**Open Journal of Obstetrics and Gynecology, 2014, 4, 81-89** **OJOG**
http://dx.doi.org/10.4236/ojog.2014.42015 Published Online February 2014 (http://www.scirp.org/journal/ojog/)

# Acute pancreatitis in pregnancy—Up to date

**Konstantinos Ntzeros[1], Ioannis Fragiadakis[2], Michael Stamatakos[1]**

[1]Department of Surgery, General Hospital of Korinthos, Korinthos, Greece
[2]1st Department of Surgery, Theageneio Hospital, Thessaloniki, Greece
Email: mixalislak@gmail.com

Received 26 December 2013; revised 20 January 2014; accepted 28 January 2014



## ABSTRACT

**Acute pancreatitis during pregnancy is a rare event with wide variation in the incidence, ranging from 1:1000 to 1:10000. Pancreatitis in pregnancy presents the same etiological causes as in general population. However, differences are observed in the underlying mechanisms and the prevalence of each cause in the pregnant population. Acute pancreatitis is a complicated in diagnosis and treatment disease with various complications and severe prognosis in general population as well as pregnant women. The severity of acute pancreatitis is probably the most important issue that must be elucidated as early as possible since pancreatitis is an evolving disease. Clinical characteristics of acute pancreatitis in pregnancy do not differ from the non-pregnancy state. The most important disease during the first trimester which should be differentiated from acute pancreatitis is hyperemesis gravidarum. Complications of acute pancreatitis affect differently the mother and the fetus during pregnancy. Management of acute pancreatitis in pregnancy is a controversial issue since the initial treatment is similar to the non-pregnant patient but the subsequent management might differ due to the risk of fetal disturbances or teratogenesis. The initial management of acute pancreatitis is restricted in aggressive intravenous hydration. The interventional treatment of acute pancreatitis in pregnancy can be divided into three subcategories; the operational intervention for the disease itself, the operational intervention for biliary tract cormobidities and the endoscopic intervention. In conclusion, the initial assessment of acute pancreatitis severity and the initial management of the patient are of great importance in order to support the function and avoid failure of main organs.**

## KEYWORDS

**Acute Pancreatitis; Pregnancy; Diagnosis; Treatment; Complications**

## 1. INTRODUCTION

Acute pancreatitis during pregnancy is a rare event with wide variation in the incidence, ranging from 1:1000 to 1:10000 [1]. This inconsistence in the incidence is based on the different susceptibility of each population on the etiological and risk factors of acute pancreatitis.

### 1.1. Etiopathogenesis and Risk Factors of Acute Pancreatitis

Pancreatitis in pregnancy presents the same etiological causes as in general population. However, differences are observed in the underlying mechanisms and the prevalence of each cause in the pregnant population. Biliary tract diseases are the most common cause of acute pancreatitis in pregnancy, with gallstone disease being responsible for more than 70% of cases [2]. The susceptibility of gallstone formation during pregnancy is attributed to the lithogenic effect of gestation through estrogen and progesterone [1]. A very important issue is that up to 10% of women develop stones or sludge during each pregnancy and 4% of pregnant women maintain them to the post-partum period classifying this lithogenic phenomenon as semi-reversible [3]. Therefore, the number of pregnancies as well as parities may be considered as indirect risk factors of acute pancreatitis via their accumulative lithogenic effect.

Another cause of acute pancreatitis with high prevalence during pregnancy is hyperlipidemia and more specifically hypertriglyceridemia. The trigger for acute pancreatitis is estimated at approximately 1000 mg/dl of serum triglycerides. During the second and third trimes-

ter of pregnancy there is an increase in the serum levels of triglycerides and lipoproteins up to three-fold due to estrogenic effects [1]. However, it is not common for triglycerides to reach the trigger levels except from the cases where there is a metabolic background such as familial hypertriglyceridemia or acute fatty liver [4].

Other causes of pancreatitis in pregnancy are hyperparathyroidism, alcohol, antibiotics, gene mutations and even trauma [1,5-8]. However, except from the recognized causative factors, there are also risk factors which predispose pregnant women to acute pancreatitis. **Table 1** describes the most common etiological and risk factors [1,5-8].

### 1.2. Acute Pancreatitis Definition and Severity

Acute pancreatitis is a complicated in diagnosis and treatment disease with various complications and severe prognosis in general population as well as pregnant women. There is a subtle inconsistence in the definition of diagnosis, onset, types and severity of acute pancreatitis the last years between the centers which manage acute pancreatitis patients. Therefore, a revision of the Atlanta classification was published recently which standardizes the definitions and classification of acute pancreatitis [9]. We would try to highlight the importance of incorporating these new recommendations in the pregnant patient since there is no classification of acute pancreatitis for this group of patients. The most important definitions and classification of acute pancreatitis according to severity are shown in **Table 2** [9].

Due to the sensitivity of fetus to radiation effects CT examination should be the least used imaging technique. The first choice should be ultrasonography either transabdominal or endoscopic. As for MRI there are few concerns about thermal effects on fetus during the first trimester of pregnancy [10]. However, it is important to notice that imaging is only crucial for the diagnosis of acute pancreatitis since the severity of the disease at admission or during the first 24 hours is defined by the presence or absence of organ failure. The local complications are not the predominant determinants of severity and may change through the course of the disease [9]. Therefore ionizing forms of diagnostic imaging might not be necessary during the early phase of the acute pancreatitis.

