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Case Report

Clinical analysis of 16 patients with acute pancreatitis in the third trimester of pregnancy

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Abstract: Aim: Acute pancreatitis (AP), in particular, severe acute pancreatitis (SAP), is a rare but challenging complication during pregnancy in terms of diagnosis and management. The objective of this paper is to investigate the causes and therapeutic strategies of AP in patients during the third trimester of pregnancy. Methods: We performed a retrospective analysis of the clinical features, laboratory data, and outcomes in 16 patients with acute pancreatitis during the third trimester of pregnancy. Results: Information was collected on admission, management, and outcome. A total 16 patients were diagnosed with acute pancreatitis during pregnancy. In 7 of 9 patients with mild AP, pregnancy was terminated by cesarean section and all 9 cases were cured. In 4 out of 7 patients with SAP, pregnancy was terminated by cesarean section in conjunction with peritoneal irrigation and drainage, and the mothers and infants survived. In the remaining 3 patients with SAP, there was one case of intrauterine death in which Induced labor was performed and 2 patients died of multiple organ failure. Conclusion: A high-fat diet and cholelithiasis are the triggers of AP in pregnancy. Conservative treatment is the preferred therapeutic method; in particular, for mild AP. Endoscopic surgery and peritoneal drainage are effective for acute biliary pancreatitis. Patients with hyperlipidemic pancreatitis should undergo lipid-lowering therapy, and hemofiltration should be done as soon as it becomes necessary. For patients with SAP, termination of pregnancy should be carried out as early as possible.

Keywords: Acute pancreatitis, pregnancy, hyper triglyceride, treatment

Introduction

Acute pancreatitis (AP) is a rare but serious complication of pregnancy. Hyperlipidemic pancreatitis is more dangerous than biliary pancreatitis. The main causes include biliary diseases, hyperlipidemia, and congenital malformation of the pancreaticobiliary junction [1-3]. The majority of severe acute pancreatits (SAP) cases in pregnancy occurs in the third trimester, and can be associated with preeclampsia and HELLP syndrome [4, 5]. AP during pregnancy is life threatening for the mother and fetus. Prompt diagnosis and treatment could reduce maternal and fetal morbidity and mortality [2]. Therefore, we carried out a retrospective analysis of the clinical features, laboratory findings, and outcomes of 16 patients with AP in the third trimester of pregnancy to investigate possible causes and therapeutic strategies.

Materials and methods

Inclusion criteria

A diagnosis of AP was made according to the Chinese Medical Association criteria (Pancreas Disease Panel) and the standards of the Chinese Medical Doctor Association (Gastroenterology Panel) [6]. In 9 of 16 cases, AP was classified as mild and the other 7 cases as severe AP according to the aforementioned criteria, a diagnosis of hyperlipidemic pancreatitis can be made by a blood triglyceride level greater than 11.3 mmol/L in parallel with clinical manifestations, or a blood triglyceride level of 5.56-11.30 mmol/L when chylous effusion is

Table 1. Summary of SAP cases

Diagnosis	Cases (n)	Treatment	Gestational age (weeks)	Maternal outcome	Fetus outcome
SAP	2	CM, CS	FTD	Survived	Survived
Biliary SAP	1	CM	35	Died of multiple organ failure before delivery	Died of fetal distress
SAP with acute pulmonary edema	1	CM, CS	36	Survived	Survived
SAP	1	VD	28	Survived	Dead before labor induction
SAP with hyperlipidemia	1	CM, CS	34+2	Died of multiple organ failure	The twins survived
Biliary SAP with Pre-eclampsia	1	VD	32	Survived	Dead before labor induction

SAP: Severe acute pancreatitis, CS: cesarean section, CM: conservation management, VD: vaginal delivery, FTD: full term delivery.

