

# Acute pancreatitis and pregnancy

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## ABSTRACT

Acute pancreatitis in pregnancy is a rare, but severe medical condition, occurring in 1 in 1,000 to 1 in 10,000 pregnancies and may present as mild, moderate, or severe disease. Diagnosis of acute pancreatitis in the pregnant population is hampered by biochemical and hematological alterations generated by pregnancy itself. There is an increased risk of maternal and fetal complications in cases of severe acute pancreatitis in pregnancy. Diagnosis of acute pancreatitis in pregnancy is based on clinical examination, laboratory tests and imaging techniques. Endoscopic retrograde cholangiopancreatography, magnetic resonance cholangiopancreatography and endoscopic ultrasound are diagnostic and therapeutic modalities. Surgical treatment is indicated in severe and refractory cases of acute pancreatitis in pregnancy and laparoscopic cholecystectomy is preferred over open cholecystectomy. Timely diagnosis and management of acute pancreatitis significantly improves both maternal and fetal outcome.

**Keywords:** acute pancreatitis, pregnancy, diagnosis, management

## INTRODUCTION

Pancreatitis in pregnancy remains a relatively understudied pathology. Further research must be made into understanding the incidence, etiology, mechanisms of appearance and treatment methods, in order to determine the best approach for diagnosis, management [1]. Due to its rapid onset and multiple local and systemic complications (which can extend to diabetes, infections, bleeding and renal insufficiency [1,2]), pancreatitis usually involves hospitalization, as it is associated with a mortality rate of 5% [1] (in cases of acute pancreatitis) and 69-80% (in cases of chronic pancreatitis) [1]. Increased age and the presence of comorbidities such as obesity, heart, liver and chronic kidney disease, increase the mortality risk [2].

Classification of pancreatitis includes acute pancreatitis, recurrent acute pancreatitis and chronic pancreatitis. There have been reports of acute pancreatitis (AP) evolving into recurring acute pancrea-

titis, chronic pancreatitis, and from there on in a continuous disease trajectory, depending on risk factors (such as: gallstones, genetic risk factors, alcohol abuse, hypertriglyceridemia, abdominal trauma, drugs etc.) [3].

## MATERIAL AND METHODS

Systematic review of English literature using PubMed, Medline, Google Scholar databases was conducted. Patient-specific cohort studies were identified by using the following search criteria: "pregnancy" and "pancreatitis". Inclusion criteria further included journal articles that noted etiological factors, diagnosis and treatment methods of pancreatitis in pregnancy. Non-English language articles and studies/trials not conducted on humans were excluded. No limitations were placed on geographical location, race, maternal or gestational age.

## GENERAL DATA

Acute pancreatitis in pregnancy is a rare condition, with a reported incidence rate of 1 over 1,000-12,000 pregnant women [1-3]. Maternal and fetal mortality rate (previously reported at approximately 37% and 60%, respectively) has greatly decreased due to the improvements in the understanding of diagnostic techniques and treatment [2]. Maternal death is highest during the first trimester, however, the overall mortality rate of pregnant women with AP is comparable to the general, non-pregnant population with AP [2]. Fetal death occurs most often in the third trimester and stillbirths most often during the second trimester. During the first trimester, miscarriage rates are around 20% [1,2]. Due to a longer period of time needed to achieve viable age, one cannot determine the implications of AP in the rates of miscarriage during the first trimester. Stillbirth rates during AP in pregnancy, however, are much higher than among the general pregnant population (4.4-6.2% vs. 0.5%) [1]. Women with AP in pregnancy have the highest fetal mortality rates compared with the rest of the rates for surgical emergencies in pregnancy [1]. The severity of AP in pregnancy correlates with the severity of neonatal asphyxia [2].

Acute pancreatitis in pregnancy usually develops around 28.5 years and is most frequently reported in the third trimester of pregnancy [2]. Reported causes for AP in pregnancy include gallstones (approximately 37%), hypertriglyceridemia (32%) and idiopathic (26%), biliary ascariasis, anatomical variants and gallstone complicated with hypertriglyceridemia [3].

