Acute pancreatitis during pregnancy
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Acute pancreatitis in pregnancy is a rare condition estimated to occur in 1 per 1000 to 1 per 12 000 pregnancies. The most frequent etiology in pregnancy is biliary, followed by hyperlipidemia and/or alcohol abuse. Abdominal ultrasound and endoscopic ultrasound are ideal imaging techniques for diagnosing disease because they have no radiation risk. Computed tomography, magnetic resonance cholangiopancreatography, and endoscopic retrograde cholangiopancreatography should be used with caution. Treatment could be conservative or surgical, and standard algorithms are slightly modified in pregnant women. In the last decades the outcome of acute pancreatitis in pregnancy is much better, and perinatal mortality is less than 5%. Eur J Gastroenterol Hepatol 23:839–844 © 2011 Wolters Kluwer Health | Lippincott Williams & Wilkins.

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Introduction
More than half or, in some studies, nearly 70% of cases of acute pancreatitis (AP) during pregnancy are secondary to biliary stones or sludge, followed by hyperlipidemia and/or alcohol abuse in approximately 20% of cases [1–4]. In developed countries other causes are hyperparathyroidism, iatrogenic (diuretics, antibiotics, and antihypertensive drugs), connective tissue diseases, abdominal surgery, infections (viral, bacterial, or parasitic), and blunt abdominal injuries [2–4]. Today, it is still not clear, whether the pathogenesis of AP is one entity, or whether it consists of a group of distinct pathogenetic mechanisms. The pathogenesis of AP is still unknown, but many investigators have tried to reveal the molecular steps mediating acute inflammation of the pancreas in animal models. Many theories such as the common bile duct pathway theory, pancreatic autodigestion theory, gallstone migration theory, enzyme activation theory, kinin and complement system activation theory, pancreatic acinar cell apoptosis and necrosis theory, microcirculation disturbance theory, and leukocyte excessive theory have been proposed to explain the mechanisms underlying AP [1–5].

During pregnancy, gallstones and sludge induce most of the cases of AP. These cause duct obstruction and probably pancreatic hyperstimulation that increases pancreatic duct pressure, trypsin reflux, and activation of trypsin in the pancreatic acinar cells. This leads to enzyme activation within the pancreas and causes autodigestion of the gland, followed by local inflammation. Pregnancy does not primarily predispose pregnant women to pancreatitis, but it does increase the risk of cholelithiasis and biliary sludge formation [5]. Theoretical reasons for the association of pregnancy and biliary tract diseases include increased bile acid pool size, decreased enterohepatic circulation, decreased percentage of chenodeoxycholic acid, and increased percentage of cholic acid and cholesterol secretion and bile stasis [6]. Moreover, the steroid hormones of pregnancy decrease gallbladder motility [5]. Progesterone is a smooth muscle cell inhibitor that provokes gallbladder volume increase and slows emptying [5]. Estrogens increase cholesterol secretion and minimally alter gallbladder function [5]. In addition, in the third trimester when the AP is most frequent, the uterus is enlarged and intra-abdominal pressure on the biliary ducts is increased [7–9].

Hyperlipidemic pancreatitis associated with type I, IV, or V familial hyperlipoproteinemia accounts for approximately 5–56% of AP during pregnancy [10-13]. In women with pre-existing familial hyperlipidemia the physiologic increase in serum triglycerides can precipitate AP [14], because enhanced adipose tissue lipolysis facilitates the availability to the liver substrates for the synthesis of triglycerides, inducing high flux of very-low-density lipoproteins into the circulation. This associated with simultaneous reduction in lipoprotein lipase activity causes inadequate triglyceride removal [15].

Pancreatitis as a result of hypercalcemia due to hyperparathyroidism, followed by parathyroid adenoma has a prevalence of 7 to 13% in pregnancy [16].