The severity of acute pancreatitis is probably the most important issue that must be elucidated as early as possible since pancreatitis is an evolving disease. The classification of acute pancreatitis according to severity defines three degrees: mild, moderately severe and severe [9]. It is important to know that mild acute pancreatitis usually does not require imaging which is of great importance for the pregnant population. Moderately severe acute pancreatitis could resolve with or without the need of special care or intervention. Finally, patients with severe acute pancreatitis have high mortality rates.

**Table 1.** The most common etiological and risk factors of acute pancreatitis in pregnancy.

| Etiological factors | Risk factors |
|---|---|
| Biliary disease: chololithiasis, cholecystitis, common bile duct stone, congenital choledochal cyst | Number of pregnancy and parity |
| Metabolic conditions: hyperlipidemia-hypertriglyceridemia, acute fatty liver, familial hypertriglyceridemia | Weight gain and hormonal changes of pregnancy |
| Hyperparathyroidism | Rapid weight loss mainly post-partum |
| Autoimmune | Ethnicity |
| Traumatic | |
| Drugs: tetracycline, thiazides | |
| Viral infections | |
| Alcohol | |
| Cystic fibrosis | |
| Augmented uterus which compresses the pancreatic billiary duct | |
| Surgery/ERCP | |

The advances in diagnosis and treatment of acute pancreatitis in pregnancy have decreased the maternal mortality to almost 0% and the perinatal mortality to 0% - 18% compared to studies of previous decades [7]. However, diseases in pregnancy affect two lives and the morbidity is another issue of great importance since it affects two especially young persons (the mother and the fetus). Therefore, the complications of the disease itself, the side effects of the diagnostic management and the treatment are very important and unfortunately not inspected enough.

## 2. DISCUSSION

### 2.1. Clinical Manifestation

Clinical characteristics of acute pancreatitis in pregnancy do not differ from the non-pregnancy state. The usual symptoms are abdominal pain, anorexia, nausea, vomiting, dyspepsia, low-grade fever, tachycardia, fatty food intolerance [11]. The hematological and biochemical examination shows leukocytosis, an increase in inflammatory and pancreatic markers as well as in cholostatic markers if the etiopathogenic reason is billiary disease [11]. More specifically, the clinical and laboratory findings are described in **Table 3** [9,11]. However, some of the hematological, biochemical and clinical findings of acute pancreatitis are evident on normal pregnancies suggesting that the diagnosis of acute pancreatic requires a deeper investigation of the patient's clinical presentation.

 

**Table 2.** Definitions and classification of acute pancreatitis.

1) Diagnosis: two of the three features

- Abdominal pain consistent with acute pancreatitis
- At least three-fold increase than the upper normal levels of serum lipase or amylase
- Imaging findings characteristic of acute pancreatitis on:
  - Ultrasonography
  - MRI
  - CT

2) Onset time of the disease: The start time of abdominal pain

3) Types of acute pancreatitis:

| Interstitial oedematous | Necrotizing |
|---|---|
| • Diffuse enlargement of pancreas<br>• +/− peripancreatic fluid | • Necrosis of pancreatic parenchyma<br>• Necrosis of peripancreatic tissue<br>• Or both |

4) Phases of the course of acute pancreatitis

| Early | Late |
|---|---|
| • Lasts for the first week and may expend to the second<br>• Systemic effects of pancreatic inflammation:<br>▪ SIRS<br>▪ Organ failure | • Lasts for weeks to months<br>• Persistence of systemic inflammation<br>• Development of local complications |

5) Severity: three subtypes

Mild acute pancreatitis

- Uncomplicated course
- Regression through first week at early phase
- No organ failure
- No local or systemic complications
- Usually no necessity for imaging

Moderately severe acute pancreatitis

- Complicated course
- Transient but no persistent organ failure
- Local or systemic complications
- Resolve with or without special care or intervention

Severe acute pancreatitis

- Highly complicated
- Single or multiple persistent organ failure
- One or more local or systemic complication

## 2.2. Diagnosis

The diagnosis of acute pancreatitis in pregnancy according to the revised Atlanta classification requires two of the three following features: 1) abdominal pain consistent with acute pancreatitis, 2) serum lipase and amylase activity increased at least three times the higher normal serum levels, 3) characteristic imaging findings of acute pancreatitis on U/S, MRI or CT [9]. It is important to mention that if the clinical and laboratory examinations suggest strongly the presence of acute pancreatic inflammation, the diagnostic imaging is not necessary at first hours.

**Table 3.** Clinical manifestation and laboratory findings of acute pancreatitis in pregnancy.

| Symptoms | Laboratory findings |
|---|---|
| Abdominal pain:<br>• Colicky or stabbing character<br>• Rapid onset<br>• Focused on epigastrium or right hypochondrium<br>• Radiating to the right flank, scapula, shoulder | Pancreatic:<br>• Increased serum lipase activity (up to 3 times greater than the upper limit of normal)<br>• Increased serum amylase activity (up to 3 times greater than the upper limit of normal) |
| Gastrointestinal:<br>• Anorexia<br>• Vomiting<br>• Nausea<br>• Dyspepsia<br>• Fatty food intolerance<br>• Jaundice | Metabolic:<br>• Hyperglycemia<br>• Hypertriglyceridemia<br>• Hypocalcaemia<br>Cholestatic:<br>• Increased ALP and γ-GT<br>• Increased AST/ALT<br>• Increased Bilirubin |
| Circulatory:<br>• Tachycardia<br>• Orthostatic hypotension | Hematological:<br>• Leukocytosis up to 16,000/μl<br>• Elevated neutrophils >75% |
| Systematic:<br>• Low-grade fever | Markers of acute inflammation:<br>• Increased CRP<br>• Increased ESR |
| Signs:<br>Hemorrhagic:<br>• Gray-Turner<br>• Cullen<br>Pain:<br>• Kehr<br>• Murphy | Urine:<br>• Increased amylase activity |

