Pancreatitis In Pregnancy: What has Remained The Same and What has Changed?

Norman Oneil Machado*

Senior Consultant Surgeon, Sultan Qaboos University Hospital, Muscat/Oman

*Corresponding author: Norman Oneil Machado, Department of Surgery

Sultan Qaboos University Hospital, PO Box 38, Postal Code 123, Muscat/ Oman, Tel: + 00968 99432723; E-mail: oneilnorman@gmail.com

Rec date: Nov 11, 2015; Acc date: Nov 20, 2015; Pub date: Nov 23, 2015

Copyright: © 2015 Machado NO. This is an open-access article distributed under the terms of the Creative Commons Attribution License, which permits unrestricted use, distribution, and reproduction in any medium, provided the original author and source are credited.

Keywords: Pregnancy; Pancreatitis; Clinical outcomes; Acute pancreatitis

Introduction

Pregnancy associated pancreatitis (PAP) is uncommon with a reported incidence of approximately one in 25001 to 10,002 live births. Literature reveals a wide range of incidence, clinical outcomes and risk factors related to PAP. The incidence is reported to vary between 0.1% to 0.008% of pregnancy [1-7]. Even though the incidence is still rare, the potential complication is doubled compared to non-pregnant patients, as it deals with 2 lives. In evaluating PAP it is important to address four important queries. 1) does the patient have acute pancreatitis (establishing the diagnosis and ruling out potential differential diagnosis); 2) what is the severity, if the diagnosis of acute pancreatitis is established; 3) is it of biliary origin and if so, is there persistent CBD obstruction or complication like cholangitis; 4) which trimester of pregnancy is the patient in and is there any sign of preterm labour or abortion. This editorial addresses the etiopathogenesis, complications and management and notes what has remained the same and what has changed in recent times regarding PAP.

Actio-Pathogenesis

The most common causes for acute pancreatitis in pregnancy are: gallstones (66%), alcohol abuse (12%), idiopathic (17%), hyperlipidemia (4%), obesity and rarely hyperparathyroidism, trauma, medication and fatty liver of pregnancy [4-7]. The physiological changes that enhances the risk of gallstone formation in pregnancy include, progesterone induced relaxation of smooth muscle with resultant bile stasis along with reduction in gall bladder ejection fraction [8]. These changes in pregnancy, increases the gall bladder volume and decreases bile flow [9]. Moreover, there is estrogen induced increase in cholesterol content in bile and its supersaturation [9]. A rise in leptin levels in pregnancy compared to prepregnancy levels (hormone secreted by white adipose tissue) increases the risk of biliary disease [10]. Leptin affects biliary cholesterol elimination and enhances subsequent stone formation [11-13]. High-density lipoprotein (HDL) is inversely related to sludge and gallstone formation [13]. While the real pathogenesis is unclear, it may be related to the co-existence of low HDL with obesity, hypertriglyceridemia and insulin resistance [14]. Migration of theses calculi into CBD and obstruction of the ampulla with subsequent activation of trypsin is the precursor of impending acute pancreatitis [15].

Alcohol abuse is observed to be another etiological factor of acute pancreatitis in pregnancy and may predispose to it, by its acinar toxic effect with or without other contributing factors [15]. Alcohol is reported to increase the risk in dose dependent manner [15]. Hyperlipidemia may play a role in causing PAP in some of these patients [3-7]. A rise in plasma triglyceride by 2 to 4 fold is often noted in pregnancy, principally in third trimester [16]. However they rarely reach levels above 300 mg/dl (3.42 mmol/L). The patients with abnormal lipid metabolism may however develop significant elevations in triglycerides and chylomicrons in the circulation, which may cause ischemic lesions related to the pancreatic circulation [17]. The risk of pancreatitis occurs when the levels of plasma triglyceride levels exceed 1000 mg/dl (11.3 mmol/l) [16]. Reports of lipoprotein lipase mutation causing severe hypertriglyceridemia during pregnancy are found in the literature [18].