The diagnosis of AP in pregnancy is based on the Atlanta criteria [4], requiring the presence of at least two of the following: (1) acute upper abdominal pain that radiates posteriorly; (2) serum amylase or lipase level three times higher than normal; (3) cross-sectional imaging evidence. Acute pancreatitis in pregnancy can be classified into three clinical entities: mild acute pancreatitis (involving pancreatitis without association of organ dysfunction/systemic complications), moderate to severe pancreatitis (pancreatitis involving transient organ dysfunction or localized/generalized complication within 48 hours after treatment) and severe pancreatitis (pancreatitis associated with persistent organ dysfunction or localized/generalized complication for more than 48 hours after treatment).

According to its pathophysiology, AP may be diagnosed using the following: gallstone pancreatitis by an ALT level over 150 U/l within 48 hours of onset and radiological findings consistent with AP (such as abdominal ultrasonography or magnetic resonance cholangiopancreatography) [5]; hypertriglyceridemic pancreatitis with either a serum tri-

glyceride over 11.3 mmol/l or serum triglyceride between 5.65 and 11.3 mmol/l, associated with a lipid turbidity appearance (in the absence of other known risk factors such as drugs, gallstones or alcohol intake) [6] and, lastly, idiopathic pancreatitis (presence of radiological evidence of pancreatitis without the identification of any known risk factors for AP) [5].

Acute pancreatitis can include local and systemic complications, classified according to the Atlanta criteria [4]. Local complications are identified via CT scan and include pancreatic free fluid, pancreatic pseudocysts, infected or sterile patches of necrotic peripancreatic or pancreatic tissue, which, in time, may develop into walled off necrosis [4-6]. Systemic complications include aggravation of pre-existing comorbidities or organ dysfunction (with severity calculated based on the modified Marshall scoring [4]) [4-6]. Exacerbation of AP may develop into multi-organ system failure, pancreatic exocrine insufficiency, pulmonary, renal or heart failure, gastrointestinal bleeding or shock [4], referred as the presence of two of the following: body temperature of above 38 degrees Celsius or below 36 degrees Celsius; white blood cell count above 12,000/mm<sup>3</sup> or less than 4,000/mm<sup>3</sup>; tachycardia (over 90 bpm), tachypnea (respiratory rate more than 20/min) or PCO<sub>2</sub> below 32 mmHg [4].

Treatment of AP is based on pain relief, nutritional support, proper fluid resuscitation and inflammatory response management. In order to prevent infection, prophylactic antibiotic therapy is required in some cases, especially in cases of confirmed infected pancreatic necrosis [5,6]. Presently, there are no guidelines for empirical antimicrobial treatment in the case of necrotic pancreatitis, however, treatment should be tailored in each case with prior antibiotic sensitivity testing [5].

Termination of pregnancy may be indicated and is usually recommended by a multidisciplinary team, including an obstetrician, a gastroenterologist, and a general surgeon, in cases of confirmed intrauterine fetal death, necessary use of teratogenic or fetal toxic medication for treatment. Pregnancy termination may be achieved by natural or drug induced abortion or via cesarean section or natural birth (including preterm and termed birth) [5,6], on an individualized basis.

## RECURRENT ACUTE PANCREATITIS

According to studies, recurrent AP can be caused by conservatively managed biliary disease, thus cholecystectomy is recommended in such cases [5]. Another study developed in 2019 identified genetic variants as being responsible for the progression of AP into recurrent AP, such as SPink1 mutations [3].

## ETIOLOGY

### Preeclampsia

Predisposing factors for developing preeclampsia are similar to those reported in pregnancies complicated by pancreatitis, and include obesity, advanced maternal age, history of preeclampsia in previous pregnancies, preexisting hypertension, preexisting diabetes, chronic kidney disease, autoimmune disorders (such as systemic lupus erythematosus and antiphospholipid syndrome) and multiple pregnancy [7-9]. Preeclampsia, characterized by improper placenta perfusion via endothelial dysfunction, leading to microvascular anomalies and ischemia [7], is also considered to be an etiological factor for AP in pregnancy [7-9], associated with an almost 2-fold risk of developing this condition than the general pregnant population [8].

### COVID-19

Although there is limited information regarding the impact of COVID-19 in obstetrics, studies have shown that around 40 to 50% of de novo COVID-19 infections initially involve gastrointestinal symptoms [10], with the potential of evolving into pancreatitis over time.

### Hyperparathyroidism

It is an often underdiagnosed condition in pregnancy. Hypercalcemia secondary to hyperparathyroidism is a risk factor for developing acute pancreatitis (1.5-7.0% of cases of AP in the general population), which can then lead to preeclampsia. Hypercalcemia-induced AP presents with common gastrointestinal symptoms, such as nausea, vomiting and abdominal pain, as well as transient seizures, impaired visual field, or repeated eye deviation [11]. Clinical examination complicated by these signs and symptoms in a pregnant patient should prompt lab workups that include ionized calcium levels [11].