## 2.3. Differential Diagnosis

The differential diagnosis of acute pancreatitis in pregnancy should comprise all the possible gynecological/obstetrical, surgical, non-surgical or urological diseases which could be presented as acute abdomen. Additionally, all the diseases which are presented with consistent vomiting, nausea or anorexia accompanied by abdominal pain are included in the list of differential diagnosis of pancreatitis in pregnancy. A short listing of the most usual disease that should be differentiated before diagnosing pancreatitis is described in **Table 4**. However, it is of great importance to highlight diseases which have the same clinical presentation of mild acute pancreatitis, since most of them do not require admission to a hospital while on the other hand mild acute pancreatitis requires multi-day admission with conservative treatment.

The most important disease during the first trimester which should be differentiated from acute pancreatitis is hyperemesis gravidarum, since it has a consistent clinical picture with a wide range of symptoms due to the electrolytic disturbances that might cause to the pregnant woman. However, the diagnosis of hyperemesis gravidum is considered only when other diseases such as pyelonephritis, pancreatitis, cholecystitis, hepatitis, ap-

 

**Table 4.** Differential diagnosis of acute pancreatitis in pregnancy.

| Obstetrical | Gynecological | Surgical | Urological | Non-surgical | Diseases presented with mild symptoms found in mild acute pancreatitis |
|---|---|---|---|---|---|
| Ectopic pregnancy | Rupture of ovarian cyst | Biliary disease | Pyelonephritis | Gastroenteritis | Acute or chronic viral hepatitis |
| Chorioamnionitis | Adnexal torsion | Acute cholangitis | Nephrolithiasis/ Renal colic | Pneumonia | Hyperemesis gravidarum |
| Retroverted gravid uterus | Ruptured corpus luteum cyst | Acute appendicitis | Renal forniceal rupture | Pulmonary embolism | Gastroesophageal reflux disease |
| Spontaneous uterine rupture | Fibroid "red-degeneration" | Diverticulitis | | Mesenteric lymphadenitis | Constipation |
| Threatened abortion/ premature labor | Tubo-ovarian abscess | Gastric perforation | | | |
| Acute fatty liver of pregnancy | Endometriosis | Bowel obstruction | | | |
| HELLP syndrome/ Preeclampsia-eclampsia | | Intestinal Volvulus | | | |

pendicitis, gastroenteritis, peptic ulcer disease, thyrotoxicosis and hyperthyroidism are ruled out [12].

## 2.4. Imaging

The usual imaging techniques used in acute pancreatitis in pregnancy either for diagnostic or therapeutic reasons are transabdominal ultrasound (US), endoscopic ultrasound (EUS), computed tomography (CT), magnetic reasonance imaging (MRI), endoscopic retrograde cholangiopancreatography (ERCP), magnetic reasonance cholangiopancreatography (MRCP).

Transabdominal ultrasound is the preferred diagnostic imaging technique because there is no danger of emitting harmful radiation to the fetus. However, there are limitations in the efficiency of this technique to depict the lesions of pancreas and peripancreatic tissues because it depends on operator skill, patient obesity and bowel dilatation. However, it is ideal on detecting dilated pancreatic ducts, pseudocysts and local collections >2 - 3 cm [11]. Additionally, it is possible to detect other signs which could determine the severity of acute pancreatitis such as the thickening of gall bladder wall (biliary pancreatitis concurrent with cholecystitis), the collection of peritoneal, peripancreatic or pericholecystic fluid and oedematous enlargement of pancreas. However, it has low sensitivity in detecting biliary sludge or common bile duct stones and complicated morphological changes in pancreas [1]. The most important advantage is the repeatability of this examination without affecting the mother or the fetus.

EUS is suggested for detecting common bile duct stones with positive predicting value nearing 100%, superior even to MRCP [1]. It is a semi-invasive technique requiring intravenous sedation. However, in expert hands can detect even small gallstones and biliary sludge although it is not considered as the best imaging technique for such findings. The EUS is highly suggested prior to ERCP in evaluating the necessity of such an operative technique, especially when MRCP is contraindicated [1]. Although, no harmful radiation is emitted there is a minimal risk related to the sedation [1].

CT is undoubtedly the most efficient diagnostic imaging technique in confirming the diagnosis, classifying pancreatitis in interstitial oedematous or necrotizing, depicting the local complications and finally defining the severity of the disease. Therefore all the morphological features of acute pancreatitis according to the revised Atlanta classification are defined by this imaging technique. However, in pregnancy and especially during the first trimester where fetal development takes place, CT is highly restricted because of the possible radiation harm to the fetus. On the other hand, there is the opinion that ionizing radiation can harm the fetus only if surpasses certain levels [1,13]. Most clinicians avoid to use CT no matter the benefits to the diagnosis due to the fact that mild acute pancreatitis do not require any intervention and conventional treatment is curable enough and also because acute pancreatitis is an evolving disease which might complicate at the late phase of the disease. Therefore, CT could be used only in the severe acute pancreatitis where local and systemic complications threaten the mother's life and not at admission time since most of the severe local complications develop later.

