INTRODUCTION

The three most common gastrointestinal emergencies during pregnancy are acute cholecystitis, appendicitis and intestinal obstruction (1). The incidence of gallstone related diseases including acute cholecystitis and biliary pancreatitis complicating pregnancy is 0.05% to 0.8% (2). Acute pancreatitis (AP) in pregnancy occurs rarely with a reported incidence of approximately one in 1,000 to one in 10,000 births (3). The wide variation in the incidence is influenced by ethnicity of the patient population. AP complicated one in 3,300 pregnancies at a large public hospital in Dallas, Texas (4) whereas in southern California one in 1,500 women were affected (5). AP during pregnancy, in the past had been regarded as dangerous to the mother as well as to the fetus. A few reports from the 1970’s suggested overall maternal mortality of 3%–5% and up to 15% in severe AP (6). In 1973 Wilkinson reviewed 98 cases of AP in pregnancy and reported a maternal mortality of 37% (7). The above data is not valid anymore with a few contemporary reports documenting a much improved outcome of AP in pregnancy, during a period when the overall management of acute pancreatitis, secondary to biliary causes has undergone substantial changes (8,9). A recent publication in 2007 by Hernandez and colleagues in a single center experience spanning 10 years with 34 episodes of AP reported no maternal deaths and a fetal loss of only 4.7% (9). Date and associates in a review of six studies published in 2008, comparing conservative and surgical management of cholecystitis in pregnancy noted no difference in fetal mortality (2.2% versus 1.2%, p = 0.57) (10), and there was no maternal mortality. The overall improvement in the outcome of AP is attributed to better diagnosis, early assessment of severity of AP, triaging of patients to ICU and excellent management in the ICU setting. More specifically, there are substantial improvements in the diagnostic and therapeutic modalities of a biliary etiol-
ogy. High perinatal mortality rates described in earlier series reflect neonatal deaths after preterm delivery. The marked reduction in perinatal mortality described in more recent series reveal improvements in neonatal intensive care. Excellent diagnostic options currently available in addition to abdominal US include, endoscopic ultrasound (EUS), magnetic resonance cholangiopancreatography (MRCP) and in selected cases endoscopic retrograde cholangiopancreatography (ERCP). The introduction of laparoscopic cholecystectomy in 1986, a major advancement in surgical technique, has reduced the morbidity of surgical intervention by open surgery even in high-risk pregnant patients. In addition, the safe applications of therapeutic ERCP, endoscopic sphincterotomy (ES) in pregnant patients have safely permitted a delay in cholecystectomy.

In evaluating pregnant patients with AP as in the non-pregnant, the three 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, the predicted severity and finally 3) is there a biliary etiology (11). 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 with gallstone induced pancreatitis, unless gallstones are removed (12–14). In one study (9), 50% of those with conservative management had a recurrent episode of AP during the same pregnancy, similar to another study by Swisher, et al (8), who noted a relapse rate of 70% in pregnant patients with gallstone-induced acute pancreatitis. Identification of a biliary etiology for AP is important since various safe and definitive management options are currently available.

The etiological associations of AP during pregnancy are similar to those in the general population. Pancreatitis 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(4). Even in patients who had prior cholecystectomy, a biliary etiology may exist. Based on data from previous studies the prevalence of microlithiasis after cholecystectomy is 5% to 10% (15,16). Hypertriglyceridemia occurs especially during the third trimester of pregnancy, because of a three-fold rise in serum triglyceride levels. This is thought to be due to estrogen-induced increases in triglyceride synthesis and very low-density lipoprotein secretion. Hypertriglyceridemia may be more severe in persons with familial hyperlipidemia, predisposing them to develop pancreatitis on this basis (17). Other etiological factors of AP in the general population like chronic alcoholism, drug induced, viral infections, and idiopathic are rare (11). Rarer causes of AP that need to be considered in the differential diagnosis are hyperemesis during the first trimester; hyperparathyroidism; preeclampsia; genetic mutations (18–20) and acute fatty liver of pregnancy. AP can also complicate the course of thrombotic thrombocytopenic purpura (TTP) during pregnancy (21) and pregnancy induced hypertension (22).