Smoking is also considered to be a potential risk for acute pancreatitis in pregnancy in a dose proportional manner (tobacco/day) [19-21]. Of interest to note is that, these patients have a rise in triglyceride levels. Among the drugs that can predispose to acute pancreatitis include those in category B for use in pregnancy, such as erythromycin, mesalamine, sulfasalasine, acetaminophen, didanosine and steroids, used in the treatment of co-existing disease during pregnancy [22]. Rarely, hypercalcemia from a functioning parathyroid adenoma could cause acute pancreatitis in pregnant patient [7].

Obesity is being reported more often these days as a significant association with PAP. In a recent study 6 of 29 cases of PAP, 65% of those with prepregnancy body mass index (BMI) more than 30 kg/m2 had PAP versus 24% with BMI between 25 and 30 kg/m2 and 10% with BMI less than 25 kg/m2. Also noticed was increasing trend of PAP with gestational age and number of pregnancy [6]. Insulin resistance associated with obesity is found to increase the risk of gallstones and sludge formation during pregnancy [23].

Clinical presentation

The reported incidence of PAP is 19% in first trimester, 26% in second trimester and 53% in third trimester with incidence being more common with advancing gestational age paralleling with the frequency of gallstone disease in pregnancy [6]. They could present within hours or may have a mild presentation over weeks. The symptoms of PAP are non-specific but attention to drawn to the possible diagnosis when a patient presents with pain in upper abdomen, progressively increasing in intensity associated with nausea and vomiting [24-27]. This could radiate to the back in 40% of the cases [27]. In patients with a known history of biliary disease or excessive alcohol consumption, the possibility of of PAP increases. Presentation can occur at any stage of pregnancy but as noted, increases with gestational age [6,27]. Patients with severe pancreatitis at presentation may be haemodynamically abnormal with tachycardia, tachypnea and hypotension and in these patients one may entertain in their differential diagnosis, the
possibility of complications associated with pregnancy [6,24,27]. Based on the time and nature of presentation, the differential diagnosis include acute cholecystitis and perforated peptic ulcer within the first few hours, and intestinal obstruction in next few days once abdominal distension sets in those who present with hypotension, ectopic pregnancy, rupture of splenic artery aneurysm or rupture of hepatic adenoma should be considered. Rarely myocardial infarction in high risk patient with ischemic heart disease could occur [27].

The diagnosis is usually established by a significant rise in serum amylose or lipase levels [27]. The LFT, blood sugar may be normal or elevated and complete blood picture may show hemococentration and leucocytosis [16,27]. In patients with alcoholic pancreatitis, the activity of gamma glutamyl transpeptidase may be increased. Increase in ALT levels by three times the normal, strongly suggests the diagnosis of biliary pancreatitis [28,29]. The triglyceride levels >1000 mg/dl (11.3 mmol) are associated with pancreatitis. The average rise in triglycerides levels in PAP may be over 5000 mg/dl (56.5 mmol/l) as reported in some studies [7]. In those patients with elevated calcium, parathormone levels may be elevated suggestive of hyperparathyroidism [7].

Abdominal ultrasound with no risk of radiation to the fetus would be the initial choice of investigation to identify biliary pathology. Its drawback however is in detecting stones in terminal CBD and in visualizing pancreas in presence of pancreatitis. MRCP plays a major role in assessing the terminal part of CBD (not usually feasible with US) to look for CBD calculi in view of its excellent soft tissue contrast and images of bilo-pancreatic duct systems [5]. Early complications of pancreatitis and its severity can also be simultaneously established in MRI. It avoids the need of invasive procedure like ERCP in delineating the terminal CBD, restricting its use to therapeutic purpose, in those with CBD calculi [5,30]. The absence of radiation exposure to mother and fetus in MRCP compared to CT is of special significance in pregnancy [30,31]. However some have raised the concern of fetal radiation injury to fetus in first trimester [32,33]. According to safety committee of the society for Magnetic Resonance Imaging, MR procedure are indicated in pregnant women if other non-ionizing forms of diagnostic studies are inadequate or if the examination provides important information that would otherwise require exposure to ionizing radiation (eg X-ray, computerized tomography) [34]. Endoscopic ultrasound (EUS), which is a semi-invasive procedure, gives accurate imaging of the terminal biliary tree and is sensitive in detecting stones in them [5,35]. It has a positive predictive value nearing 100% in detecting terminal CBD calculi and may be considered superior to MRCP, particularly in detecting small calculi. Its limitation however, is that it is operator dependent, requires expensive equipment and sedation and needs technical expertise [35].