ERCP is an ionizing radiation based technique and it is necessary to use sedation in order to fulfill the examination, both of which incorporate danger for the fetus. This means that the diagnostic character of this technique is surpassed by the possible harm to the fetus. However, there is still place of this technique in severe biliary acute pancreatitis as a therapeutic intervention, by combining the ERCP with endoscopic sphincterectomy. The mother after decompressing the common bile duct and removing the gallstones would avoid any further complications and

 

morbidity as well as mortality of severe biliary acute pancreatitis will be reduced. However, improvements should be done to reduce firstly the emitted harmful radiation and secondly the sedation risks to the fetus to use therapeutic ERCP without hesitations. The first step is before therapeutic ECRP to precede a diagnostic MRCP or EUS and if a common bile duct gallstone is identified then to continue with ERCP over the same sedation. The second step is to reduce the ionizing radiation reaching the fetus to a level lower than that considered to be teratogenic. There are several reports which support that ERCP with modified techniques is safe during pregnancy [14,15]. This can be succeeded by limiting fluoroscopy time to less than 1 minute, fetal shielding with lead of thickness 0.5 to 1.0 mm and avoiding direct X-ray films [6,13,14]. A new development in this field is the ERCP without radiation, where the endoscopist cannulates the common bile duct with a guidewire through the papilla and continues to sphincterotomy and gallstone extraction without the use of ionizing radiation [16,17]. Second trimester is ideal for ERCP since the first trimester is the most sensitive period of the fetus [6]. However, there are other complications of ERCP which persist even if the radiation risk is diminished such as bleeding, perforation and pancreatitis [14]. Additionally, prophylactic antibiotics and tocolytics could be used in pregnant women undergoing ERCP [6].

MRI and MRCP provide excellent images of the peri/pancreatic tissues and the biliopancreatic duct systems. Although, the magnetic reasonance imaging techniques do not emit harmful radiation to the fetus, there are several concerns about the risk of thermal injury to the developing fetus during first trimester [10,18]. Therefore, the suggestion for these imaging techniques is that until conclusive safety data become available, MRI should be used only when other non-ionizing forms of diagnostic imaging are inadequate or the patient care depends on further imaging that would otherwise require exposure to ionizing radiation [13,18]. As for the MRCP is a non-invasive method with good common bile duct evaluation, although some small ductal stones located at the distal part of the common bile duct could be missed [13].

## 2.5. Complications

Complications of acute pancreatitis affect differently the mother and the fetus during pregnancy. The onset of pancreatitis at the first trimester is mostly associated with higher rate of fetal complications (pre-term delivery) and mortality [19]. The incidence of acute pancreatitis is increased at advancing gestational age due to a parallel increase in gallstone disease [1]. Additionally, the third trimester is associated with higher incidence of severe acute pancreatitis accompanied by systemic and local complications increasing both maternal morbidity and fetal mortality [5]. Therefore, the first trimester is safer for the mother while the third is associated with severe systemic complications and increased maternal and fetal mortality.

### 2.5.1. Systemic Complications

Systemic complications of acute pancreatitis in pregnancy comprise the same range as in general population. They are by definition associated with severe acute pancreatitis and affect all the main systems of the pregnant woman.

The respiratory system function is compromised during pancreatitis by pleural effusion, atelectasis, acute pulmonary oedema or ARDS resulting in hypoxemia and dyspnea [6,19].

The circulatory complications are characterized by shock due to hypovolemia and/ or hypotension. The main reasons are loss of fluids retroperitoneally or in the abdominal cavity and/or peripheral vasodilatation [19].

The cardiac complications are characterized by manifestations of tachycardia and non-specific disturbances rather than depression of cardiac function due to the young age of the pregnant patient.

Coagulation disturbances and especially DIC (Disseminated Intravascular Coagulation) are very important during pregnancy since they are accompanied by multiple organ failure and result in high rate of fetal and maternal death [19].

Gastrointestinal bleeding is described during pancreatitis in pregnant and could be accompanied by coagulation disturbances [19].

Renal function is easily impaired during severe acute pancreatitis resulting in uremia and oliguria either through prerenal azotemia or acute tubular necrosis [5,19].

Metabolic complications comprise hypocalcaemia, hyperglycemia, hypertriglyceridemia, hypoglycemia and acid-base disturbances [20].

Despite the maternal danger during severe acute pancreatitis, it is important to evaluate the fetal distress and morbidity during the exacerbation of systemic complication of pancreatitis in pregnancy. The most prominent consideration is that the incidence of preterm delivery and perinatal morbidity is higher in moderately severe and severe acute pancreatitis than mild acute pancreatitis because of lower supportive efficiency of the maternal-fetal interface which increases the fetal distress [21]. The maternal acid-base disturbances affect the fetal acid-base status which activates the fetal mechanisms of homeostasis as in the cases of fetal hypoxemia which results in redistribution of fetal blood to support the vital organs [11]. Additionally, the uterus could prematurely contract because of the diffuse peritonitis [20]. Therefore, prematurity and mortality of the fetus could be associated with the severity of the disease.

