

Review Article

Clinical analysis of pregnancy associated with acute pancreatitis

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Received: 20 June 2016

Revised: 17 August 2016

Accepted: 22 August 2016

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ABSTRACT

The incidence of pregnancy associated with acute pancreatitis is relatively low, the incidence rate in pregnant women is 1/1000 to 1/12000. Once attacks, the disease develops quickly, easily leading to multiple organ dysfunctions. Foreign reports showed that maternity and perinatal mortality in the 1980s were 0.37% and 11.37%. Pancreatic tissues contain estrogen receptors that increase the risk of pregnancy associated with acute pancreatitis (AP) in a high estrogen environment during pregnancy.

Keywords: Acute pancreatitis, Pregnancy

INTRODUCTION

The incidence of pregnancy associated with acute pancreatitis is relatively low, the incidence rate in pregnant women is 1/1000 to 1/12000.¹ Once attacks, the disease develops quickly, easily leading to multiple organ dysfunctions. Foreign reports showed that maternity and perinatal mortality in the 1980s were 0.37% and 11.37%. Pancreatic tissues contain estrogen receptors that increase the risk of pregnancy associated with acute pancreatitis (AP) in a high estrogen environment during pregnancy.

With the development of modern medicine, the mortality rate has dropped, but still remains at a very high percentage. An important reason for high mortality is that currently it is still very hard to predict those patients with acute pancreatitis may develop from mild acute pancreatitis to severe acute pancreatitis.² In recent years its incidence is increasingly rising, becoming the death cause of pregnant women with acute abdomen in some areas.³ Pregnancy associated with severe acute pancreatitis brings severe harm to pregnant women and perinatal infants.

Etiology and pathogenesis

Gallbladder diseases currently

Gallbladder diseases currently most scholars believe that gallbladder diseases are the first causes of pregnancy associated with acute pancreatitis, among which cholelithiasis is the main cause that accounts for 67% to 70% according to some reports.⁴ Endocrine changes during pregnancy cause a series of physiological changes of biliary system. An increase in estrogen during pregnancy can increase blood and bile cholesterol concentration, reduce the secretion of cholate, cause the imbalance of cholate, cholesterol and lecithin; an increase in pro-gestational hormone can cause gallbladder smooth muscle relaxation, decrease biliary tension prolonging gallbladder emptying time, cholestasis; at the same time in late pregnancy the uterus enlarges, causing mechanical compression of bile duct, which slows down the bile secretion. All these changes may cause cholesterol deposition, facilitating gallstones formation. Biliary obstruction or obstruction of the common bile duct sphincter of Oddi caused by gallstones leads to bile duct

retrograde flow to pancreatic duct or direct oppression on pancreatic duct, resulting in poor drainage of pancreatic juice, thereby increasing the pancreatic duct pressure. This is the reason that gallbladder disease is one precipitating factor of pregnancy associated with acute pancreatitis.

Hyperlipidemia

Hyperlipidemia is one of the important causes of pregnancy associated with acute pancreatitis. High-fat and high-protein diet of pregnant women is easily to stimulate excessive secretion of the pancreas. Affected by hormones, the triglyceride and cholesterol of pregnant women significantly rise. Elevated triglycerides cause increased plasma viscosity, decreased erythrocyte deformability and increased blood flow resistance, causing pancreatic microcirculation disturbance.⁵ Whilst as pregnancy month increases, increasingly pressure on pancreatic duct cause increased resistance increases. High pressure on pancreatic duct may cause rupture of pancreatic acinar, bile distributing perivascular pancreatic interstitial substance may cause pancreatic vasospasm and endothelial cell detachment. The blood viscosity of small and medium-sized veins and capillary veins on pancreatic low-shear-rate area increases, which can lead to pancreatic microcirculation bleeding and thrombosis, thereby soon appearing pancreatic microcirculation.⁶ The mechanisms that cause AP include:

- Fat is hydrolyzed by enzymes in the pancreatic microvessels, releasing free fatty acids that combine with calcium, thereby causing pancreatic microvascular damage or small embolism
- Causing pancreatic ischemia
- Free fatty acids directly be toxic to pancreatic acinar cells.⁷

Gursoy et al consider that obesity and increased nutrition during pregnancy especially high-fat diet are an important incentives for AP.⁸

Alcohol consumption and overeating

Alcohol consumption and overeating high-protein and high-fat diet during pregnancy increases vessel pressure, and endocrine changes during pregnancy can increase the secretion of pancreatic acini, which can cause surrounding tissue hyperemia, exudation, edema, thereby causing pancreatitis. Generally pregnant women do not drink alcohol, so that we can conclude that AP is unrelated with alcohol consumption.

