapillary neoplasms.[78] The risk of malignant transformation in the majority of incidentally found pancreatic cysts is very low but also depends on the type of cyst. The risk if very low for serous cystic tumors, whereas the risk is moderate to high in mucinous cystic neoplasms, solid pseudopapillary tumors, and some intraductal papillary mucinous tumors.[79]

Our understanding of PCN's in pregnancy is limited to case reports or case series. With limited data to develop consensus guidelines for the management of PCNs in pregnancy, we are guided by expert opinion during these cases. US can be used to diagnose PCNs, however, MRI remains the imaging modality of choice in pregnancy. Management recommendations are contingent on the gestational age of diagnosis as well as the level of concern for underlying malignancy. There are several case reports demonstrating successful resection of PCNs in the second trimester.[80,81] If a PCN is diagnosed in the third trimester, surgical management is typically postponed until postpartum. There are reported cases of successful vaginal delivery in the setting of PCNs.[82] Elevated concern for malignancy, does potentially alter recommendations (as noted in more detail below).

Pancreatic Cancer

Pancreatic cancer is one of the leading causes of cancer mortality in developed countries, accounting for >400,000 deaths per year.[83] In the United States, pancreatic cancer is the fourth leading cause of cancer-related death.[84] Pancreatic cancer is most often diagnosed in advanced stages and carries a 5-year survival rate of <5%. The majority of pancreatic cancer is adenocarcinoma, accounting for 85% of cases. The term "exocrine pancreatic tumors" is used to refer to all tumors that arise from the pancreatic ductal and acinar cells and their stem cells, which account for 95% of pancreatic tumors. Endocrine pancreatic tumors account for only 5% of pancreatic cancers.

Pancreatic cancer is rare before the age of 45 years and has a higher incidence in males than females. Only 3% to 4% of pancreatic cancers occur in females of reproductive age.[85] Because of this, pancreatic cancer in reproductive age women is rare. Certain factors do increase the risk of pancreatic cancer. Approximately 5% to 10% of cases, the patient has a positive family history. Genetic risk is either categorized based on genetic predisposition syndromes (eg, Lynch syndrome, hereditary pancreatitis) or familial pancreatic cancer. A few other identified risk factors include a history of cystic fibrosis, pancreatic cysts, CP, diabetes, and smoking.

Pancreatic cancer has a similar presentation in pregnancy as nonpregnancy with abdominal pain, biliary obstruction, and many nonspecific symptoms such as fatigue and weight loss. Many of these vague symptoms can be mistaken for normal pregnancy symptoms, and more common causes of abdominal pain are often sought after. Because of this, the initial diagnosis of pancreatic cancer can be delayed in pregnancy. Wakefield and colleagues performed a literature search for pancreatic cancer in pregnancy and found 21 published case reports from 1954 to 2017. The average age of diagnosis in these reports was 35 years old (95% CI: 33-37 y) and the average

gestational age at diagnosis was 24 weeks (95% CI: 21-27 wk).[86]

Pancreatic cancers are categorized as resectable, locally advanced/unresectable, or metastatic. This assessment is based on a staging CT scan and is determined by the presence or absence of metastasis to local structures of vascular involvement. Only 15% to 20% of patients have resectable disease at the time of diagnosis.[87] Only those with tumors categorized as resectable are candidates for surgery. Those with locally advanced or metastatic cancer are not surgical candidates and are offered palliative treatment and consideration for chemotherapy. The median survival for untreated locally advanced is about 8 to 12 months and for those with metastatic disease is about 3 to 6 months.[88]

Treatment of pancreatic cancer in pregnancy can pose a difficult clinical dilemma given the concerns of performing surgery or the use of chemotherapy in pregnancy. These risks must be weighed against the risk of nonintervention and its effects on the pregnant patient. The 2 most salient factors in determining a treatment strategy for pancreatic cancer diagnosed in pregnancy are the stage of disease and the gestational age at diagnosis. If pancreatic cancer is diagnosed in the first trimester, consideration for termination of pregnancy should be discussed. Delaying treatment >3 months could potentially allow progression of the disease, and in cases of resectable cancer, this could advance to nonresectable disease during that time.[89]

As with other nonobstetric surgeries, the second trimester is the ideal to perform resection if the patient is a candidate. This historically is done due to concerns for increased risk of miscarriage in the first trimester, as well as better access to the pancreas before increasing the size of the uterus in the third trimester. However, there are studies that demonstrate nonobstetric surgery does not pose a higher risk of miscarriage than the general population.[90] Decisions to proceed with surgery must be taken in the context of the long-term prognosis. There are several case reports of pancreatic cancer resection in pregnancy, most of which demonstrate a low risk of surgical complications.[91,92]

Summary

In conclusion, pancreatic disorders are relatively uncommon in pregnancy, but their frequency is increasing with time. As such, one must remain clinically vigilant with pregnant patients. Many of these pancreatic disorders present with vague symptoms, that are often similar in presentation to other etiologies such as preterm labor or gastroenteritis. Maintaining a high index of suspicion can often prevent a delayed diagnosis of AP or CP.

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