 

### 2.5.2. Local Complications

Local complications of acute pancreatitis in pregnancy incorporate: acute peri/pancreatic fluid collections, pancreatic pseudocyst, acute necrotic collections, walled-off necrosis and the less common complications of gastric outlet dysfunction, splenic vein thrombosis, portal vein thrombosis and colonic necrosis. A special issue is the complication of the necrotic collections with infection. The term of pancreatic abscess although used to describe a localized collection of purulent material without significant necrotic material is no longer suggested by the revision of Atlanta Classification. Local complications should be suspected when the symptoms of the disease as well as the clinical picture of the patient persist or worsen no matter the conventional treatment. However, it is important to highlight the classification of local complication to early and late, since the diagnosis of most of them is based on morphological characteristics shown by CT, MRI or U/S. Therefore the timing of the onset of the local complication is very important in order to evaluate the necessity for CT or MRI.

1) Early Local Complications

Acute peri/pancreatic fluid collections are defined as homogenous fluid collections without well-defined wall but confined by fascial planes, localized at the region of pancreas. They develop in early phase of pancreatitis, usually resolve without intervention and most of them remain sterile. Radiation exposure is not necessary in the early phase since these fluid collections do not require treatment and might develop into a pancreatic pseudocyst after 4 weeks [9].

Acute necrotic collections are associated with necrotizing pancreatitis and combine various amounts of fluid and solid necrotic material of the pancreatic or peripancreatic tissues. They are characterized by no well-defined wall and develop during the first 4 weeks. The diagnosis of acute necrotic collections is very important since they confirm the necrotic pancreatitis but they are also in danger of infection. However, during the early phase it is difficult to differentiate an acute necrotic collection from an acute peri/pancreatic fluid one. Therefore, it is suggested to use MRI or ultrasonography in order to detect the presence of solid content [9].

2) Late Local Complications

Pancreatic pseudocyst is characterized by the presence of a well-defined wall which contains a fluid collection with no solid material. It develops more than 4 weeks after the onset of interstitial oedematous pancreatitis. Although CT is the most used diagnostic imaging method, in pregnant women might be enough the MRI or ultrasonography just to confirm the absence of solid material [9].

Walled-off necrosis is a necrotic collection confined by an enhancing wall of reactive tissue. It develops more than 4 weeks after the onset of necrotizing pancreatitis. Although CT will show the morphological characteristic of this collection, it might be unable to show the solid material. Therefore, it might be enough for the pregnant women to use MRI or ultrasonography [9].

## 2.6. Treatment

Management of acute pancreatitis in pregnancy is a controversial issue since the initial treatment is similar to the non-pregnant patient but the subsequent management might differ due to the risk of fetal disturbances or teratogenesis. Therefore it is important the medical team to consist of several different specialties such as obstetrician, surgeon, gastroenterologist and radiologist [13]. However, before the initial treatment it is crucial to predict the severity of acute pancreatitis. The available acute pancreatitis-specific score systems have limited value [22]. The same applies for any laboratory test, even C-reactive protein [23]. A combination of clinical and laboratory findings which could be associated with a severe course of acute pancreatitis used for initial risk assessment have been proposed from the American college of gastroenterology for the general population [23]. We present the applicable findings in pregnant women.

Patient characteristics are very important for the initial assessment of the pregnant patient. Women with high BMI reaching the obese class with altered mental status and other comorbid diseases are in increased risk of severe acute pancreatitis course.

The presence of systemic inflammatory response syndrome (SIRS), which is related with the development of organ failure, especially if the SIRS is persistent through the course of the disease indicates close monitoring of the patient and even admission to an intensive care unit.

Other findings such as sings of hypovolemia (elevated or rising blood urea nitrogen), elevated or rising hematocrit, elevated creatinine and clinical sings of pulmonary participation such as in the case of pleural effusions and/or infiltrates indicate that this patient might have a severe course of acute pancreatitis. Additionally, the presence of organ failure and/or pancreatic necrosis classifies instantly the acute pancreatitis as severe.

### 2.6.1. Conventional Treatment

The initial treatment focuses on diminishing the pancreatic exocrine secretion, restoring the third space fluid sequestration, and supporting the patient by providing the necessary nutrition, oxygen, anaelgetics and monitoring the vital signs of mother and fetus [13].

The initial management of acute pancreatitis is restricted in aggressive intravenous hydration by 250 - 500 ml/ hour of isotonic crystalloid solution, preferably lactated Ringer's solution, unless cardiovascular, renal or other comorbidities exist [23]. Early aggressive intrave-

 

nous hydration is indicated for the first 12 - 24 hours. More aggressive hydration is suggested in patients with circulatory manifestations of severe fluid loss such as hypotension and tachycardia. Fluid requirements should be reassessed at frequent intervals for the next 48 hours by evaluating the levels of blood urea nitrogen [23].

The cessation of pancreatic exocrine secretion is achieved by stopping the oral feeding while on the other hand nourishing the patient either by total parenteral nutrition through central venous catheters or by enteral nutrition through a naso-jejunal catheter. It is well known that central venous catheters have higher incidence of complications in pregnant women than in general population [13]. It is also suggested that peripherally inserted central catheters should be preferred when total parenteric nutrition is required [1]. The enteral feeding is superior to total parenteric nutrition in two ways, firstly the central venous catheters' complications are avoided and secondly the bowel continues to function which means that the gut flora maintains the enteric mucosal immunity and reduces the translocation of bacteria [1].