Other causes

Other causes acute fatty liver, preeclampsia, hypercalcemia, hyperparathyroidism, multiple births, multiple pregnancy, hyperemesis gravidarum, infections and drugs. Besides, recently some scholars conclude diabetes is also an inventive of AP that cannot be

neglected. Pregnancy-induced hypertension also can cause microvascular coagulation and vascular inflammation, inducing pancreatic avascular necrosis; using diuretics to control edema can also cause pancreatitis.

Characteristics of pregnancy associated with acute pancreatitis

Severe pancreatitis

The incidence of severe acute pancreatitis of pregnant women is higher than that of non-pregnant women, with many complications and high mortality. The mechanism may be:

- Increase the nutritional and metabolic disorders of pregnancy
- Inhibitory effect of hormone on smooth muscle cause intestinal bacterial translocation and enterogenous toxic absorption, increasing multiple organ dysfunctions, thereby increasing mortality
- Increase the burden of every organ during pregnancy, reduce the damage tolerance.

The main features of this type include enlarged and hardened pancreas, acinar and adipose tissue necrosis, and vascular necrosis and bleeding. There are hoary or yellow patchy adipose tissue necrotic lesions visible to the naked eyes. The ones who have severe bleeding could have brownish black pancreas with fresh bleeding. Adipose tissue necrosis may invade mesentery and tissues behind omentum. Histological examination shows pancreatic necrotic lesions are intermittent, surrounded by inflammatory cells. It is common to have phlebitis, lymphatitis and thrombosis.

Acute edematous pancreatitis

It is a common type. Swollen pancreas, edema, blurred lobes, lesions invading the partial or whole pancreas, surrounded by a small amount of adipose tissue necrosis. It is visible scattered punctate adipose tissue necrosis but no parenchymal necrosis and haemorrhage.

Diagnosis

Clinical manifestations

Symptoms

Three major symptoms of AP include nausea, vomiting and abdominal pain, which the severity degree varies according to pathological changes. 90% of patients have left upper abdominal pain that may extend to the lower back, accompanied with fever, shock, jaundice, gastrointestinal bleeding etc. The pain cannot be relieved after vomiting. 10% of patients have pulmonary manifestations such as hypoxemia. Severe cases may develop to adult respiratory distress syndrome.

Signs

Acute edematous pancreatitis cases have less abdominal signs, but still have upper abdominal tenderness, distension and without muscle tension and rebound tenderness. Severe acute pancreatitis cases have obvious upper abdominal tenderness with muscular tension, rebound tenderness, decreased or disappeared bowel sounds, shifting dullness (+). If the signs such as abdominal mass, subcutaneous ecchymosis (Grey-Turner sign) on the lumbocostal area and Cullen sign appear, which means the case has SAP, the mortality rate can be as high as about 40%.

Experimental examination

Hematuria amylase

Hematuria amylase has an important diagnostic significance in acute pancreatitis. Amylase may have increased in varying degrees in peritonitis, biliary tract disease, ulcer perforation, strangulated intestinal obstruction, gastrectomy with obstruction, but generally it is lower than 500 Sioux units. Therefore, only when the measured value > 256 Wen's units or > 500 Sioux units, has a diagnostic significance in AP. The foreign data indicates that the sensitivity of AMY is 75.0% ~ 92.0%, whilst the specificity is 60.0% ~ 90.0%.⁹ Serum LIP is more sensitive than AMY in the diagnosis of pregnancy associated with acute pancreatitis, because hypertriglyceridemia during pregnancy may lead to elevated serum AMY but serum LIP keeps the same. Generally speaking, LIP begins to rise 12 ~ 24 h after the onset of illness and reaches the peak during 24 ~ 72 h that can last about 7 days. Pezzilli et al measured sensitivity of LIP is 82.0% and specificity is 90.0%.¹⁰

Determination of serum markers CRP

CRP, a nonspecific inflammatory response protein synthesized by hepatocytes. IL-6: IL-6 is produced mainly by monocytes in the induction of IL-1, TNF, etc. or activated by macrophages.

Imaging diagnosis

Ultrasound is a kind of simple, non-invasive, low-price examination, commonly used in the preliminary diagnosis of SAP. Ultrasound can also show pancreatic abscess, calcification, pseudocyst, pancreatic duct dilatation and gallbladder wall thickening, volume increases, cholestasis and biliary stones and ascites. The study found that 70% of pregnancy associated with AP has abdominal abnormalities from ultrasound that include 56% of multiple gallstones. Besides, fetal condition and the presence of placental abruption could contribute to differential diagnosis. But sometimes affected by enlarged uterus and flatulence, pancreas cannot be shown fully that affects accurate judgment of ultrasound. In addition, biliary endoscopic ultrasonography has a special

significance in the diagnosis of biliary pancreatitis during pregnancy, from which can clearly show biliary stones.