GALLSTONE DISEASE IN PREGNANCY

The prevalence of cholesterol gallstone disease in women is influenced by age and ethnicity, most series indicating a range from 5%–20% between the ages of 20–55 years. Genetic factors play a role in the prevalence along with other factors. There is a high prevalence of gallstones in Scandinavians, Mexicans, native Americans, populations from many Latin American countries and those from Northern parts of India (23,24). Obesity is a well known risk factor. Rapid weight loss is a recently recognized factor for microlithiasis and gallstones. Although, pregnancy itself is a risk factor, the risk increases with parity. Weight gain and hormonal changes predispose pregnant women to biliary sludge and gallstone formation. The pathogenesis of cholesterol gallstone formation is attributed to a disproportionate increase in hepatic biliary cholesterol levels in relation to bile acids and lecithin (lithogenicity). Estrogen increases bile lithogenicity whereas progesterone impairs gallbladder emptying (25,26). The reported incidence of biliary sludge and gallstones during pregnancy ranges from as high as 31% to 3% (24,27–29). After delivery gallbladder motility becomes normal, sludge as well as stones may disappear (26,27). 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. This may be related to the obstruction of the secretion of pancreatic juice. The impacted stones may
be passed into the duodenum within a few hours or may stay impacted leading to biliary ductal dilatation, continued pancreatitis and cholangitis. Pigment stones as a result of bilirubin precipitation account for 10% of all gallstones in the U.S. population. Unless otherwise specified, the discussion in this paper is exclusively on cholesterol stones (Table 2).

Most pregnant women with gallstones are asymptomatic and no therapy is indicated (30). Although symptomatic gallstone disease can occur at any time during the course of pregnancy, it usually occurs late in the third trimester or in the early postpartum period. In a study by Ramin, et al (4), spanning 11 years, 43 pregnant women out of 147,197 were diagnosed with pancreatitis; 19% of these were diagnosed in the first trimester, 26% in the second, and 53% were in the third trimester (one was postpartum), demonstrating that AP was more common with advancing gestational age. In a retrospective study spanning 10 years by Legro and Laifer (31), 25 cases of pancreatitis in pregnancy were identified. Eleven of these 25 patients were diagnosed in the first trimester of pregnancy; stressing that AP can present as early as the first trimester when physicians have to clearly distinguish between hyperemesis gravidarum and pancreatitis.

SEVERITY OF BILIARY AP IN PREGNANCY

The manifestation’s of AP in pregnant women are similar to those seen in non-pregnant women (32). AP usually presents as sudden and severe epigastric pain that radiates to the back. Post prandial nausea and vomiting are also common, as is fever. The patient often appears acutely ill and lying in the “fetal position” with flexed knees, hips and trunk. Bowel sounds are usually hypoactive, secondary to ileus, and the abdomen is diffusely tender. The assessment of severity of AP in pregnancy follows the general principles of those recommended in the evaluation of any patient with AP. While no study has carefully assessed the utility of well-known clinical scales, including Ranson’s, Imrie’s Criteria, APACHE II Score or other newer single prognostic markers in pregnancy, AP in pregnancy is a unique situation that falls outside the clinical scenario of AP in the non-pregnant individual. Pregnancy is not just a co-morbid condition; it poses limitations on diagnostic options and restricts surgical options (Table 1).

EVALUATION OF AP

Diagnostic Blood Test

Initial blood tests are done to establish the diagnosis of AP and to assess the severity. Serum amylase and lipase are reliable markers of AP during pregnancy. The lipase level is unchanged during pregnancy, and the amylase level is either normal or only mildly elevated during pregnancy (33). The alterations in blood chemistry in normal pregnancy do not hinder assessment of severity. Elevation of serum alanine amino transferase levels to >3 times the upper limit of normal

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is a very sensitive marker of biliary pancreatitis (34,35). In general, any abnormality of liver enzymes and bilirubin should suggest a biliary etiology.

Abdominal Ultrasound (AUS)

AUS is the imaging technique of choice to identify a biliary etiology. Gallstones as a potential cause of AP are identified by AUS in most cases (36). However, it is insensitive for the detection of common bile duct stones, sludge and the pancreas cannot be well visualized. With ultrasound, there is obviously no radiation exposure to the fetus.