Mild acute pancreatitis usually resolves within the first seven days and do not need nutritional support since the patient can feed immediately as long as the nausea, vomiting and abdominal pain subsides [11,23]. A low-fat solid diet appears as safe as a clear liquid diet [23].

Another issue is the pharmacological medication of the patient since there are restrictions due to the pregnancy. In most cases the parenteral administration of anelgetics and antiemetics is without consideration. Antibiotics on the other hand, have raised considerations about the timing of administration, the benefit of prophylactic use, the efficacy of monotherapy, the possible risks of polytherapy and the necessity of antibiotics which are classified on FDA pregnancy category B or C.

The latest recommendations on the use of antibiotics support that there is no benefit from their administration: 1) in mild acute pancreatitis, 2) in normal common bile duct size and without evidence for cholangitis, 3) in routine use of prophylactic antibiotics in patients with severe acute pancreatitis, 4) and/or sterile necrosis [13,23]. The same applies for the routine administration of antifungal agents along with antibiotics [13].

However, the indications for therapeutic antibiotic use are extrapancreatitic infection (such as cholangitis, catheter-acquired infections, bacteremia, urinary tract infections, pneumonia) and infected necrosis [23].

As for the infected pancreatic necrosis, there are situations where the systematic antibiotic therapy is able to resolve the infection. However, if the patient deteriorate or fail to improve within 7 - 10 days then percutaneous drainage or endoscopic necresectomy should be considered [23].

The great issue of antibiotic use in pancreatitis becomes even bigger when the pregnancy and the possible danger for the fetus take place in the equation. The suggested antibiotics are those which show good penetration in the pancreatic necrosis such as carbapenems, quinolones, metronidazole, high-dose cephalosporins and those having therapeutic effect on the ascending cholangitis such as monotherapy of ampicillin-sulbactam, piperacillin-tazobactam, imipenem or dual therapy with metronidazole plus ceftriaxone or fluoroquinolone [13,23]. However, these suggestions are based on general population studies. Most of these antibiotics are categorized as class B or C in the antibiotics safety classification for the fetus.

More specifically, metronidazole is classified in FDA pregnancy category B which means that animal reproduction studies have failed to demonstrate a risk to the fetus and there are no adequate and well-controlled studies in pregnant women. It passes freely across the placenta and is secreted in human milk in concentrations similar to those found in plasma. There is no association of metronidazole with increased risk of teratogenic effects [13]. Additionally, ampicillin-sulbactam, piperacillin-tazobactam and ceftriaxone are classified as FDA pregnancy category B antibiotic with no evidence of risk in humans.

Carbapenems as a category shows differential categorization in FDA pregnancy classification. Meropenem is classified as a category B drug while imipenem resides in category C which means that animal reproduction studies have shown an adverse effect on the fetus and there are no adequate and well-controlled studies in humans, but potential benefits may warrant use of the drug in pregnant women despite potential risks.

Quinolones are also classified as category C in FDA pregnancy classification with some adverse effects in animal studies but no adequate studies in humans.

Although the use of such antibiotics might overcome the possible fetal risks in cases of severe acute pancreatitis where the mother's life is in risk, the effect of polytherapy is still another great issue. Recent studies revealed that the effect of antibiotics in fetus might be indirect via epigenetic changes which could affect the birth weight of newborns [24].

Other pharmacological agents such as somatostatin, actreotide, n-acetyl-cystein, gabexate mesylate, lexipafant and probiotics do not show a strong positive association with better course of acute pancreatitis, therefore should be avoided during pregnancy [13,23].

### 2.6.2. Interventional Treatment

The interventional treatment of acute pancreatitis in pregnancy can be divided into three subcategories; the operational intervention for the disease itself, the operational intervention for biliary tract comorbidities and the

 

endoscopic intervention.

As far as the disease itself is concerned, the surgical treatment is suggested in specific cases of necrotizing pancreatitis. Sterile necrosis as well asymptomatic local collections such as pancreatic pseudocyst do not require interventions regardless the size, the location and/ or the extension [11,23]. In stable patients with infected necrosis the operation should be postponed for more than 4 weeks from the onset of symptoms, in order to let the lesions to get organized in a more concrete form (walled-off necrosis).

The biliary acute pancreatitis in pregnancy requires surgical treatment only when there is: 1) acute cholecystitis which does not resolve with conventional treatment, 2) peritonitis, 3) obstructive jaundice and severe symptoms which will resolve after the operational interventions [13]. However, in necrotizing biliary acute pancreatitis cholecystectomy has to wait until active inflammation subsides and fluid collections resolve or stabilize in order to avoid infection of the necrotic tissue no matter the severity of the disease [23]. As for the preferred approach, although laparoscopic and open cholecystectomy show no significant difference in maternal or fetal outcome, there are still the benefits of laparoscopic operations such as less postoperative pain, less postoperative ileus, significantly reduced hospitalization, decreased narcotic use, quick return to regular diet, faster recovery, less manipulation of the uterus and less chances of postoperative deep vein thrombosis [11,13]. As for the timing of laparoscopic operation, recent guidelines of the Society of American Gastrointestinal and Endoscopic Surgeons (SAGES) suggest that cholecystectomy is safe in all trimesters of pregnancy [11]. However, there are considerations about the effect of sedation during the organogenesis of the first trimester and the increased surgical capacity required as the uterus augments in size during the third trimester. Therefore, the best timing might be the second trimester, although there is no indication to delay the operation if it is necessary, no matter the trimester of pregnancy. Finally, there are few precautions that should be followed during laparoscopic operation of pregnant woman, such as the use of an open technique in order to insert the umbilical trocar, special caution at the intraperitoneal pressures, left lateral position to diminish aortocaval compression and avoiding the use of electrocautery near uterus [11].