### Estrogen

It is a rare etiological factor of drug-induced AP. According to studies, estrogen has a latency varying from two months to two years between treatment initiation and the onset of AP [12]. The exact mechanism of estrogen-induced AP is still unclear, although studies have identified hypertriglyceridemia as a potential cause [12]. Clinical findings in patients with estrogen-induced AP are similar to those identified in AP secondary to other causes. The key factors needed for the successful identification of pancreatitis secondary to estrogen intake are typical short episodes of abdominal pain and

moderate to severe increase of amylase and serum lipase, which quickly normalize after cessation of estrogen intake. Estrogen-induced AP cases are rarely fatal, most of the time they present as mild to severe cases [12].

### Gallstones

Usually diagnosed in the third trimester of pregnancy, represent the main etiological factor of AP in pregnancy [3], most often presenting as mild or moderate forms. Changes in the secretion of cholesterol, which ends up surpassing the levels of biliary acids, aid in the appearance of cholesterol crystals and calcification. Gallstone formation is also determined by biliary stasis secondary to the relaxation of the smooth muscles found in the gallbladder due to progesterone secretion. Patients with gallstone AP occurring in the first trimester of pregnancy have a reported recurrence rate of 50% [3]. Gallstone-induced AP has the same clinical presentation in both the pregnant and non-pregnant population. Symptoms such as vomiting and upper abdominal pain (most frequently) are accompanied by modified laboratory findings (levels of amylase and lipase more than three times higher than the normal limit) and pathological imaging findings. Treatment of gallstone AP is similar to that of AP caused by other factors. Severe forms of pancreatitis, presence of obstructive jaundice, pancreatitis accompanied by acute cholecystitis, peritonitis or AP refractory to medical treatment, are indications for surgical treatment (cholecystectomy), either laparoscopy (which can be safely in all the trimesters of pregnancy and is the current preferred surgical procedure) or laparotomy [13].

### Hypertriglyceridemia

Hypertriglyceridemia-induced AP is considered to be the third most common etiological factor, after gallstone and alcohol abuse [1-3]. It is involved in up to 10% of all the pancreatitis episodes and can trigger pancreatitis in more than 50% of all cases of pancreatitis in pregnant patients [14]. Primary hypertriglyceridemia is triggered by genetic factors. Familial hypertriglyceridemic AP during pregnancy is a form of primary hypertriglyceridemic AP and is the main etiological factor of hypertriglyceridemic AP during pregnancy, most notably during the third trimester. Another entity of primary hypertriglyceridemia is familial lipoprotein lipase deficiency, a genetic disorder associated with recurrent AP, caused by severe hypertriglyceridemia and chylomicronemia. Secondary hypertriglyceridemia is generated by multiple factors such as pregnancy, alcohol abuse, uncontrolled diabetes and drugs (tamoxifen, propofol, beta blockers, oral estrogen,

isotretinoin, clomiphene, mirtazapine and protease inhibitors). During the third trimester, there is a natural two-fold increase of serum triglyceride levels compared to pre-pregnancy levels. Moreover, initial clinical symptomatology (such as nausea, vomiting and abdominal tenderness) may also be attributed to pregnancy itself, further delaying diagnosis. Patients presenting with hypertriglyceridemia-induced AP tend to belong to a relatively younger age group. Regardless of this fact, severity and the rate of complications are generally higher in patients with this type of pathology. Uncommon clinical elements, which can indicate the presence of AP, are represented by pleural effusions, subcutaneous fat necrosis, rebound tenderness, Gray Turner's sign (ecchymosis or skin discoloration located in the flanks) or Cullen sign (periumbilical ecchymosis). Laboratory work-up in hypertriglyceridemia-triggered AP consists of a markedly elevated triglyceride level (i.e., >1000 mg/dl). Severity and prognosis factors are also determined by a measurement of complete blood count, C-reactive protein, lactate dehydrogenase, serum calcium, glucose and electrolytes, renal function tests, creatinine and blood urea nitrogen [14].