CT Scan of Abdomen

Although CT scan is the most commonly used imaging modality in diagnosing and in assessing severity of AP among adults, it is not recommended among pregnant patients because of the fear of radiation exposure to the fetus (37). However, as per the National Council for Radiation Protection (NCRP) “At dose levels below 10 mGy (1 rad) the probability of detectable effect induced by such exposure is so small as to be outweighed by any significant medical benefits” (38). Other authors have supported this statement, and added that we need to take into account the effect of delayed attention to the health of the mother, which can harm both the mother and the fetus (37). The decision to perform CT scan will have to be made on an individual basis by the clinician depending on the clinical scenario (37).

MRI/MRCP

Magnetic resonance imaging (MRI) and magnetic resonance cholangiopancreatography (MRCP) provide multi-planar large field of view images of the body with excellent soft-tissue contrast and images of biliary-pancreatic duct systems. MRCP does not require any contrast injections and has no risk of renal injury. MRCP is a preferred method of evaluating common bile duct (CBD) in many clinical situations. In some cases, small ductal stones in particular, located in the distal CBD could be missed by MRCP (39). While preliminary evidence suggests that MR imaging is safe in the setting of pregnancy, several specific concerns regarding fetal safety deserve additional comment (40–42). There is paucity of data on the safety of MRI in the first trimester of pregnancy. Also, it is well known that dividing cells, as in the case of the developing embryo during the first trimester, are susceptible to injury from a variety of physical agents. A few authors have raised concerns of thermal injury to the fetus in the first trimester (43,44).
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According to the Safety Committee of the Society for Magnetic Resonance Imaging (45), MR procedures are indicated for use in pregnant women if other non-ionizing forms of diagnostic imaging are inadequate, or if the examination provides important information that would otherwise require exposure to ionizing radiation (i.e., X-Ray CT, etc.). It is required that pregnant patients be informed that, to date, although there is no indication that the use of clinical MR procedures during pregnancy produces deleterious effects according to the FDA, the safety of MR procedures during pregnancy has not been definitively proven (46).

Endoscopic Ultrasonography
EUS, a semi-invasive procedure of the biliary tree is an accurate modality for detecting common bile duct stones (47). EUS requires intravenous conscious sedation and technical expertise. Its role in pregnancy however has not been defined. EUS is appropriate prior to the consideration of therapeutic ERCP in patients where non-invasive imaging such as MRCP is not available, contraindicated or difficult to interpret. If expertise is available, EUS may even be preferred to MRCP. EUS has a high positive predictive value nearing 100% in detecting CBD stones and in many instances EUS may be considered superior to MRCP (48). EUS entails no radiation exposure and is extremely safe apart from minimal sedation related risk. If a common bile duct stone is detected, an ERCP with sphincterotomy can be performed at the same time.

Endoscopic Retrograde Cholangiopancreatography (ERCP)
ERCP, solely as a diagnostic study has lost its value because of the risks of radiation and incidence of AP post-procedure. It involves risks of complications and death from 5% to 10% and 0.1% to 0.2% respectively (49). However, the clinical usefulness of therapeutic ERCP when indicated is unchallenged. Persistent biliary obstruction worsens the outcome, increases the severity of AP, and predisposes the patient to bacterial cholangitis. ERCP along with endoscopic sphincterotomy (ES) helps to extract impacted gallstones and drain infected bile in severe AP (50). Several reports have shown that ERCP can be carried out successfully in the management of symptomatic choledocholithiasis in pregnancy (26,51). But the major concern of this procedure is harmful ionizing radiation to the fetus. Tham, et al reported their experience with ERCP in pregnancy (15 patients over five years) with fetal dose radiation measurement (52). The authors showed that the fetal radiation dose could be reduced to a level less than that considered teratogenic. Kahaleh, et al looked at seventeen ERCPs performed in pregnant women between January 1995 and August 2003 (53). They reported a mean gestational age of 18.6 weeks, mean fluoroscopy time of 14 seconds 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 unnecessary high risk ERCP (54).