Epidemiology
AP in pregnancy is a rare condition estimated to occur in 1 per 1000 to 1 per 12 000 pregnancies [3]. This discrepancy in incidence is because of the rarity of this condition, the low number of reviews and typically small number of cases included in the studies [17]. The largest study is from 1995 reports in which 43 cases of AP out of 147 197 pregnant women were studied [3]. The differences between studies are great because they span...
different decades and countries. Some studies include all cases of pancreatitis, and some only AP or biliary pancreatitis [17]. In addition, some studies include cases of AP only during pregnancy, whereas other studies include the postpartum period. AP appears to be more prevalent with advanced gestational stage, occurring more commonly in the second and the third trimesters [2,5]. Ramin et al. [3] noted that the incidence of AP was 19% in the first, 26% in the second, 53% in the third, and 2% in the postpartum period, while Hernandez et al. [2] reported most cases, 56%, in the second trimester.

Clinical presentation
AP in pregnancy is mainly related to gallbladder disorders and correlates with cholelithiasis and biliary sludge (muddy sediment, precursor to gallstone formation) as the most likely predisposing causes [5]. The symptoms of gallbladder disease can be present or can precede the clinical presentation of AP. The symptoms include the classic colicky or stabbing pain in the right upper quadrant and/or epigastric area, which can radiate to the right flank, scapula, and shoulder [5]. Other symptoms of gallbladder disease include anorexia, nausea, vomiting, dyspepsia, low-grade fever, tachycardia, and fatty food intolerance [5]. In accordance with AP abdominal pain could be mild-to-incapacitating, along with the existence of abdominal tenderness, muscle rigidity, jaundice, paralytic ileus, and hypoxemia [5]. Two most common types of AP in pregnancy differ according to history, physical examination, values of some laboratory parameters, and findings on imaging methods. Characteristics of the two most common types of AP in pregnancy biliary and hyperlipidemic are presented in Table 1.

Diagnosis
AP is diagnosed in pregnancy by laboratory investigations and imaging methods. Laboratory investigations are the same as in nonpregnant population; elevation of serum amylase and lipase levels three times over upper limit of normal have diagnostic value. Amylase-to-creatinine clearance ratio greater than 5% additionally suggests AP [7].

Abdominal ultrasound is the ideal imaging technique for detection of gallstones, with no radiation risk to the fetus in pregnant women. Computed tomography should be avoided because of the fear of radiation exposure to the fetus. Endoscopic ultrasound has a high positive predictive value nearing 100% in detecting suspected common bile duct stones, even small stones of 2 mm or less or sludge [18]. It is superior to magnetic resonance cholangiopancreatography (MRCP), an imaging method providing multiplanar large field of view images of the bilopancreaticoduodenal system. There are some concerns about the safety of MRCP in the first trimester of pregnancy because radiofrequency pulses result in energy deposition and would potentially result in tissue heating [19]. Endoscopic retrograde cholangiopancreatography (ERCP) should be used only as a therapeutic option in selected cases with confirmed bile duct stones. Many diseases, such as biliary colic, acute cholecystitis, etc., can mimic AP in pregnancy. Serum amylase, lipase, bilirubin, and transaminase can help us in a diagnostic process because of some differences in their levels. Differential diagnoses of AP in pregnancy are presented in Table 2.

| Table 1 Characteristics of two most common types of acute pancreatitis in pregnancy |
|-----------------------------------------------|----------------|----------------|
| Hyperlipidemic pancreatitis | Biliary pancreatitis |
| Abdominal pain | Diffuse | Colicky, diffuse |
| Serum lipase level | ↑ | ↑ |
| Serum amylase level | N or ↑ | ↑ |
| Triglyceride > 10 mmol/l | N |
| Serum Lipemic, milky coloration | N |
| Ultrasound | N or hepatosplenomegaly | Stones |
| Hyperglycemia | N or ↑ | N or ↑ |
| BMI | N or ↑ | N or ↑ |
| Diabetes mellitus | Type I, type II | Type II |
| Family history | Hyperlipidemia | None |
| Alcohol | Yes | No |
| Xanthoma | Yes | No |
| Lypemia retinalis | Yes | No |

↑, elevated; N, normal.

| Table 2 Differential diagnosis of acute pancreatitis in pregnancy |
|-----------------------------------------------|----------------|----------------|
| Serum amylase and lipase level | Serum bilirubin level | Serum transaminase level |
| Acute pancreatitis | ↑ | N or ↑ | N or ↑ |
| Biliary colic | N | N | N |
| Acute cholecystitis | N | N | N |
| Acute cholangitis | N | ↑ | N or ↑ |
| Acute fatty liver in pregnancy | N | ↑ | ↑ |
| HELLP syndrome | N | ↑ | ↑ |
| Penetrating peptic ulcer | N or ↑ | N | N |
| Intestinal obstruction | N or ↑ | N | N |

↑, elevated; HELLP, hemolytic anemia, elevated liver enzymes, low platelet count; N, normal.