Management

Once the diagnosis is established, it is of paramount importance to resuscitate the patient with adequate amount of IV fluids [36,37]. Up to 150-300 ml per hour of crystalloids for the first 24 hours may be required to maintain an adequate urine output. This is reduced once the urine output of 0.5 ml/hr is achieved and a mean arterial pressure of 65 mmHg is maintained [36,37]. These patients are extremely susceptible to hypovolemia, due to loss of large amount of fluid into the third space in the first 24 to 48 hours [36,37]. The consequence of inadequate fluid resuscitation would be hypoperfusion of kidneys and pancreas, leading to pre-renal failure and progression of pancreatitis. Acid base gas (ABG) should be performed to rule out subclinical hypoxemia and the severity of pancreatitis should be established using Ransons criteria or an APACHE score [37]. Most patients would benefit with oxygen by mask in the first 24 to 48 hours and good analgesia. Based on the severity of pain, the analgesia could be in the form of epidural or fentanyl and meperidine, all of which can be used safely in pregnancy [38]. Antibiotics are not used prophylactically in every patient [36,37]. However, when indicated as in documented necrotizing pancreatitis, meta-analysis has indicated that imipenem/ cilastin are the most appropriate antibiotics [37,39]. Even though there are no studies indicating the proposed dose, a dose adjustment for pregnancy is advised [39]. The patient can be given oral diet in mild and moderately severe pancreatitis once he recovers from acute phase in few days and by when the patient’s nausea, abdominal pain and distension would have settled. In the event she does not tolerate oral intake, feeding through a well-placed jejunal tube, well beyond the duodenum, is highly recommended [36,37]. It is proved to be superior to TPN, in view of maintaining the integrity of bowel mucosa, reduction of transmigration of bacteria into the lymphatics and hence risk of infection of inflamed pancreatic tissue. In addition, it is significantly cheaper and easier to administer. If that fails, then patient may need TPN, as in those with severe pancreatitis. In a large study, TPN was required in 25% of the cases of whom 9% were in ICU [7]. The role of new emerging drugs such as ethyl pyruvate, which has anti-inflammatory and cytoprotection in animal models of acute pancreatitis, has to evolve [40].

Treatment of Predisposing Cause

Gallstone pancreatitis

Traditionally, gallstone pancreatitis has been managed conservatively in PAP [4,7]. However off late, the management of CBD calculi causing PAP would generally follow the same principle as in non-pregnant women [41-46], ERCP sphincterotomy (ES) and extraction of calculi within in the first 24 to 48 hours, would be required in patients with cholangitis, progressing jaundice, poor candidates for surgery and in those with severe biliary pancreatitis [41,44]. In those in whom LC cannot be carried out, ES alone may be effective [42]. The effectiveness of ES in preventing further episodes of biliary pancreatitis as an alternative to cholecystectomy in high-risk patients has been reported [41-46]. ES has been carried out safely in pregnant women based on the clinical studies and short term follow up [45,46]. Even though during the follow up there are no or minimal fetal complications, studies with long-term neonatal follow up are needed to prove the safety of ERCP radiation5. However, every measure should be taken to minimize fetal radiation exposure during the procedure. Tham et al. reported their experience with ERCP in pregnancy (15 patients over 5 years) with fetal radiation measurement [45]. The fetal radiation dose could be reduced to a level less than that considered teratogenic. In another report, 17 ERCPs were performed in pregnant women with a mean gestational age of 18.6 weeks and mean fluoroscopy time of 14s and in these patients an estimated fetal radiation exposure of 40mrad was achieved [46]. This was possible by limiting the fluoroscopy time, shielding the pelvis and fetus with lead and avoiding direct X-ray films [46]. By these measures, fetal radiation dose was reduced far below the maximum permissible dose. If this is not feasible then the procedure should be performed without radiation [5]. It is important that potential risk of complications of ERCP, including (premature delivery or abortion) and maternal risk of post ERCP radiation exposure, bleeding, duodenal perforation or worsening of pancreatitis is explained to the patient [41-44]. This
procedure fortunately would be required in less than 15% of the patients as in most cases, the calculi would slip beyond the papilla relieving the obstruction [36,37]. The role therapeutic ES in the management of pregnant patients without CBD stones continues to be controversial [47]. Some advocate biliary stent placement rather than performing sphincterotomy and stone extraction and therefore eliminating complications that accompany sphincterotomy [48].

