From Acute Pancreatitis to Pancreonekrosis during Pregnancy

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Abstract

Acute pancreatitis during pregnancy, although a rare but extremely formidable complication, is accompanied by a high level of perinatal and maternal mortality. Excessive hypertriglyceridemia is an extremely important risk factor for pancreatitis, especially during pregnancy. The secretion of cholesterol in hepatic bile increases in the second and reaches a peak in the third trimester compared with bile acids and phospholipids, which leads to a supersaturation of bile. Which determines the highest incidence of acute pancreatitis in pregnant women in the third trimester.The acute onset, the nature of the disease and the difficulties in diagnosis in the treatment of acute pancreatitis in pregnant women significantly threaten the health of the mother and fetus.Although most authors argue that treating acute pancreatitis during pregnancy is similar to treating non-pregnant patients, this is actually far from the truth. During pregnancy, the features of the pathogenesis of acute pancreatitis in pregnant women come to the fore, which must be taken into account when managing these patients.

Index terms— pregnancy, acute pancreatitis, pancreatic necrosis, treatment, obstetric tactics.

1 Introduction

lexander the Great was the Macedonian king from 336 to 323 BC. It was assumed that he could have died from malaria, pneumonia, typhoid fever or West Nile fever, but recently researchers have rejected the old versions of his death. It turned out that the king of Macedonia from the Argead dynasty, the outstanding commander Alexander the Great died as a result of acute pancreatic necrosis -an acute form of pancreatic disease [1]. Acute pancreatitis is defined as a sudden inflammation of the pancreas that is clinically present with abdominal pain, nausea and dehydration, which is usually selflimiting, but can sometimes progress to severe illness and even death.

While acute pancreatitis accounts for nearly 1 in every 200 hospitalizations in the United States each year, fortunately, the incidence of acute pancreatitis in pregnant women is rare [2].

It is estimated that acute pancreatitis occurs in about 1 in every 10,000 pregnancies, but this rate varies by region and type of hospital [2].

Acute pancreatitis in pregnant women (APP) most often occurs in the third trimester, and, according to some authors, stones in the gallbladder are the most common cause [3,4]. This proportion is similar to previously reported studies that also show the majority of cases of stones in gallbladder appealing in the third trimester [4,5].

In the study, the majority of patients had APP onset during the third trimester (68%), but 31% also had APP in the first and second trimesters. This date is similar to previously reported studies [6,7].

Acute onset, disease progression, difficulties in diagnosis and in treatment of acute pancreatitis in pregnant women significantly threaten the health of the mother and fetus [8,9].

In previous studies it was shown that the mortality rate was approximately 37% for a mother and 60% for a fetus, while, more recent studies show that these numbers have decreased due to improvements in diagnostics, intensive care and newborn care [7,8].

With regard to diagnosis, treatment, management of pregnancy and timing of delivery, specific guidelines for acute pancreatitis in pregnant women (APP) are still lacking. This is largely due to the low incidence rate and

poor clinical data; it is also due to the multidisciplinarity of this condition, when medical care is provided by obstetricians, surgeons, therapists, gastroenterologists, anesthesiologists, etc. [10].

2 Features of etiology and pathogenesis in pregnant women

There are many causes of acute pancreatitis, but the two most common are:

? alcohol consumption, ? disease of the gallbladder / bile ducts [2].

It is believed that most cases of APP are caused by gallstone disease. With weight gain and hormonal changes caused by pregnancy, gallstones are more likely to form and thus travel through the common bile duct, obstructing pancreatic drainage.

Excessive hypertriglyceridemia (chylomicronemia) is also an extremely important risk factor for pancreatitis, especially during pregnancy. The secretion of cholesterol in hepatic bile increases in the second and reaches a peak in the third trimester compared to bile acids and phospholipids, which leads to bile oversaturation [11,12].

