

Acute pancreatitis in pregnancy

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Abstract

Acute pancreatitis (AP) is a rare event in pregnancy, occurring in approximately 3 in 10000 pregnancies. The spectrum of AP in pregnancy ranges from mild pancreatitis to serious pancreatitis associated with necrosis, abscesses, pseudocysts and multiple organ dysfunction syndromes. Pregnancy related hematological and biochemical alterations influence the interpretation of diagnostic tests and assessment of severity of AP. As in any other disease associated with pregnancy, AP is associated with greater concerns as it deals with two lives rather than just one as in the non-pregnant population. The recent advances in clinical gastroenterology have improved the early diagnosis and effective management of biliary pancreatitis. Diagnostic studies such as endoscopic ultrasound, magnetic resonance cholangiopancreatography and endoscopic retrograde cholangiopancreatography and therapeutic modalities that include endoscopic sphincterotomy, biliary stenting, common bile duct stone extraction and laparoscopic cholecystectomy are major milestones in gastroenterology. When properly managed AP in pregnancy does not carry a dismal prognosis as in the past.

Key words: Acute pancreatitis; Pregnancy; Pancreatitis in pregnancy

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INTRODUCTION

Acute pancreatitis (AP) is a common problem with an annual incidence of 5 to 80 per 100000 of the general population. The incidence of AP in pregnancy varies and is approximately 1 in 1000 to 1 in 10000 births^[1]. The wide variation in the incidence is influenced by the prevalence of its most important etiological factor i.e. gallstone disease. While biliary pancreatitis complicated 1 in 3300 pregnancies at a large public hospital in Dallas, Texas^[2], in southern California 1 in 1500 women were affected^[3]. In a retrospective study from USA spanning 10 years Legro and Laifer^[4] identified 25 cases of AP in pregnancy. Eleven of these 25 patients were diagnosed in the first trimester of pregnancy when physicians had to clearly distinguish between hyperemesis gravidarum and AP. In another study 43 pregnant women out of 147197 were diagnosed with AP^[2]; 19% of these were diagnosed in the first trimester, 26% in the second, and 53% in the third trimester (one was postpartum), demonstrating that AP was more common with advancing gestational age, paralleling the frequency of gallstone diseases in pregnancy.

Older reviews of AP in pregnancy reported maternal and fetal mortality rates as high as 20% and 50% respectively^[2,5-9]. The above data from the pre-endoscopic retrograde cholangiopancreatography (ERCP), pre-laparoscopic cholecystectomy era are not valid anymore. Contemporary reports document a much improved outcome of AP in pregnancy, when the management of AP secondary to gallstones has undergone substantial changes^[10,11]. Hernandez *et al*^[11] in 2007, based on a single center experience spanning 10 years, reported 34 episodes of

AP with no maternal deaths and a fetal loss of only 4.7%. Date *et al*^[12] in 2008 compared conservative and surgical management of cholecystitis in pregnancy and noted no difference in fetal mortality (2.2% *vs* 1.2%, $P = 0.57$), and there was no maternal mortality. The major changes are the availability of many options in abdominal imaging and less invasive therapeutic options. In addition to abdominal ultrasound (US) we have endoscopic ultrasound (EUS), magnetic resonance cholangiopancreatography (MRCP) and ERCP. The introduction of laparoscopic cholecystectomy in 1986 is a milestone that has reduced the morbidity of surgical intervention by open abdominal surgery even in high-risk pregnant patients. Above all the safe applications of therapeutic ERCP, endoscopic sphincterotomy (ES) have permitted delaying cholecystectomy to safer periods in pregnancy or postpartum.

The etiological associations of AP during pregnancy are similar to those in the general population. AP in pregnancy is most often associated with gallstone disease or hypertriglyceridemia. Gallstones are the most common cause of AP during pregnancy responsible for more than 70% of cases^[2]. The incidence of gallstone related diseases including acute cholecystitis and biliary pancreatitis complicating pregnancy is 0.05%-0.8%^[13]. Even in patients who had prior cholecystectomy, a biliary etiology may exist. The prevalence of microlithiasis after cholecystectomy is 5%-10%^[14,15]. The pathogenesis of AP in gallstone disease is attributed to lodging or impaction of a stone or microlithiasis in the ampulla of Vater initiating premature activation of intracinar trypsinogen to trypsin.

AP OF BILIARY ETIOLOGY IN PREGNANCY

The prevalence rate of gallstones varies with ethnicity. Native American Indians, Mexicans, Latin Americans and Pima Indians all have a high incidence while the incidence is lower in Asia and Africa. Many studies have reported a high incidence of gallstones in the population from northern states of India^[16,17]. Gallbladder disease is strongly related to the metabolic syndrome, a problem that is growing in incidence all over the world^[18-21]. Rapid weight loss is a recently recognized factor for microlithiasis and gallstones^[22]. Although pregnancy itself is a risk factor, the risk increases with parity^[23]. Weight gain and hormonal changes predispose pregnant women to biliary sludge and gallstone formation^[24]. Identification of a biliary etiology for AP is important because as in the non-pregnant patient recurrence of AP episodes will occur in one-third to two-thirds of patients unless gallstones are removed^[10,11,25-27].