The gall bladder calculi are preferably dealt with laparoscopic cholecystectomy (LC) during the index admission for PAP [5,7,35,36,41,50]. This recommendation stems from the fact that nearly 50% of the pregnant patients managed conservatively, develop recurrent episodes of biliary pancreatitis [2,51]. LC has been carried out safely in all trimesters of pregnancy in experienced hands [51-53]. However, in very advanced pregnancy, there are technical difficulties in performing the surgery in view of the size of the gravid uterus and LC in these patients may ideally be performed in postpartum phase [52,53]. LC is recommended in all patients with mild and moderately severe PAP, prior to patients discharge [5,56]. In severe pancreatitis, it will be delayed to several weeks depending on the patient’s stage of pregnancy and till the acute inflammation completely settles down [51-53]. LC is generally carried out in second trimester as organogenesis is complete and spontaneous abortion is less frequent than in first trimester [51-53]. However there are some who feel it can be safely carried out in all trimesters [52,53]. The main advantages of LC is early mobilization, lower dose of analgesia, lower risk of thromboembolic phenomenon, early discharge and the smaller port wound that would ensure minimal discomfort of abdominal contraction during the spontaneous vaginal delivery in patients close to term [51-53]. The concerns of potential complications of performing LC in pregnant patients include uterine injury induced by trocar or instruments resulting in serious bleeding and fetal death, preterm labour and fetal acidois [51-53]. These could be reduced by following the guidelines of performing LC during pregnancy [54]. In a review of world literature of 107 patients, most of the LC was performed in the second trimester (75%) with 10(9.3%) and 16(14.95%) patients in the first and third trimester respectively. Premature labour was rare, with only 2 of the 16 reported patients (12.5%) in the third trimester developing preterm labour and these were successfully treated with tocololytic agents [55]. Overall results were good with excellent maternal (100%) and fetal (96%) survival [55].

Hyperlipidemic pancreatitis

Patients who are known to be hyperlipidemic, need to take precautionary measures during pregnancy to keep the triglycerides level low. These include low fat diet alone [54] or in combination ω-3 fatty acids [55-57] to control triglyceride levels which could prevent the occurrence of PAP. The diet used should aim to keep the triglyceride levels below 885 mg/dl (10 mmol/L) in the index pregnancy and subsequent ones [57]. Statins are contraindicated in pregnancy as its use has been reported to have adverse fetal outcome in the presence of maternally toxic levels, in animal models [58]. However in patients with severe hyperlipidemic PAP where conservative management has failed, plasma exchange has been used safely and successfully with no adverse effect on mother and fetus [59]. Some have even considered premature delivery when feasible, as an option of decreasing pregnancy induced rise in triglyceride levels. Premature delivery achieves a decrease in triglyceride levels by 10 to 20% in the next 24 hours [59].

In an rare event of hypercalcemia causing PAP due to functioning parathyroid adenoma, it could be excised during the pregnancy with excellent outcome [7].