## LABORATORY FINDINGS

The predictive value of laboratory tests in cases of AP in pregnancy decreases after 48 hours since the onset of disease. Patients suffering from AP in pregnancy have substantially elevated levels of neutrophil/lymphocyte (N/l) ratio and white blood cells, alanine aminotransferase (ALT), aspartate aminotransferase (AST), blood urea nitrogen, creatinine, C-reactive protein, direct bilirubin, D-dimer, fibrin degradation products, gamma-glutamyl transpeptidase (GGT), glucose, lipase, and pH. In contrast, levels of red blood cells, albumin, fibrinogen, high-density lipoprotein (HDL), hemoglobin, low-density lipoprotein cholesterol (LDL-C), and total proteins are significantly lowered [15-19].

## TREATMENT

### Treatment for hypertriglyceridemic acute pancreatitis

Accurate management and treatment of AP in pregnancy is achieved by a multidisciplinary team consisting of an obstetrician, a nutritionist, an endocrinologist and a lipidologist. Long-term treatment of comorbidities is vital in the prevention of recurrent pancreatitis.

The key points of treatment of hypertriglyceridemia-induced AP are similar to those used in the treatment of AP secondary to other etiological factors, entailing restriction of oral intake (bowel rest), intravenous hydration and treatment of pain

[5,6,14]. After initial stabilization, intravenous heparin administration, insulin therapy or both and/or apheresis, may be selected as therapeutic methods used to promptly lower serum triglyceride levels. In order to prevent recurrence, oral anti-hyperlipidemic agents (fenofibrates, nicotinic acid, or omega-three fatty acids) or nonpharmacological interventions like weight loss, dietary-fat restriction, and strict glycemic control in diabetic patients must be implemented [5,6,14].

In order to reduce chylomicrons, diet in AP secondary to hypertriglyceridemia should be isocaloric and low in fat, with less than 1/5 of calories obtained from fat [14]. If serum triglyceride levels are not properly lowered, fasting and intravenous administration of 5% dextrose may be used. In cases of severe AP, parenteral nutrition or feeding via a nasogastric tube is recommended. Omega-3 fatty acids are the cornerstone of therapy, they contain eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA). Deficiency of EPA and DHA (intake of less than 300 mg of EPA and DHA) is a risk factor for impaired fetal brain and visual development. Oral anti-hyperlipidemic drugs, such as fibrates (fenofibrate, gemfibrozil) lower triglycerides by 20 to 30% [20] in the non-pregnant patients, although their use in pregnant patients is controversial, since they are associated with adverse effects in the mother (elevated levels of liver enzymes, AP and myalgia) [20], as well as the fetus (risk of teratogenicity). This type of drug has proven to be ineffective in cases of patients with lipoprotein lipase deficiency [14].

Intravenous heparin promptly lowers triglyceride levels by releasing lipoprotein lipase (LPL) into the plasma from the endothelium. Prolonged use of intravenous heparin leads to secondary paradoxical hypertriglyceridemia, due to depletion of LPL levels, and it can also trigger or exacerbate hemorrhagic pancreatitis [20,21].

Insulin therapy lowers triglyceride levels secondary to the timely activation of LPL. In non-diabetic patients, insulin therapy poses the risk of hypoglycemia, thus it is not presently recommended for use in nondiabetic patients [20,21]. There is no consensus regarding the type of heparin used for treatment of hypertriglyceridemia, or regarding the best route of administration (subcutaneous or intravenous) [21].

Apheresis (plasmapheresis, double-membrane lipid apheresis and therapeutic plasma exchange) lowers serum triglyceride levels up to 66 to 70% [22] and can be an effective therapeutic method in cases of severe gestational hypertriglyceridemia complicated by pancreatitis. Apheresis may also be utilized for the prophylaxis of recurrent pancreatitis. Due to its transient effect, apheresis is generally used in cases of severe and refractory hypertriglyceridemia.

eridemia, as a temporizing method of treatment while initiating other therapies. It is best used in cases of serum triglyceride levels of over 1,000 mg/dl [14,22].

Combination of insulin with plasmapheresis has higher efficacy rates in the treatment of hypertriglyceridemia, although higher rates of complications have been noted when this method of treatment was employed (acute kidney disease, respiratory failure) [14].