Table 2. Biological parameters by acute pancreatits categories

	MAP (n=9)	SAP (n=7)
Serum Amylase (U/L, 0-100)	143.42±79.81	723.76±543.05
Urine Amylase (U/L, 32-640)	1173.75±406.76	9116.25±7925.91
Serum Lipase (U/L, 23-300)	636.93±411.93	3311.70±3071.40
Serum Triglyceride (mM/L, 0.4-1.53)	1.71±0.21	7.67±9.03
Serum Cholesterol (mM/L, 2.53-5.4)	3.67±0.73	8.27±7.40
White blood cell (10^9/L, 0.4-1.0)	16.12±4.91	13.50±5.28
Neutrophil (%, 40-75)	86.96±1.65	87.08±5.86

MAP: Mild acute pancreatitis, SAP: Severe acute pancreatitis.

confirmed with the exclusion of other diseases [7].

Clinical data

All data are expressed as mean±standard deviation. The mean age of patients was 31.50± 4.00 (range, 25-37 years) years, the mean length of the hospital stay was 11.13±10.00 days, and the mean gestational age was 36.44±3.00 weeks. There were 11 cases of biliary pancreatitis, 4 cases of hyperlipidemic pancreatitis, and 1 case with an unexpected cause by etiology. Out of 16 cases, 6 patients had eaten high-fat foods before the clinical symptoms occurred, and 9 patients had histories of cholelithiasis and cholecystitis. Major clinical manifestations included upper abdominal pain in 12 patients, nausea and vomiting in 8, left back pain in 5 and abdominal distension in 6.

Examinations

Laboratory data (**Table 2**) revealed a mean blood amylase of 433.60±444.05 U/L, urine amylase of 5145±6276.17 U/L, and blood lipase of 1974.31±2321.59 U/L. Two patients had hyperglycemia with the maximum blood glucose of 8.0 mmol/L. In 4 patients with hyperlipidemic pancreatitis, the mean triglyceride level was 4.69±6.29 mmol/L, total cholesterol was 5.97±5.10 mmol/L, and blood amylase was 461.45±488.12 U/L. All 16 patients had leukocytosis with the mean number of leukocytes of $14.81±4.61×10^9$/L and the mean percentage of neutrophils of 87.03±3.37%.

B-ultrasound revealed pancreatic enlargement with echo reduction in 14 cases, and a peripancreatic and peritoneal anechoic area was found in 4 cases. Eight cases had gallstones and 1 case had choledocholithiasis. Computed tomography (CT) showed that one patient had pancreatic necrosis with an indistinct boundary in which the peripancreatic fat tissue disappeared, and 4 patients with SAP had concurrent ascites. Respiratory alkalosis and metabolic acidosis were noted in 2 cases.

*Therapeutic strategies and pregnancy outcomes (**Table 1**)*

All 9 patients with mild acute pancreatitis were biliary pancreatitis and underwent conservative treatment, which included fasting, gastric decompression, ECG monitoring, acid suppression (omeprazole), protease secretion inhibition (octreotide and somatostatin), antibiotic treatment (cephalosporins), rehydration, spasmolysis, blood lipid reduction, and enhanced fetal monitoring. Meanwhile, fetal heart monitoring and ultrasonography were performed to moni-

tor the fetal status. Two patients were administered magnesium sulfate until delivery. In all 9 cases, the fetuses survived, and both moms and infants were discharged with satisfaction.

7 patients with SAP also underwent conservative treatments including nutritional support, correction of electrolyte imbalance, maintenance of acid-base homeostasis, and preservation of organ function. The patients with biliary pancreatitis underwent surgery to release bile reflux. Pregnancies were terminated by cesarean section as soon as the challenges were not met by conservative management. One patient with biliary pancreatitis at the 35th week of pregnancy had high fever, tachycardia, micturition, xanthochromia, and massive ascites with urine amylase of 8280 U/L. The cesarean section was performed due to fetal distress, however, the fetal death was observed during surgery and followed by maternal death due to multiple organ failure. Pregnancy was terminated by cesarean section for another patient at 36th weeks' gestation due to acute pulmonary edema. Dark brown ascitic fluid and widespread distribution of saponification plaques in the intestine and omentum were observed during surgery and a drainage tube was left in the abdominal cavity after irrigation. Not only did mother and fetus survived, they were both in perfect health. One patient chose to terminate pregnancy at 28th week by labor induction because she was not satisfied with therapeutic efficacy and after that Endoscopic Retrograde Cholangiopancreatography (ERCP) was performed upon her request. One patient with hyperlipidemic pancreatitis (serum triglyceride was 21.09 mmol/L) was also given cesarean section to terminate pregnancy at 34^{+2} weeks' gestation. Twin newborns survived, however, their mother died of multiple organ failure 35 days after delivery in spite of comprehensive treatment including hemodialysis. One patient with biliary SAP complicated with early-onset severe preeclampsia was admitted to our hospital after labor induction for intrauterine fetal death, and recovered from surgery and subsequent conservative support.