Pathogenesis of increased prevalence of gallstone in pregnancy

Cholesterol secretion in the hepatic bile increases in the second and third trimester compared to bile acids and phospholipids, leading to supersaturated bile; in addition, fasting and postprandial gallbladder volumes are greater, with reduced rate and volume of emptying.

This large residual volume of supersaturated bile in the gallbladder of the pregnant patient leads to the retention of cholesterol crystals and eventual gallstones. The formation of biliary sludge and stones is strongly associated with frequency and number of pregnancies^[25].

Up to 10% of patients develop stones or sludge over the course of each pregnancy, with obesity and increased serum leptin being risk factors^[28]. After delivery gallbladder motility becomes normal when sludge as well as stones may disappear^[26,27].

In evaluating pregnant patients with AP the four important questions to be answered are (1) does the patient have AP (establishing the diagnosis and ruling out other causes)? (2) if it is AP, what is the predicted severity? (3) is there a biliary etiology? and (4) what is the trimester of pregnancy?^[29] The answer to the last question determines the choice of imaging studies and mode of therapy.

In the management initial blood tests are done to establish the diagnosis of AP and to assess the severity. Serum amylase and lipase levels are reliable markers of AP during pregnancy. The serum lipase level is unchanged during pregnancy, and the amylase level is either normal or only mildly elevated^[30]. The alterations in blood chemistry in normal pregnancy do not hinder the assessment of severity. Elevation of serum alanine aminotransferase levels to > 3 times the upper limit of normal is a very sensitive biochemical marker of biliary pancreatitis^[31,32]. Any abnormality of liver enzymes and bilirubin as well as rapid change in the levels should suggest a biliary etiology.

IMAGING STUDIES

Abdominal ultrasound (AUS) with no radiation to the fetus is the initial imaging technique of choice to identify a biliary etiology. Gallstones as a potential cause of AP are identified by AUS in most cases^[33]. However, it is insensitive for the detection of common bile duct stones or sludge. When a common bile duct (CBD) stone is suspected based on AUS or biochemical abnormalities EUS, a semi-invasive procedure of the biliary tree is an accurate modality for detecting common bile duct stones^[34]. However EUS requires expensive equipment, intravenous sedation and technical expertise. EUS can be considered the best imaging study to evaluate CBD, although not for gallbladder stones. In expert hands small gallstones as well as sludge can be picked up by EUS, however it is operator dependent. EUS is appropriate prior to the consideration of therapeutic ERCP in patients where non-invasive imaging such as MRCP is not available, contraindicated or inconclusive. EUS has a high positive predictive value nearing 100% in detecting CBD stones and in many instances EUS is superior to MRCP^[35]. EUS entails no radiation exposure and is extremely safe apart from a minimal sedation related risk. If a common bile duct stone is detected, an ERCP with sphincterotomy can be performed following the EUS study during the same sedation.

Magnetic resonance imaging (MRI) and MRCP provide multi-planar large field of view images of the

body with excellent soft-tissue contrast and images of bilio-pancreatic duct systems. MRCP does not require any contrast injections and has no risk of renal injury. MRCP is a preferred method of evaluating CBD in many clinical situations. There is paucity of data on the safety of MRI in the first trimester of pregnancy^[36-38]. Some authors have raised concerns of thermal injury to the fetus in first trimester^[39,40].

According to the Safety Committee of the Society for Magnetic Resonance Imaging^[41], MR procedures are indicated in pregnant women if other non-ionizing forms of diagnostic imaging studies are inadequate, or if the examination provides important information that would otherwise require exposure to ionizing radiation [i.e. X-Ray computerized tomography (CT), *etc.*]. Gallstone pancreatitis is generally associated with small gallbladder stones and sludge^[42]. Small ductal stones in particular, located in the distal CBD could be missed by MRCP^[43]. Claustrophobia remains the major barrier in the use of MRCP and MRI.

CT scan of the abdomen is the most commonly used imaging modality in diagnosing and later on in assessing severity of AP among adults. It is not recommended in pregnant patients because of the fear of radiation exposure to the fetus^[44]. In general CT is not the preferred modality of imaging in all trimesters of pregnancy in view of a small radiation risk to the fetus.