Complications

Pregnant women who develop pancreatitis are at risk of developing the same complications as those seen in non-pregnant patients [36,37]. These include the general complications of acute renal failure, ARDS, sepsis, diabetes coagulopathy. They are also at the risk of developing local complications, including acute fluid collection, pseudocyst, pancreatic necrosis, generalized peritonitis, multiorgan failure, bleeding from pancreatitis induced aneurysmal visceral vessels and death [36,37]. In addition, they are prone for pregnancy related complications including preterm contractions, preterm delivery and fetal loss [61-63]. Fortunately majority of the patients (85 to 90%) developed PAP without any of these complication. However majority these patients (50-70%) managed conservatively are at risk of developing recurrent gallstone pancreatitis, if they have not undergone laparoscopic cholecystectomy for biliary pancreatitis during their index admission [63]. Pancreatic pseudocyst is reported to occur in 6.9% of the cases of PAP [7]. They are more likely to develop in nonbiliary pancreatitis (alcohol or hyperlipidemia induced) rather than biliary [7]. One should suspect this to have occurred in patients with persistent rise in amylase level [64]. Limited number of pseudocyst complications in PAP, makes drawing guidelines of their management difficult and the clinician hence has to use his judgment on case by case basis, in managing them [64]. These patients are at potential risk of pseudocyst rupture during valsalvas effort during delivery [64].

Outcome

In a retrospective study in USA comprising of 96 patients with PAP, complications were noted in 4 of them [62]. These included peripancreatic fluid collection (1 in 1st trimester) and 3 in third trimester (1 of them died). In this study patients who developed pancreatitis in 1st trimester had the lowest percentage probability to reach term pregnancy (60%), highest risk of fetal loss (20%) and preterm labour (16%) [62]. Term pregnancy was achieved in about 80% of all causes of acute pancreatitis. It was also observed that non gallstone pancreatitis (eg-hyperlipidemia induced, alcohol use or hyperparathyroidism related) were associated with more complications and poor outcome [62].

The Change in Outcome in Recent Years

In reports from 1970s to 1980s, the maternal and perinatal mortality rate observed were 20 % to 50% in pregnant women and 12 to 33% in non-pregnant women respectively [65]. There is a distinct improvement in the outcome of PAP over the years. Presently, maternal mortality of <1% and perinatal mortality of 0-18% are reported. In a recent report, the fetal and maternal mortality was 0% and the overall preterm labour was 3.4% in PAP compared to 3% in non-PAP patients (p > 0.5) [7]. This improvement in outcome is attributed to several factors including advances in biochemical assay, advances in recent years both in diagnostic and therapeutic management of biliary pancreatitis. Diagnosis of biliary disease has been enhanced by ultrasound, MRCP and endoscopic ultrasound. Expertise in endoscopic retrograde cholangiography (ERCP) / sphincterotomy/ stone extraction and laparoscopic cholecystectomy,
even in advanced pregnancy has improved the overall outcome. Hence the significant improvement is attributed to the advent of rapid assay methods for amylose and lipase, advances in imaging, better supportive measures for gallstone pancreatitis and overall improvement in maternal and perinatal care.

Conclusions

The management of acute pancreatitis has significantly improved over the years due to the recent progress made in the understanding of the pathophysiology, improvement in investigations and advances made in endoscopic and laparoscopic management of biliary disease. However, what remains the same over the years are the common causes for PAP and includes gallstone, alcohol and hypertriglyceridemia. It is important to note that obesity is emerging off late as a predominant etiological factor for PAP due to its endemic nature in many communities. Also, what has changed over the years is the willingness to perform LC in pregnant patients in all trimester, predominately in second trimester in sharp contrast to conservative approach in the past. In centers with expertise, the CBD calculi are dealt with ERCP sphincterotomy or at least with CBD stent insertion to prevent an attack of pancreatitis during pregnancy. Significant improvement in management of metabolic causes like hyperlipidemia induced PAP has also contributed to good outcomes. This along with overall improvement in maternal and perinatal care has led to a dramatic improvement in outcome in recent years.

References