However, levels achieved are never high enough to cause acute pancreatitis. In patients with familial hypertriglyceridemia, pregnancy can significantly increase hyperlipoproteinemia and may be the cause of acute pancreatitis. Changes in triglyceride clearance of apoprotein or lipoprotein lipase metabolism have been discussed since the 1980s. Timely diagnosis and treatment of familial hypertriglyceridemia can prevent pregnancy complications [13,14]. Some genetic changes in 30-35% of cases increase the risk of acute pancreatitis Hormonal changes during pregnancy can predispose to the development of hypertriglyceridemia. When triglyceride levels get too high, oxygen cannot adequately reach the pancreas through the bloodstream and pancreatitis can develop. Of course, during pregnancy, all other causes of acute pancreatitis should be taken into account: alcohol consumption, reactions to certain medications, trauma to the pancreas (Fig. 1). To determine organ failure, three organ systems must first be assessed:

This classification [5] defines three degrees of severity of the disease course:

3 Mild acute pancreatitis [16]

It is characterized by the absence of organ failure and the absence of local or systemic complications. Patients with mild acute pancreatitis. Patients with mild acute pancreatitis usually do not require imaging of the pancreas, are discharged early and mortality is very rare (but possible).

4 Moderate acute pancreatitis [16]

It is characterized by the presence of temporary organ failure, local or systemic complications in the absence of permanent organ failure. An example of a symptomatic local complication is peripancreaticedema resulting in prolonged abdominal pain, leukocytosis, and fever, or which interferes with the ability to maintain oral nutrition.

An example of a symptomatic systemic complication is exacerbation of coronary artery disease or chronic lung disease caused by acute pancreatitis.

Moderate acute pancreatitis may resolve without intervention (as with temporary organ failure or with the absorption of additional fluid), or long-term specialized care may be required (as with extensive sterile necrosis without organ failure).

Mortality in acute pancreatitis of moderate severity with 15-50% is much less than in acute severe pancreatitis.

5 Severe acute pancreatitis [16]

Severe acute pancreatitis is characterized by persistent organ failure. Organ failure, which develops at an early stage, is triggered by the activation of cytokine cascades leading to SIRS -systemic inflammatory response syndrome.

When SIRS is present and persistent, there is an increased risk that pancreatitis will be complicated by persistent organ failure and the patient should be treated as if they had severe acute pancreatitis.

Persistent organ failure can be single or multiple organ failure.

Patients with persistent organ failure usually have one or more local complications.

Patients who develop persistent organ failure during the first few days of illness are at increased risk of death, and mortality is $> 50\%$.

The development of infected necrosis in patients with persistent organ failure is associated with extremely high mortality.

The severe course of acute pancreatitis [17] is characterized by such data as:

In addition, the presence of organ failure and/or pancreatic necrosis immediately classifies acute pancreatitis as severe.

Systemic complications of acute pancreatitis during pregnancy: ? Respiratory function is impaired due to pleural effusion, atelectasis, acute pulmonary edema, or ARDS, resulting in hypoxemia and dyspnea [18,19]. ? Circulatory complications are characterized by shock due to hypovolemia and/or hypotension. The main causes are retroperitoneal or peritoneal fluid loss and/or peripheral vasodilation [19]. ? Cardiac complications are characterized by tachycardia and nonspecific abnormalities rather than decreased cardiac function due to a young age in a pregnant woman. ? Disorders of coagulation and especially DIC (disseminated intravascular coagulation) are very important during pregnancy, as they are accompanied by multiple organ failure and lead

to a high incidence of intrauterine and maternal mortality [19]. ? Renal function is impaired during severe acute pancreatitis, resulting in uremia and oliguria, either through prerenal azotemia or acute tubular necrosis [19,20]. ? Metabolic complications include hypocalcemia, hyperglycemia, hypertriglyceridemia, hypoglycemia, and acid-base disorders [21]. APP can be classified for various pathogenic reasons [5].

? Acute gallstone pancreatitis is diagnosed by an elevated ALT level> 150 U/l within 48 hours from the onset of the disease, as well as by X-ray data, abdominal ultrasound and magnetic resonance cholangiopancreatography (MRCP) [5]. ? Interstitial edematous pancreatitis ? Necrotizing pancreatitis.?

? Respiratory,

? Cardiovascular ? Renal.

? Mild acute pancreatitis,

? Moderately acute pancreatitis,

? Severe acute pancreatitis.

? Signs of hypovolemia (elevated blood urea),

? Increased hematocrit,

? Increased creatinine,

? Clinical signs of pulmonary involvment, such as pleural effusion and/or infiltration, indicate that this patient may have severe acute pancreatitis.

diagnosed based on abnormal serum triglyceride levels ? 11.3 mmol/ l or serum triglyceride levels between 5.65 and 11.3 mmol/l. ? Idiopathic pancreatitis is diagnosed by radiological signs of pancreatitis after excluding gallstones, alcohol, hypertriglyceridemia, drug treatment, trauma, autoimmune and surgical factors [5].