Discussion

Causes of acute pancreatitis in pregnancy

To determine the etiology of the acute pancreatitis is crucial to the management of this potentially life threatening condition during pregnancy. Although a wide variety of etiologies have been proposed, the exact causes still remains controversial, and the association between pregnancy and pancreatitis has not yet been clearly elucidated. Available data demonstrates that there are two primary mechanisms behind the pathogenesis of AP. Cholelithiasis, the most common scenario of pancreatitis symptoms during pregnancy, is regarded as the most likely predisposing cause [8]. Previous studies demonstrated that AP during pregnancy is a rare disease, with an incidence of 1 out of 1000 to 4000 pregnancies [9] while the incidence of gallbladder disease in pregnancy is approximately 0.05-0.3% [10] and asymptomatic gallstones occur in 3.5-10% of all pregnancies [11].

The second mechanism underlying AP in pregnancy is hypertriglyceride induced pancreatitis [12]. There is a significant increased risk of developing AP in individuals with a greatly elevated plasma triglyceride level [13] and 1.7-6% of cases of AP were attributed to hypertriglyceride in pregnancy [14]. However, pregnancy is also a well known cause of secondary hypertriglyceride, with cholesterol sometimes increasing by 25-50% and triglycerides by 200-300%, respectively [15]. Evidence indicates that regardless of cause, more than 50% of all cases of AP in pregnancy occurred in the final trimester [8]. Although the association between plasma triglyceride and AP in pregnancy has been intensively investigated, the exact mechanism behind it is still illusive. During pregnancy, placental lactogen secreted by trophoblast cells could promote adipose tissue lipolysis and elevate free fatty acids level in serum [16]. These factors lead to increased fat embolism formation and subsequent microcirculatory disturbance and hyperlipidemia, which result in AP [17, 18]. In our study, the 6 cases of AP were triggered by high fat food and the causative factor in the other 8 cases, AP was attributed to a history of cholelithiasis, which consistent with previous investigations.

Diagnosis

Early diagnosis of AP during pregnancy contributes to improved maternal and neonatal outcomes [19]. The main clinical manifestation of pancreatitis is upper/left upper abdominal pain

with or without nausea and vomiting [20, 21]. The patient may have a history of eating greasy food or cholelithiasis. Our observation indicated that the patient with the intrauterine fetal death had sustained tachycardia and hypertension, which may be easily misdiagnosed as pregnancy-induced hypertension. Among laboratory examinations, dynamic monitoring of blood and urine amylase is the key to making a correct diagnosis. However, elevation of serum amylase lasts only 72 hours after onset of AP. Serum lipase level remains elevated longer than that of amylase, and can be helpful for diagnosis. Hypertriglyceridemia is a causative factor for AP and could also be consequence of a damaged pancreas due to AP. Currently, our study showed that 2 of 4 patients with hyperlipidemic pancreatitis complicated with hypocalcaemia died of multiple organs failure. Among the remaining 2 cases, 1 patient was rescued from multiple organ failure via prompt therapeutic treatment, and a stillbirth was observed in another case. Our findings suggest that higher maternal and neonatal mortality were found in AP patients complicated with hypertriglyceridemia, hypocalcemia, or hyperglycemia, which is in agreement with a previous report [14].

Medical imaging may be valuable for AP diagnosis. Computed tomography (CT) scan and ultrasonography are two of the most widely used medical imaging techniques. CT scan is more accurate but the fetus has to be exposed to x-ray radiation. Therefore, ultrasonography is preferred over CT and 70% of pregnant women with AP have abnormal ultrasound findings, which include pancreatic enlargement and echo reduction. Magnetic resonance imaging (MRI) also has a certain diagnostic value.