Novel therapies have been developed, although their safety and efficacy during pregnancy remains to be studied. Alipogene tiparvovec is a gene therapeutic method in which intact LPL genes are transported into muscle cells via a viral vector [23]. It is recommended in cases of patients with familial lipoprotein lipase deficiency. The link between apolipoprotein C3 (APOC3) mutation and lower triglyceride levels has been pinpointed following studies involving exome sequencing. Volanesorsen, an antisense inhibitor of APOC3 synthesis, decreases plasma levels of APOC3 and triglycerides and is best used in familial hyperchylomicronemia [24].

Endoscopic retrograde cholangiopancreatography (ERCP)

It is indicated in biliary disease, including but not limited to biliary pancreatitis [25-27], and has proven to be a safe diagnostic and therapeutic procedure during pregnancy [26]. An increased risk of small for gestational age or preterm birth is associated with use of ERCP during pregnancy [25,26]. Intrauterine fetal death, malformation, fetal retardation, cancer [25,26] can be triggered secondary to fetal radiation exposure during ERCP. Due to these concerns, use of ERCP in the pregnant patient is endorsed provided if therapeutic intention is present [25]. Otherwise, endoscopic ultrasound (EUS) and magnetic resonance cholangiopancreatography (MRCP), less invasive diagnostic methods, are preferred [27].

ERCP is best performed in the second trimester, after organogenesis has concluded, however, in cases of severe biliary disease (gallstone-induced AP associated with documented choledocholithiasis, pyrexia, jaundice, severe abdominal pain, leukocytosis, significantly altered liver function tests, cholangitis or common bile duct dilatation found on imaging studies [25]), ERCP can be safely executed throughout gestation [26].

Maternal adverse outcomes identified in literature, post-ERCP, consisting of infection, perforation, pancreatitis or post sphincterotomy bleeding, development of preeclampsia, spontaneous abortion, premature rupture of membranes or premature induction of labor, are less documented risks [25-27]. Risk of post-ERCP complications is slightly higher in pregnant patients than in the general population [26].

In order to limit exposure to radiation, radiation-free ERCP techniques have been developed. Despite lower radiation exposure levels, pregnancy and fetal-related complications have not decreased, in contrast with non-pregnancy related complications [26]. These methods have proven to be problematic, since they do not typically offer the definition of the anatomy of the biliary system as well as ERCP does, and pose an increased risk of residual gallstones being left in situ, thus possibly leading to cholangitis and recurrent pancreatitis (in cases of non-radiation-ERCP with biliary aspiration) [27]. Endoscopic ultrasound, another NR-ERCP technique, is limited by the need to use experts, typically prolonged procedural times and elevated costs.

Surgical treatment (laparoscopy vs. laparotomy)

Surgical treatment for symptomatic biliary disease in pregnant patients is recommended. Conservative treatment of biliary disease in pregnancy implies higher risks of fetal death and disease recurrence [13,28]. Regardless of method, surgical treatment is best reserved in the second trimester, after fetal organogenesis has ended [13,28]. Postoperative complication rates are comparable in both pregnant and non-pregnant women [28]. Conversion from laparoscopy to laparotomy in pregnant patients is less frequently documented than in the general population [28]. Fetal outcome is comparable in both laparoscopy and laparotomy [13].

Advantages of laparoscopic cholecystectomy include reduced procedure time, faster mobilization and recovery and lower fetal exposure to analgesic drug and anesthesia. Moreover, it can be performed safely all throughout the gestational period [13,28]. During the surgical procedure, premature contractions and birth, especially in the last trimester of pregnancy, can set in motion by the manipulation of the gravid uterus. Routine administration of prophylactic tocolytics during the third trimester is not recommended [13], although there have been reports of postoperative tocolytic use [13,28]. Fetal heart rate should be monitored preoperatively and postoperatively [13], however, the decision to do so should be individualized and based on available facilities, surgery method and gestational age [2,13,28].

## CONCLUSIONS

Acute pancreatitis in pregnancy is an uncommon but severe condition, involving increased risk of fetal and maternal complications. Gallstones and hypertriglyceridemia are the most often noted etiological factors. Severity of AP is correlated with lower calcium levels and increased risk of neonatal asphyxia and maternal and fetal mortality. Termination of pregnancy must be considered in

severe and refractory cases of AP. Treatment of AP in pregnancy, with the exception of severe forms, is generally recommended to be conservative during the first trimester. Endoscopic or surgical treatment is favored for the second trimester of pregnancy, al-

though it can be safely performed during the entire pregnancy period. Further research must be done in order to fully elucidate the etiology, pathophysiology, risk factors and treatment methods of AP in pregnancy.

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