6 Main clinical symptoms:

? Extremely important: acute pain in the upper abdomen, similar to the girdle (+ increased serum pancreatic enzyme). ? Other common symptoms: ? Fever, tachycardia, nausea, vomiting. ? Tension of the abdominal wall ("rubber bellysensations resemble pressing on a slightly deflated rubber ball"), flatulence, paralytic incomplete (partial) intestinal obstruction, Blumberg sign symptom is doubtful or negative. With the development of peritonitis, Blumberg sign becomes positive.

One of the studies [5] indicated that abdominal pain and vomiting remained the two most predominant clinical symptoms in pregnant women with APP. Abdominal pain was localized mainly in the upper abdomen, which was observed in 86.8% of patients (105/121), while only 11.6% had lower (5.0%, 6/121) or generalized pain in abdomen (6.6%, 8/121). More than half of the patients had vomiting (73.6%, 89/121) and fever was less common (23.1%, 28/121). The tension of the muscles of the anterior abdominal wall was mainly in the upper abdomen (91%, 90/99), while only 3% was in the lower abdomen (3/99) and 6% of the entire anterior abdominal wall (6/99) [5].

Depending on the severity of the APP and the cause, the following complications may be present:

? Circulatory reaction: hypotension, shock, ? Ascites, pleural effusions (left> right),

? Jaundice (often only shortly) in the presence of common bile duct stones, ? Rare, but prognostically unfavorable signs: cyanosis of the skin around the navel -with hemorrhage into the abdominal cavity (Cullen sign) or hemorrhagic cyanotic spots on the left lateral wall of the abdomen, sometimes with a yellowish tinge (Gray-Turner sign) ? Scoring systems for determining severity, such as the Ranson Criteria (clinical prediction rules for predicting the disease and mortality risks of acute pancreatitis) are of secondary importance in practice.

Important criteria that indicate a severe course are: clinical symptoms (pain, shock symptoms), CRP increase (>120 mg/l), creatinine increase (>1.2 mg/dl) and decrease in pO2.

7 Complications of APP:

? Shock due to lack of circulating blood volume, release of vasodilators and toxic substances. Consequences: acute renal failure, pulmonary shock (ARDS), consumption coagulopathy.

8 Laboratory deviations and severity of APP

Increased serum lipase and pancreatic amylase. Sensitivity of lipase> amylase; absolute values do not correlate with the severity of the disease (it is not always a reliable "marker" for controlling the course of the disease).

9 Depending on the cause and course:

? leukocytosis(leukocyte count> 10 × 109 /l) ? increase in CRP and LDH, CRP = marker of severity! ? by cholestasis an increase in AP, ?GT, as well as "direct" bilirubin ? by diabetes mellitus hyperglycemia(fasting glucose ? 7.8mmol/l) ? hypocalcemia(serum calcium <1.75mmol/l) ? an increase in urea and creatinine.

Hypertriglyceridemiais defined as fasting serumtriglyceride level ?11.3mmol/l.

10 Signs of systemic inflammatory response syndrome (SIRS)

SIRS -determined by the presence of two or more criteria: 1. Heart rate> 90 /min 2. Body temperature <36 °C or >38 °C 3. The level of leukocytes in the blood <4000 or >12000 /mm 3 4. Breathing rate >20/min or pCO2 art. <33 mmHg.

According to one of the studies [5], only serum calcium level correlated negatively with the severity of APP (p <0.01), which corresponds to date from nonpregnant patients with pancreatitis. Serum glucose, triglycerides, or leukocyte levels did not correlate with the severity of APP. Some of the most commonly used laboratory results were compared based on the severity of APP (Table 1). Testing serum calcium may indicate(D D D D)

K the severity of the disease, but more investigation is needed to confirm this [5].

11 Therapy

Although most authors claim that the treatment of acute pancreatitis during pregnancy is similar to that in non-pregnant patients, this is actually should be taken with caution. During pregnancy, the features of the pathogenesis of APP must be taken into account when managing these patients. The medical stuff (primarily obstetricians) are faced with the question of the feasibility of maintaining the pregnancy, the fetus, the timing and method of termination of pregnancy, and today these are extremely controversial decisions. And it is no coincidence that in the scientific obstetric literature there are many articles on surgical tactics, but not on the obstetric-surgical management of patients with APP.