MANAGEMENT

Management of AP
Management of AP in pregnancy should, from the very beginning be a team approach. The team of physicians should include the obstetrician, gastroenterologist with experience in endoscopic ultrasound and ERCP/ES, a surgeon, a radiologist and when necessary an intensivist (12,55). Many of the standard recommendations in the management of AP in the non-pregnant are applicable to pregnant patients. The decisions are to be clear with regard to the need for appropriate diagnostic studies, nutritional support, antibiotic if needed and endoscopic or surgical therapy. A discussion on the early determination of severity by different prognostic criteria is beyond the scope of this paper. Every patient with AP is to be evaluated for admission to the Intensive care unit, based on the presence of Systemic Inflammatory Response Syndrome (SIRS), organ failure, co-morbid conditions, or other single markers of poor prognosis (obesity, hemoconcentration, elevation of creatinine, blood sugar, pleural effusion). Presence of hypoxia, tachypnea, evidence of fluid loss into third space (hypotension, tachycardia, azotemia, hemoconcentration) warrants intensive care.
After initial attempts to provide pancreatic rest by NPO, oral intake is to be restarted within three days or as early as possible when the abdominal pain subsides. Some patients who progress to severe AP may need total parenteral nutrition or TPN. Successful outcomes can be achieved in obstetric patients requiring parenteral nutrition. However, the frequency of maternal complications secondary to centrally inserted central venous catheters is greater than that reported in non-pregnant patients (56). Peripherally inserted central catheters may be preferable when parenteral nutrition is required during pregnancy. There is strong evidence that enteral nutrition by naso-jejunal feeding is preferable to TPN (11). Enteral nutrition is physiological, helps the gut flora maintain the gut mucosal immunity, reduces translocation of bacteria, while simultaneously avoiding all the risks of TPN.

Patients with mild AP, normal CBD size and with lack of evidence for cholangitis do not need antibiotics. The topic of prophylactic use of antibiotics is very controversial. However, in suspected cholangitis there is no controversy with regards to the need for appropriate antibiotic therapy. It is clear that empiric antibiotic therapy for ascending cholangitis in a non-pregnant patient should include broad-spectrum parenteral antibiotics and could include any of the monotherapy with ampicillin-sulbactam, piperacillin/tazobactam, imipenem or dual therapy with metronidazole plus ceftriaxone or fluoroquinolone. However, in a pregnant patient there are a few concerns with regard to the transfer of the antibiotic across the placenta to the fetus. Metronidazole passes freely across the placenta. However, recent studies do not show any association with an increased risk of teratogenic effects with metronidazole (57,58). Imipenem (N-formimidoyl theinamycin) belonging to the carbapenem class of antibiotics has 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 (59). 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 Gallstones

In pregnant woman with gallstones and CBD stones a major decision is on the choice of methods to clear the CBD of stones. The second decision is on timing and approach to cholecystectomy (60). 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 cholecystectomy to prevent recurrence of AP later on in the pregnancy when it could be more serious and dangerous (12–14). It is a well respected surgical concept that the second trimester is the best 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 safer for both the mother and the fetus (8,10,61).

Cholecystectomy is the second most common indication for non-gynecologic surgical intervention in pregnancy but the most common laparoscopic procedure performed during pregnancy (62–65). 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 (66). The gravid uterus does not interfere with visualization of the operative field. The indications for surgery in pregnancy are severe symptoms, obstructive jaundice, acute cholecystitis intractable to medical treatment and peritonitis. However, similar to that of appendicitis, uncomplicated cholecystectomy is associated with a 4% fetal loss rate with no increase in maternal mortality (67).

Four retrospective studies comparing open cholecystectomy versus laparoscopic cholecystectomy did not find any significant difference in maternal or fetal outcomes (10). Gouldman, et al reviewed the available world literature on laparoscopic cholecystectomy in pregnancy and found 107 patients who had the cholecystectomy during pregnancy (68). Most had been per-
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formed in the second trimester, with 10 and 16 in the first and third trimesters, respectively. Premature labor was rare, with only two 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 when all series were considered. There is a view that when surgical intervention is warranted, laparoscopic cholecystectomy can be safely performed in any trimester, preferentially during the second trimester. Performance of cholecystectomy is desirable in the second trimester as organogenesis is complete, and spontaneous abortions are less frequent than in the first trimester (67).