Therapeutic regimens

The principle of therapeutic regimens for AP in pregnant women is in accordance with that in non-pregnant women. Conservative therapy for AP, which includes gastric decompression, aprotinin application, octreotide, antispasmodic drugs, and antibiotics, is the first choice although there has been no evidence from large sample clinical study [22]. The efficacy of surgical treatment has been controversial. However, surgical treatment could be considered under certain circumstances, such as pancreatic enlargement and necrosis, gastrointestinal perforation, or no improvement after 2-3 days of conservative management [20]. The improvement of 2 patients with SAP in our study by termination of pregnancy and conservative management confirmed the efficacy of conservative regimens. For SAP with hypertriglyceridemia, interventions including a low-fat diet, nutrients supplementation, oral traditional Chinese medications, and plasma replacement [23] could be effective. Altun et al [24] reported 2 cases of gestational hyperlipidemia, which were successfully treated by plasma replacement. In our study, 1 patient with hyperlipidemic pancreatitis died due to delayed application of plasma replacement.

Recently, there has been a major breakthrough in the medical treatment of biliary pancreatitis and it is now considered that removal of bile duct stones by endoscopic sphincterotomy (transendoscopic biliary drainage) is more effective than conservative treatment. However, its effectiveness for pregnant women with biliary pancreatitis is still under debate [25]. ERCP is relatively safe, but cannot be performed during pregnancy [26]. Unlike ERCP, magnetic resonance cholangiopancreatography (MRCP) has lower risks for the mother and fetus compared with other methods in terms of radiation exposure. However, MRCP can be used only for diagnosis, not treatment. Overall, a multiple disciplinary approach, which includes obstetricians, surgeons and gastroenterologists, is key to making the best choices for SAP management.

Obstetric management

The timing of pregnancy termination for patients with SAP has long been an issue for obstetricians. Indications for pregnancy termination include full-term gestation, deteriorated condition after 24-48 hours of treatment, no improvement of paralytic ileus, stillbirth, fetal malformation, and severe pancreatitis. For the majority of the patients, AP alone is not an indication for pregnancy termination. However, the 1 child policy has a significant impact on every family in China and more attention is focusing on the fetus during pregnancy. When a pregnant woman experiences SAP, the patient and her family members may choose to terminate pregnancy in cases where medications are applied or a CT examination is performed.

Conservative treatment can be applied for mild pancreatitis, nevertheless, nutrition from long

period of low fat diet consumption during treatment may not meet the requirements for normal fetal development. Moreover, higher levels of inflammatory cytokines caused by acute pancreatitis have an important effect on the placental blood supply and fetal development. Early nutritional support in a pregnant woman modulates the stress response, promotes more rapid resolution of the disease process and results in better outcomes [27]. Therefore, parenteral nutrition should be given as early as possible to reduce the adverse effects of treatment on maternal and fetal health, and fetal monitoring should be emphasized during conservative management. In addition, higher levels of inflammatory cytokines in AP patients stimulate the uterus and cause abnormal uterine contractions, which could result in premature labor and preterm birth. Pregnancy should be terminated as soon as possible once acute hemorrhagic-necrotizing pancreatitis or hyperlipidemic pancreatitis is identified during pregnancy because these complications will raise the maternal and fetus mortality significantly. Cesarean section still is the preferred method for pregnancy termination. In our observation, both the mother and the child died in 1 SAP case due to delayed termination of pregnancy, and twin babies survived after prompt termination of pregnancy in another case.

Prevention

Early diagnosis and classification of severity of AP at presentation is an essential step for successful management in patients suffering from acute abdominal pain during pregnancy. Maternal blood lipid levels should be monitored to prevent the occurrence of SAP. For pregnant women with hyperlipidemia, diet should be adjusted and the patient should be followed closely. Plasma triglyceride levels should be controlled, and hemofiltration or plasmapheresis should be applied if necessary to protect against pancreatitis.

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