CT

It is well known that traditional medical imaging examination means such as ultrasound. However, the introduction of CT in the diagnosis of AP is an important foundation for the early diagnosis of SAP in recent years. Because acute edematous pancreatitis can be diagnosed by blood test and urine amylase, whilst it is very difficult to make the correct diagnosis of necrotizing pancreatitis by general laboratory alone. Only CT, especially enhanced CT scan or dynamic contrast-enhanced CT scan can make a correct diagnosis. Currently the issue whether contrast agent will increase necrotizing pancreatitis still remains controversial.

ERCP

Endoscopic retrograde cholangio pancreatography (ERCP) has a certain value in the early diagnosis of gallstone pancreatitis. A thesis (review part) on clinical research progress of pregnancy association with acute pancreatitis from Zhengzhou University in 2006 showed that relieving biliary obstruction, reducing pancreatic pressure and preventing further development of the disease can avoid emergency surgery as well as create the conditions for elective surgery.

MRI

MRI may show pancreas swelling, poor-defined margin. Those patients who cannot undergo CT scan because of pregnancy or other reasons could get similar results from magnetic resonance imaging (MRI). What's more, MRI has neither the risks of iodine allergies and X-rays, nor the danger of AP caused by iodine preparation.

Harmful effects on mother and fetus by pregnancy associated with acute pancreatitis

AP's harmful effects on mother: shock and DIC are common in patients with severe acute pancreatitis. Water, electrolyte and acid-base disorders, and multiple organ failure are major complications and causes of death of severe acute pancreatitis. Acute lung injury and acute respiratory distress syndrome (ARDS) are the most important complications and major causes of death in the early pregnancy associated with acute pancreatitis. Heart, kidney and liver injury increase the incidence of gastrointestinal ulcers and so on.

AP's harmful effects on fetus: Acute pancreatitis may cause abortion and fetal malformation in the early stage, whilst acute pancreatitis may cause abortion, premature delivery, stillbirth caused by fetal distress and fetal growth restriction and so on.

Treatment

Non-surgical treatment

General treatments

The treatment principle of pregnancy associated with pancreatitis and non-pregnant pancreatitis is consistent, including fasting, gastrointestinal decompression, apportioning, water and electrolytes replacement; general conservative treatment for patients with mild symptoms can have better clinical results, but mother's condition as well as fetal condition shall be closely observed during the treatment. And the impact of drugs on the fetus should be fully considered to ensure the safety of mother and fetuses far as possible.

Drugs that can inhibit pancreatic enzyme secretion

Applying drugs that can inhibit pancreatic enzyme secretion such as octreotide and stilamin is the most basic clinic treatment for AP. Clinical reports showed that octreotide and stilamin have significant effects on SAP which can improve symptoms and reduce complications and mortality. Except for inhibiting pancreatic secretion, regulating inflammatory mediators, octreotide can also reduce the rate of bacterial translocation. But some scholars believed that octreotide is merely a somatostatin analogue rather than a real somatostatin, because it can contract Odd sphincter, desensitize somatostatin receptor after 7 days and stabilize plasma concentration required for 7.5-10 hours. In contrast, stilamin is a real somatostatin that can relax Odd sphincter, not desensitize somatostatin receptors and stabilize plasma concentration required only 15 minutes etc.

Trypsin synthesis inhibitors

Gabexate is commonly used, which can inhibit trypsin, bradykinin, plasmin, phospholipase A₂ and oxygen free radicals, and relax Oddi sphincter. Clinical trials confirm that gabexate can effectively relieve symptoms, reduce the incidence of organ failure and mortality. Gabexate is a recommended in the guidelines of AP on the World Congress of Gastrointestinal Diseases in Thailand in 2000.

Drugs that can improve microcirculation

The role of pancreatic microcirculation disorder in the onset and development of pancreatitis is increasingly given great importance, therefore drugs that can improve microcirculation are widely used, such as 654-2, compound salvia miltiorrhiza, prostaglandin E₁ preparation and platelets activating factor antagonist. Currently, combined medication therapy is adopted according to different pathophysiological features of pancreatitis. Regional infusion therapy is a trend. Zhang Wang de et al used antibiotics that is high-efficient and easy to pass through blood pancreatic barrier, 5Fu, salvia

miltiorrhiza injection and dexamethason etc play an anti-bacterial anti-inflammatory effect, neutralize toxins, relieve stress state, improve blood and oxygen supply and protect major organ function to achieve the purpose of improving the cure rate and reducing mortality .