ERCP with sphincterotomy and clearance of bile duct stones is indicated in patients with severe AP, in those with cholangitis, in those with strong evidence of persistent biliary obstruction, in those who are post-cholecystectomy and finally, in those who are poor candidates for surgical therapy (12). 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 stone is detected and cholecystectomy has to be delayed because of pregnancy. The effectiveness of endoscopic sphincterotomy in preventing further episodes of biliary pancreatitis, as an alternative to cholecystectomy in high risk patients has been demonstrated (69–73).

Endoscopic sphincterotomy (ES) for choledocholithiasis is presently recommended as a palliative procedure when surgery is not feasible (74), and several studies have demonstrated that ERCP/ES can be successfully and safely performed during pregnancy (51,75). In a recent excellent editorial Baillie discussed the advances in ERCP during pregnancy (75). In the first trimester of pregnancy when the abdominal girth is not increased, performing an ERCP on the patient is not difficult, while the uterus can be shielded to prevent radiation to the fetus. Baillie and coworkers (51) have reported the use of endoscopic sphincterotomy under IV sedation in five pregnant women. Four of these women had acute cholangitis and one had gallstone pancreatitis. The combined use of a lead apron over the maternal abdomen and limiting the fluoroscopy time (<10 seconds at 90 kv) kept internal radiation scatter low at 40 mrem (0.0004 rad) and no fetal exposure was detected by a dosimeter placed on the fundus. The authors concluded that this approach is safe and effective during pregnancy until cholecystectomy can be performed postpartum. The risk for ERCP induced pancreatitis is to be clearly assessed and the procedure is to be performed only with definite indication (76). The diagnosis of CBD stones can be made by MRCP or better by EUS. The use of MRCP/EUS has been discussed earlier. During laparoscopic cholecystectomy intraoperative cholangiography can be performed, and a next day ERCP/ES if the cholangiogram demonstrates stones in the CBD.

The role of therapeutic endoscopic sphincterotomy (ES) in the management of pregnant patients with AP without CBD stones continues to be controversial (77). ES would potentially prevent AP attacks by facilitating the passage of stones from the gallbladder through the papilla in those without bile duct stones. May and Shaffer (77) proposed that endoscopic biliary sphincterotomy replace cholecystectomy in high risk patients with gallstone pancreatitis regardless of the presence of stones in the common bile duct on ERCP. Barthel, et al (78) performed biliary sphincterotomy in three patients (two in the second trimester, one in the third) with gallstone pancreatitis despite the absence of choledocholithiasis. One patient had post ERCP pancreatitis that resolved within forty-eight hours. None of the three patients had recurrent pancreatitis, and all pregnancies had healthy outcomes. Tham, et al (52) considered endoscopic sphincterotomy (ES) as an alternative to cholecystectomy in pregnancy to prevent recurrent pancreatitis. Others suggest performing prophylactic sphincterotomy in symptomatic patients with a clean bile duct, early on in gestation until cholecystectomy could be performed in the second trimester or preferably postpartum.

However, we need to be careful with this practice as there is no evidence that outcome is beneficial. Moreover, endoscopic sphincterotomy may increase the risk of complications of ERCP. We need to consider the long term sequelas in young patients of sphincterotomy as regards to lifelong bile reflux, bacterial colonization, and the risk of carcinoma (75). Some advocate biliary stent placement rather than performing sphincterotomy and stone extraction and therefore, (continued on page 29)
eliminating complications that accompany sphincterotomy. Farca, et al (79) placed 10-French biliary stents without sphincterotomy in ten patients, all of whom had uncomplicated pregnancies with normal deliveries. All underwent repeat ERCP with stent extraction and sphincterotomy postpartum and eight had stones extracted. In two patients, the stent remained in place for seven and eight months, 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.

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 and fetal radiation; Abdominal ultrasound, MRCP and EUS do not carry these risks. The management for AP in pregnancy is supportive and includes hospitalization, intravenous fluids, analgesia and bowel rest. Laposcopic cholecystectomy is ideally performed in the second trimester when risk to the fetus is the least and there are only limited technical problems 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, endoscopic sphincterotomy or stenting serves to prevent recurrence of AP and allows postponement of laparoscopic cholecystectomy to a more suitable period. The advances in imaging modalities such as MRCPEUS and therapeutic options such as laparoscopic cholecystectomy and ES along with improvements in supportive measures for both baby and the mother have substantially improved the outcome of a once dreaded disease.

References