ERCP solely as a diagnostic study has lost its value because of the risks of radiation, incidence of AP post procedure, and the availability of safer procedures such as EUS or MRCP. ERCP increases the risk of complications and death from 5% to 10% and 0.1% to 0.2% respectively^[45]. However, the clinical usefulness of therapeutic ERCP when indicated is unchallenged. Persistent biliary obstruction worsens the outcome, increases the severity of AP, and predisposes to bacterial cholangitis. ERCP along with ES helps to extract impacted gallstones and drain infected bile in severe AP^[46]. Several reports have shown that ERCP can be carried out successfully in the management of symptomatic choledocholithiasis in pregnancy^[47,48]. A major concern of this procedure is harmful ionizing radiation to the fetus. Tham *et al*^[49] reported their experience with ERCP in pregnancy (15 patients over 5 years) with fetal dose radiation measurement. The fetal radiation dose could be reduced to a level less than that considered teratogenic. Kahaleh *et al*^[50] looked at 17 ERCPs performed in pregnant women between January 1995 and August 2003. They reported a mean gestational age of 18.6 wk, mean fluoroscopy time of 14 s and an estimated fetal radiation exposure of 40 mrad. By limiting fluoroscopy time, shielding the pelvis and fetus with lead and avoiding direct X-ray films, the fetal radiation dose can be reduced to far below the maximum permissible doses. Performing MRCP or EUS before ERCP helps to identify patients who require therapeutic ERCP thus reducing the number of ERCP^[51].

MANAGEMENT

Several recommendations below are mostly based on

expert opinion only and not confirmed by double blind/randomized controlled trials. The difficulties in performing such studies in critically ill pregnant patients are obvious.

Nutrition

Although successful outcomes can be achieved in obstetric patients requiring parenteral nutrition, the frequency of maternal complications secondary to centrally inserted central venous catheters (TPN) is greater than that reported in non-pregnant patients^[52]. Peripherally inserted central catheters may be preferable when parenteral nutrition is required during pregnancy. Enteral nutrition by naso-jejunal feeding is preferable to TPN^[11] in patients with severe AP. Enteral nutrition is physiological, helps the gut flora maintain the gut mucosal immunity, reduced translocation of bacteria, while simultaneously avoiding all the risks of TPN.

Antibiotics

The topic of prophylactic use of antibiotics is very controversial and the choice of antibiotic in pregnancy is difficult. However, in suspected cholangitis there is no controversy with regards to the need for appropriate antibiotic therapy. Patients with mild AP, normal CBD size with no evidence for cholangitis do not need antibiotics. In a pregnant patient there are concerns with regard to the antibiotic being transplacentally transferred to the fetus with a risk of teratogenicity. Metronidazole passes freely across the placenta. However, recent studies do not show any association with an increased risk of teratogenic effects with metronidazole^[53,54]. Imipenem (N-formimidoyl thienamycin), belonging to the carbapenem class of antibiotics, has a broad spectrum of activity. It is currently classified as a category C in terms of its risk to the fetus. Although limited animal studies have shown no teratogenic risk or adverse fetal effects, data in humans are not available^[55]. Quinolones have been classified as category C because adverse effects have been noted in some animal studies. However, there are no adequate studies in humans; the benefits may outweigh the risks. Ampicillin-sulbactam and piperacillin/tazobactam are classified as category B with no evidence of risk in humans. Regardless of initial drug regimen, therapy should be modified to reflect the organisms recovered in blood cultures and the clinical status of the patient.

Management of underlying cause

Management of gallstones: In a pregnant woman with gallstones and CBD stones a major decision is on choice of procedure to clear the CBD of stones. The second decision is on timing and approach to cholecystectomy^[56]. Factors which influence the decision include the trimester of pregnancy, presence or absence of CBD dilatation, cholangitis, and the severity of AP. AP patients with gallstones need to be evaluated for early cholecystectomy to prevent recurrence of AP later on in the pregnancy when it could be more serious and dangerous^[25-27]. It is a well respected surgical concept that the second trimester is the best period for surgery since during this period organogenesis is complete and the uterus

is not big enough to obliterate the surgical view for laparoscopic approach. It has also been recognized that cholecystectomy during the second trimester is safe for both the mother and the fetus^[10,12,57].

Laparoscopic cholecystectomy in pregnant women offers all of the advantages of laparoscopic surgery in non-pregnant patients - reduced hospital stay, decreased narcotic use and a quick return to a regular diet compared to open surgery in pregnant women^[58]. In the second trimester the gravid uterus does not interfere with visualization of the operative field. The indications for surgery in pregnancy are severity of symptoms, obstructive jaundice, acute cholecystitis intractable to medical treatment and peritonitis.