A special issue is the minimally invasive management of pancreatic necrosis which comprises laparoscopic surgery from anterior or retroperitoneal approach, percutaneous drainage and video-assisted or small incision-based left retroperitoneal debridement. Although these minimally invasive methods are continuously gaining ground in the management of symptomatic patients with infected necrosis, there is still time in order to be established for the pregnant woman [23].

Endoscopic treatment of biliary acute pancreatitis includes therapeutic ERCP with sphincterotomy, endoscopic sphincterotomy and biliary stent placement. The indications of endoscopic intervention are severe acute pancreatitis with concurrent cholangitis, strong evidence of common bile duct obstruction especially after endoscopic ultrasound or MRCP confirmation, and in women having undergone cholecystectomy [13]. However, there are several concerns about the sphincteroctomy in young patients like the pregnant women because of the long-term side effects such as lifelong bile reflux, bacterial colonization and risk of carcinoma [13]. Therefore, some clinicians prefer the placement of biliary stent instead of sphincterotomy and stone extraction [25]. On the other hand stenting have its own drawbacks such as risk of stent occlusion, cholangitis and need of a second procedure to remove it [13].

## 3. CONCLUSIONS

Acute pancreatitis either in its mild form with the increased risk of recurrence if it is biliary or its severe form with the increased maternal and fetal morbidity will affect dramatically the natural course of pregnancy. Therefore, the initial assessment of severity and the initial management of the patient are of great importance in order to support the function and avoid failure of main organs. The treatment of the pregnant woman should be decided by a medical team with several specialties. Due to the fact that acute pancreatitis is a complicated evolving disease and the pregnant woman supports two lives, the scientific society should focus on establishing specific suggestions about the conventional and surgical treatment of acute pancreatitis in pregnancy rather than basing on expert opinion.

Another concern is in which degree the obstetrician is allowed to ignore the possibility of biliary acute pancreatitis in women who underwent assisted reproductive treatment and now carry a precious pregnancy. Should these women be examined for the presence of gallbladder stones or sludge before undergoing the assisted reproduction treatment? Has any predictive value the presence of gallstone, the size and mobility of gallbladder in manifesting biliary acute pancreatitis during pregnancy?

## REFERENCES

[1] Pitchumoni, C.S. and Yegneswaran, B. (2009) Acute pancreatitis in pregnancy. *World Journal of Gastroenterology*, **15**, 5641-5646. http://dx.doi.org/10.3748/wjg.15.5641

[2] Ramin, K.D., Ramin, S.M., Richey, S.D. and Cunningham, F.G. (1995) Acute pancreatitis in pregnancy. *American Journal of Obstetrics & Gynecology*, **173**, 187-191.

 

http://dx.doi.org/10.1016/0002-9378(95)90188-4

[3] Ko, C.W., Beresford, S.A., Schulte, S.J., Matsumoto, A.M. and Lee, S.P. (2005) Incidence, natural history, and risk factors for biliary sludge and stones during pregnancy. *Hepatology*, **41**, 359-365. http://dx.doi.org/10.1002/hep.20534

[4] Serpytis, M., Karosas, V., Tamosauskas, R., Dementaviciene, J., Strupas, K., Sileikis, A. and Sipylaite, J. (2012) Hypertriglyceridemia-induced acute pancreatitis in pregnancy. *JOP*, **13**, 677-680

[5] Qihui, C., Xiping, Z. and Xianfeng, D. (2012) Clinical study on acute pancreatitis in pregnancy in 26 cases. *Gastroenterology Research and Practice*, **2012**, 271925. http://downloads.hindawi.com/journals/grp/2012/271925.pdf http://dx.doi.org/10.1155/2012/271925

[6] Juneja, S.K., Gupta, S., Virk, S.S., Tandon, P. and Bindal, V. (2013) Acute pancreatitis in pregnancy: A treatment paradigm based on our hospital experience. *International Journal of Applied and Basic Medical Research*, **3**, 122-125. http://dx.doi.org/10.4103/2229-516X.117090

[7] Eddy, J.J., Gideonsen, M.D., Song, J.Y., Grobman, W.A. and O'Halloran, P. (2008) Pancreatitis in pregnancy. *Obstetrics & Gynecology*, **112**, 1075-1081. http://dx.doi.org/10.1097/AOG.0b013e318185a032

[8] Cunningham, F.G., Leveno, K.J., Bloom, S.L., Hauth, J.C., Rouse, D.J. and Spong, C.Y. (2010) Hepatic, gallbladder, and pancreatic disorders. In: *Williams Obstetrics*, 23rd Edition, McGraw Hill, New York, 1063-1078