Treatment
Conventional treatment measures
Mild pancreatitis treated conservatively usually resolves within 7 days. Treatment consists of fluid restoration, oxygen, analgetics, antiemetics, and monitoring of vital signs.

Pregnant women who develop severe AP should be admitted to an intensive care unit. The third space fluid sequestration is the most serious hemodynamic disorder leading to hypovolemia and organ hypoperfusion resulting in multiple organ failure. In volume-depleted patients the essential treatment modality is initial infusion of 500 to 1000 ml of fluid per hour [20–22]. Monitoring of
hydration, cardiovascular, renal, and respiratory functions is important for early detection of volume overload and electrolyte disturbances [23].

Many pharmacological agents (somatostatin, octreotide, \(\alpha\)-acetyl-cystein, gabexate mesylate, lepixafant, and probiotics) have been investigated in AP, but because most of them have failed to show a positive effect they should be avoided in pregnancy.

Cessation of oral feeding has been thought to suppress the exocrine function of pancreas, and to prevent further pancreatic autodigestion. The bowel rest is associated with increased infectious complications, and total parenteral nutrition (TPN) and enteral nutrition have an important role in the management of AP. Keeping the patients nil-by-mouth with the use of TPN has been for years a traditional treatment of AP. TPN, however, carries a significant risk of infections and metabolic distress. The use of enteral nutrition has shown some potential beneficial effects by improving gut-barrier function and diminishing complications of AP.

Treatment of severe necrotizing pancreatitis should include enteral feeding by nasojejunal tube and if needed, should be supplemented by parenteral nutrition [24].

Mild cases of AP do not need nutritional support, as the clinical course is usually uncomplicated and a low-fat diet can be started within 3 to 5 days.

Antibiotics have no role in the treatment of mild AP. The use of prophylactic antibiotics in severe AP remains controversial. The available evidence demonstrates that antibiotic prophylaxis might have a protective effect against nonpancreatic infections, but failed to show a benefit on reduction of mortality, infected necrosis, and need for surgical intervention [25–27]. Owing to the lack of evidence on beneficial effect of antibiotics, an even more conservative approach is recommended in pregnancy.

In cases of severe acute biliary pancreatitis (SABP), with or without cholangitis, early ERCP, preferably within 24 h, is recommended [28]. Decompression of the common bile duct and removal of gallstones with subsequent papillotomy could prevent complications and reduce mortality in SABP. Before proceeding to therapeutic ERCP, a less-invasive diagnostic method such as MRCP or endoscopic ultrasound should be performed. In pregnancy it is necessary to minimize radiation exposure during ERCP and the procedure should be carried out only by a very experienced endoscopic and radiologic team [29,30].

**Surgical treatment**

Surgical treatment of pancreatitis has two aspects, which include operative intervention for the disease itself and surgical treatment of associated biliary tract disease, once acute inflammation subsides [3]. Laparoscopic cholecystectomy (once considered contraindicated during pregnancy) [31,32], is today, probably, the optimal treatment [33,34]. Benefits of laparoscopy during pregnancy appear similar to those patients who are not pregnant, including less postoperative pain, less postoperative ileus, decreased length of hospital stays, and faster recovery [34]. Cholecystectomy is considered safe at all stages of pregnancy, and may be performed in any trimester of pregnancy without any increased risk to the mother or fetus [33,34]. Historical recommendations to delay surgery until the second trimester or gestational age limit of 26 to 28 weeks of pregnancy have been refuted [34]. Laparoscopy in pregnancy was connected with the fear of damage to the gravid uterus upon Veress or trocar insertion, technical difficulty in performing the surgery with the presence of an enlarged gravid uterus, and the concern of fetal acidemia due to decreased uterine blood flow because of increased intra-abdominal pressure from insufflation and possible fetal carbon dioxide absorption [1]. In addition, maternal hypotension, and decreased placental perfusion due to pressure of gravid uterus on the inferior vena cava could be present [6]. The use of a uterine manipulator is contraindicated in pregnancy. At the beginning of 2011, the Society of American Gastrointestinal and Endoscopic Surgeons [34] updated its guidelines for laparoscopy during pregnancy. Recent studies suggest that the risk of fetal wasting and teratogenicity from gastrointestinal operation during pregnancy is minimal [35,36]. However, some precautions should be followed such as the use of an open technique for the insertion of the umbilical port, avoidance of high intraperitoneal pressures, use of left lateral position to minimize aortocaval compression, avoidance of rapid changes in the position of the patient, and use of electrocautery cautiously and away from uterus [37].