Antibiotics

Generally antibiotics are not recommended to use for non-biliary MAP, whilst antibiotics is as a routine drug for biliary MAP, or SAP. The pathogens of pancreatic infection mainly include gram-negative bacteria and anaerobes and other intestinal resident bacteria. Applying antibiotics should follow three principles that include: gram-negative bacteria and anaerobes-oriented antibacterial spectrum, strong liposolubility, effective passing through blood pancreatic barriers. Pathogens of pancreatic infection mostly come from bacterial translocation, which mainly include *Escherichia coli*, *Klebsiella pneumoniae*, *Enterococcus*, *Staphylococcus aureus*, *Pseudomonas aeruginosa*, *Singular pseudomonas*, *Streptococcus aerogenes* and *Bacteroides fragilis*. Norfloxacin (50 mg) 1 times/ 6 hours or simultaneous short-term (7 days) application of cefoperazone sodium. SDD should be used until the patient is free from the danger of pancreatic infection. However, SDD cannot be used as routine drug in order to avoid bacterial resistance.

Nutritional support

MAP patients is only required for short-term fasting rather than enteral or parenteral nutrition. SAP patients shall firstly be given parenteral nutrition. When patient's condition is alleviated, then enteral nutrition will be considered. Enteral nutrition refers to placing nasal feeding tube to the distal ligament Treitz with infused energy density of 4187J/ml of nutrient elements. If energy is not sufficient, parenteral nutrition can be supplemented, and observe the reaction of patient. If patient can stand, so the dose will be gradually increased. Glutamine should be supplemented. Patients with hyperlipidemia shall reduce supplementing fatty substances.

Surgical treatment

Applying surgery for pregnancy associated with pancreatitis has been controversial. Emergency surgery without full consideration of patient's condition does not prevent the development of the disease in the early stage but will increase postoperative complications and mortality; therefore surgery is not the preferred treatment. Mastery of surgical indications is very important, some scholars believe.

- Patients with infection, localized necrotic intestinal fistula, serious complications such as peripancreatic bleeding

- It is difficult to improve systemic inflammatory state or control abdominal septal hypertension syndrome by a non-surgical treatment
- Patients who have received active treatment for 2 to 3 days but have worse condition are advised to undergo surgery.

Surgery refers to direct pancreatic surgery and surgery for pancreatitis-associated biliary diseases. The main purpose of pancreatic surgery is to remove necrotic tissue and drainage. Data shows that 57% to 70% of patients with pregnancy associated with acute biliary pancreatitis have recurrent pancreatitis, so it is necessary to do biliary surgery after pancreatitis is relieved.¹¹ Currently as the development of minimally invasive biliary tract surgery, combination of laparoscope, choledochoscope and duodenoscope can be applied in the biliary tract surgery for pregnant women to minimize the harm to patients and achieve good results. So when pregnant patients is suspected of biliary AP, ERCP can be firstly carried out to confirm the presence of common bile duct stones, and then EST can be done to take out stones.

Obstetrical treatment

Prevent preterm birth

During the active treatment of pancreatitis, doctors should closely observe fetal heart rate, uterine and vaginal secretions, fetal movement counting, fetal development and amniotic fluid monitoring by ultrasound and placental maturity to prevent preterm birth.

Inhibition of uterine contractions to promote lung maturation

Pregnancy associated with acute pancreatitis is not an indicator to terminate the pregnancy, but when patients with obvious indicators of miscarriage and preterm birth, fetal distress and stillbirth should terminate the pregnancy as soon as possible. Usually cesarean section is recommended. If stage of labor goes smoothly, vaginal delivery may be considered. Cesarean section shall be chosen promptly for patients with fetal distress to rescue fetus.

Prospect

In terms of non-surgical treatment, the mechanism of AP, removal of inflammatory mediators, blood purification, highly selective arterial perfusion and compound perfusion of drugs remain further studies and researches; in terms of surgical treatment, simplified or minimally

invasive surgery, interventional therapy and surgical time exploration may be the studying focuses of acute pancreatitis in the future. The high-tech 21st century appeals to bear more fruitful results through plenty high-level discussions.

Funding: No funding sources

Conflict of interest: None declared

Ethical approval: Not required

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Cite this article as: Alnaggar M. Clinical analysis of pregnancy associated with acute pancreatitis. *Int J Adv Med* 2016;3:799-803.