[9] Banks, P.A., Bollen, T.L., Dervenis, C., Gooszen, H.G., Johnson, C.D., Sarr, M.G., Tsiotos, G.G. and Vege, S.S. (2013) Classification of acute pancreatitis—2012: Revision of the Atlanta classification and definitions by international consensus. *Gut*, **62**, 102-111. http://dx.doi.org/10.1136/gutjnl-2012-302779

[10] Levine, D., Zuo, C., Faro, C.B. and Chen, Q. (2001) Potential heating effect in the gravid uterus during MR HASTE imaging. *Journal of Magnetic Resonance*, **13**, 856-861. http://dx.doi.org/10.1002/jmri.1122

[11] Stimac, D. and Stimac, T. (2011) Acute pancreatitis during pregnancy. *European Journal of Gastroenterology & Hepatology*, **23**, 839-844. http://dx.doi.org/10.1097/MEG.0b013e328349b199

[12] Sonkusare, S. (2008) Hyperemesis gravidarum: A review. *Medical Journal of Malaysia*, **63**, 272-276.

[13] Jain, V., Yegneswaran, B. and Pitchumoni, C.S. (2009) Biliary pancreatitis in pregnancy. *Practical Gastroenterology*, **33**, 16-30.

[14] Smith, I., Gaidhane, M., Goode, A. and Kahaleh, M. (2013) Safety of endoscopic retrograde cholangiopancreatography in pregnancy: Fluoroscopy time and fetal exposure, does it matter? *World Journal of Gastrointestinal Endoscopy*, **5**, 148-153. http://dx.doi.org/10.4253/wjge.v5.i4.148

[15] Kahaleh, M., Hartwell, G.D., Arseneau, K.O., Pajewski, T.N., Mullick, T., Isin, G., Agarwal, S. and Yeaton, P. (2004) Safety and efficacy of ERCP in pregnancy. *Gastrointestinal Endoscopy*, **60**, 287-292. http://dx.doi.org/10.1016/S0016-5107(04)01679-7

[16] Agcaoglu, O., Ozcinar, B., Gok, A.F., Yanar, F., Yanar, H., Ertekin, C. and Gunay, K. (2013) ERCP without radiation during pregnancy in the minimal invasive world. *Archives of Gynecology and Obstetrics*, **288**, 1275-1278. http://dx.doi.org/10.1007/s00404-013-2890-0

[17] Akcakaya, A., Ozkan, O.V., Okan, I., Kocaman, O. and Sahin, M. (2009) Endoscopic retrograde cholangiopancreatography during pregnancy without radiation. *World Journal of Gastroenterology*, **15**, 3649-3652. http://dx.doi.org/10.3748/wjg.15.3649

[18] Leyendecker, J.R., Gorengaut, V. and Brown, J.J. (2004) MR imaging of maternal diseases of the abdomen and pelvis during pregnancy and the immediate postpartum period. *Radiographics*, **24**, 1301-1316. http://dx.doi.org/10.1148/rg.245045036

[19] Tang, S.J., Rodriguez-Frias, E., Singh, S., Mayo, M.J., Jazrawi, S.F., Sreenarasimhaiah, J., Lara, L.F. and Rockey, D.C. (2010) Acute pancreatitis during pregnancy. *Clinical Gastroenterology and Hepatology*, **8**, 85-90. http://dx.doi.org/10.1016/j.cgh.2009.08.035

[20] Li, H.P., Huang, Y.J. and Chen, X. (2011) Acute pancreatitis in pregnancy: A 6-year single center clinical experience. *Chinese Medical Journal*, **124**, 2771-2775.

[21] Esmer, A.C., Ozsurmeli, M. and Kalelioglu, I. (2012) Maternal and perinatal outcomes of acute pancreatitis during pregnancy. *Gazi Medical Journal*, **23**, 133-137.

[22] Gardner, T.B., Vege, S.S., Pearson, R.K. and Chari, S.T. (2008) Fluid resuscitation in acute pancreatitis. *Clinical Gastroenterology and Hepatology*, **6**, 1070-1076. http://dx.doi.org/10.1016/j.cgh.2008.05.005

[23] Tenner, S., Baillie, J., DeWitt, J. and Vege, S.S. (2013) American College of Gastroenterology guideline: Management of acute pancreatitis. *American Journal of Gastroenterology*, **108**, 1400-1415. http://dx.doi.org/10.1038/ajg.2013.218

[24] Vidal, A.C., Murphy, S.K., Murtha, A.P., Schildkraut, J.M., Soubry, A., Huang, Z., Neelon, S.E., Fuemmeler, B., Iversen, E., Wang, F., Kurtzberg, J., Jirtle, R.L. and Hoyo, C. (2013) Associations between antibiotic exposure during pregnancy, birth weight and aberrant methylation at imprinted genes among offspring. *International Journal of Obesity*, **37**, 907-913. http://dx.doi.org/10.1038/ijo.2013.47

[25] Farca, A., Aguilar, M.E., Rodriguez, G., de la Mora, G. and Arango, L. (1997) Biliary stents as temporary treatment for choledocholithiasis in pregnant patients. *Gastrointestinal Endoscopy*, **46**, 99-101.

[26] Hu, T. and Desai, J.P. (2004) Soft-tissue material properties under large deformation: Strain rate effect. *Proceedings of the 26th Annual International Conference of the IEEE EMBS*, San Francisco, 1-5 September 2004, 2758-2761.

 