Early cholecystectomy should be performed in patients with mild acute biliary pancreatitis while patients with SABP should undergo this procedure within 4 weeks and 6 weeks, respectively, after hospital discharge [23,38].

Although sterile necrosis is treated conservatively, infected necrosis requires the use of antibiotics and surgical necrosectomy. Patients with infected necrosis should be treated surgically within 3 to 4 weeks after the onset of symptoms [38]. Minimal invasive surgical techniques are new in the management of AP with only a few relatively small series reported to date [39]. Some recent data show that direct endoscopic necrosectomy achieves better results than standard techniques of endoscopic transmural drainage in the treatment of patients with ‘walled-off’ pancreatic necrosis [40,41].

Diagnostic and therapeutic algorithm for AP in pregnancy is proposed in Fig. 1.
In 1973, Wilkinson reviewed 98 cases of AP during pregnancy of which 30 patients died. In addition, fetal death was noted in 60% of cases. Recently, the percentage of fatal outcomes of AP has been less than 5% [42] and is similar in pregnancy as well [2]. The initial management of AP during pregnancy does not differ much from management in a nonpregnant population, but subsequent management is somewhat controversial, because of fetal outcome. In the past decades high perinatal mortality rate, up to 50% [10], secondary to AP, resulted from neonatal deaths after preterm delivery, but currently, perinatal mortality has been improved (less than 5%) [2] mainly because two of three infants are delivered at term [3,43]. In addition, improvements in neonatal intensive and supportive care play an important role in premature babies’ survival. The worst outcome can be expected in very-low-birth-weight babies.
infants (< 1500 g) and extremely low-birth-weight infants (< 1000 g) [2].

Some investigators tried to find out what kind of treatment (conservative or operative) could be proposed for the most common gallstone-induced pancreatitis [37]. Risk of conservative treatment includes risk to the fetus due to recurrent episodes, other complications of AP, and risk of malnutrition caused by lack of oral intake [37]. In contrast, surgical management carries risk and, if necessary, is best deferred until the second trimester when fetal risk is the lowest [5]. The reasons for carrying out surgery at this time include the fact that organogenesis is completed and size of the uterus is not yet increased to obliterate the surgical view [37]. Laparoscopic procedures appear to be safe during all trimesters but are best carried out during the second one with pursuit of the well-known precautions [37].

Conclusions

AP is a rare entity in pregnancy, mainly caused by gallbladder disorders, in which symptoms of cholecystitis and biliary sludge in many cases precede the symptoms and clinical picture of AP. Diagnosis is based on clinical presentation, laboratory investigations, and imaging methods performed with precaution because of potential radiation risk to the fetus.

The general management of mild AP in pregnancy is conservative and supportive, while severe AP deserves hospitalization in intensive care unit and endoscopic or surgical interventions. The most common type of AP in pregnancy, biliary pancreatitis, can be resolved with urgent ERCP sphincterotomy and laparoscopic cholecystectomy, preferably in the second trimester, when technical conditions are optimal and risk for fetus and pregnant women minimized.

Although treatment of pregnant women with pancreatitis is similar to the general approach in patients with AP, a multidisciplinary team consisting of gastroenterologist, gastrointestinal surgeon, radiologist, and obstetrician should be included in the treatment and in the follow-up of these patients.

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Conflicts of interest

There are no conflicts of interest.

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