Four retrospective studies comparing open cholecystectomy *vs* laparoscopic cholecystectomy did not find any significant difference in maternal or fetal outcomes^[12]. Gouldman *et al*^[59] reviewed the available world literature on laparoscopic cholecystectomy in pregnancy and found 107 patients who had cholecystectomy during pregnancy. Most had been performed in the second trimester, with 10 and 16 patients in the first and third trimesters, respectively. Premature labor was rare, with only 2 of the 16 reported patients (12.5%) in the third trimester developing preterm labor, and these were successfully treated with tocolytics. Overall results were good with excellent maternal (100%) and fetal (96%) survival. There is a recent view that states when surgical intervention is warranted, laparoscopic cholecystectomy can be safely performed in any trimester^[60] but it is a minority view. Performance of cholecystectomy is desirable in the second trimester as organogenesis is complete, and spontaneous abortions are less frequent than in the first trimester^[61].

ERCP with sphincterotomy and clearance of bile duct stones is indicated in patients with severe AP, with cholangitis, with strong evidence of persistent biliary obstruction, and in those who are post cholecystectomy as well as patients who are poor candidates for surgical therapy^[25]. Pregnant women in the first and third trimester who are not ideal candidates for cholecystectomy fall in the last category. Biliary sphincterotomy rather than cholecystectomy may be appropriate when CBD stones are detected and cholecystectomy has to be delayed because of pregnancy. The effectiveness of ES in preventing further episodes of biliary pancreatitis, as an alternative to cholecystectomy in high risk patients has been demonstrated^[48,62-69]. The indication for ERCP in patients with severe pancreatitis without significant cholestasis is controversial. At this time there is no evidence that therapeutic ERCP is required in all patients with biliary sludge during pregnancy.

The role of therapeutic ES in the management of pregnant patients with AP without CBD stones continues to be controversial^[70]. Some advocate biliary stent placement rather than performing sphincterotomy and stone extraction and therefore, eliminating complications that accompany sphincterotomy. Farca *et al*^[71] placed 10-French biliary stents without sphincterotomy in 10 patients, all of whom had uncomplicated pregnancies with normal deliveries. All underwent repeat ERCP with stent extraction and sphincterotomy post-partum and 8 had stones

extracted. In 2 patients, the stent remained in place for 7 and 8 mo, respectively, without the development of occlusion and or cholangitis. However, stenting carries risks of stent occlusion and cholangitis and the need for a second procedure.

Hyperlipidemic pancreatitis: Hypertriglyceridemia is the second most common cause of AP, when the serum triglyceride is > 1000 mg/dL. In the third trimester of pregnancy, there is a three-fold rise in serum triglyceride levels^[72]. This is thought to be due to estrogen-induced increases in triglyceride synthesis and very low-density lipoprotein secretion^[72]. Hypertriglyceridemia may be more severe in persons with familial hyperlipidemia, predisposing them to develop pancreatitis^[73]. Rarer causes of AP that need to be considered in the differential diagnosis are hyperemesis during the first trimester; hyperparathyroidism; preeclampsia; and genetic mutations^[74-76] and acute fatty liver of pregnancy. AP can also complicate the course of thrombotic thrombocytopenic purpura during pregnancy^[77] and pregnancy induced hypertension^[78]. Medication and alcoholism are extremely rare causes of AP in pregnancy.

No formal recommendations exist for gestational hypertriglyceridemia treatment in pregnancy at present. Treatment of hyperlipidemic AP is mostly supportive. These treatments include low fat diet^[79,80], antihyperlipidemic therapy^[79,80], insulin^[79-81] (to increase lipoprotein lipase activity), heparin^[79-81] (to increase lipoprotein lipase activity), and even plasmapheresis^[79,82].

CONCLUSION

AP in pregnancy remains a challenging clinical problem to manage, with a relatively limited but expanding evidence base. Among the various etiological factors for AP in pregnancy, gallstone disease is the most common one. Abdominal ultrasound, CT scan, EUS and MRCP are the available imaging studies in diagnosing a biliary etiology for AP. Potential radiation to the fetus is a major disadvantage with CT scan, restricting their use substantially. Diagnostic ERCP is to be avoided whenever possible owing to the associated risks including bleeding, perforation, pancreatitis, fetal radiation, while abdominal ultrasound, MRCP and EUS do not carry these risks. The general management of AP in pregnancy is supportive and includes hospitalization, intravenous fluids, analgesia, and bowel rest. Laparoscopic cholecystectomy is ideally performed in the second trimester when the risk to fetus is the least and only limited technical problems exist as a result of an enlarging uterus. Whenever laparoscopic cholecystectomy is not feasible and the index of suspicion for a stone in the CBD is high based on AUS, MRCP or by EUS, ES or stenting serves to prevent recurrence of AP and allows postponement of laparoscopic cholecystectomy to a more suitable period. Hyperlipidemic pancreatitis and AP due to other etiologies are rare. The outcome of pregnant patients with AP has substantially improved with technical advances in imaging and therapeutic endoscopy.

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