When assessing pregnant women with acute pancreatitis, it is proposed to answer four important questions, namely:

12 1) Does this patient have acute pancreatitis (diagnosis and exclusion of other causes)?

2) If it is acute pancreatitis, what is the predicted severity (mild or severe?) 3) Is there a biliary pathology? 4) 1st, 2nd or 3rdtrimester of pregnancy? This last question will determine the choice of imaging and therapy regimen [23].

13 Conservative therapy

It is very important that if a pregnant woman develops any abnormal abdominal pain symptoms, she should be admitted to the emergency department as soon as possible to assess her condition. Initial treatment is aimed to reduce exocrine pancreatic secretion, restoring third-space fluid sequestration, and supporting the patient by providing adequate nutrition, oxygenation, analgesics, and monitoring of maternal and fetal vital functions [24].

Initial treatment for acute pancreatitis is limited to forced intravenous hydration of 250-500 ml/h of isotonic crystalloid solution, preferably lactated Ringer's solution, unless cardiovascular, renal, or other comorbilities are present [25]. The forces intravenous hydration is indicated within the first 12 to 24 hours.

In patients with circulatory manifestations of severe fluid loss such as hypotension and tachycardia, more aggressive hydration is recommended. Fluid requirements should be reviewed at frequent intervals over the next 48 hours by assessing blood urea levels [26].

According to SNAP-Based Recommendations (Multicenter Nutritional Study in Acute Pancreatitis was conducted in the US by the National Institutes of Health) [27]:

14 Patients with symptoms of ileus should be fed parenterally !!!!

? Nutrition improves intestinal integrity, reduces the movement of bacteria and therefore the rate of serious infections. ? Start early with a jejunaltube feeding.

? It is recommended to combine the use of enteral and parenteral nutrition, especially in the case of severe forms, since exclusively enteral nutrition cannot adequately cover the patient's energy/fluid/electrolyte costs.

? Parenteral fluid and electrolyte supply should be controlled by electrolyte balance and CVP (CVP target 4-12 cm H2O). Ultrasound control of the inferior vena cava: hypovolemie by diameter <1.8cm (norm 1.8-2 cm). Fluid requirements 2-4 l/day for mild pancreatitis, up to 10 l/day for severe pancreatitis [28]. For high fluid requirements (>4 l/day) replacement of human albumin should not be forgotten: for example, 500ml of 5% human albumin per 4l of fluid (serum albumin control). ? Caution: depending on the severity of the condition, CVP may be overestimated due to increased intraabdominal pressure, resulting elevated diaphragm, so volume requirements may be underestimated. ? Pain manegment (regular administration, dosage based on need): ? Pethidine: s/c or i/v as an injection or in a perfuser.

Single dose 50-100 mg, max.every 2-3 hours, max. 500 mg/day ? Pyritramide/Dipidolor: s/c or intravenously as an injection or in a perfuser. Single dose 15-30 mg, max.every 4 -6 hours, max. 300 mg/day ? Epidural catheter, eg with bupivacaine (eg Carbostesin® 0.25%, 5-10 mg/h = 2-4 ml/h), with a high infusion level (Th 7-10), and good prevention of ileus.

15 Advanced therapy:

? For biliary pancreatitis -ERCP and possibly simultaneous papillotomy with stone removal. not help and there is an unresolved septic focus (high mortality). ? Enteral feeding: start as early as possible in a painfree period, low-fat food, possibly additional enzyme preparations.

? Prevention of relapse: for example, debridement of the bile ducts for calculus, abstinence from alcohol, treatment of hypertriglyceridemia or hyperparathyroidism. Some recent reports [30] suggested a combination of intravenous infusion of heparin and insulin in severe cases of gestational hypertriglyceridemia caused by acute pancreatitis, which increased lipoprotein lipase activity.

In addition, although there is no clear clinical guideline, the use of plasmapheresis and hemofiltration may also be beneficial in some cases [31].

16 Surgical treatment

As for the disease itself, surgical treatment is suggested in special cases of necrotizing pancreatitis. Sterile necrosis, as well as asymptomatic local changes such as a pancreatic pseudocyst, do not require intervention regardless of size, location and/or expansion [32,33].

In case of progression of a pseudocyst ($>$ 6 cm) or complications (infection, compression of adjacent structures), an internal drainage and/or removal of the cyst is surgically performed [3].

Surgical treatment: only if conservative therapy does not help and there is a non-sanitized septic focus (high mortality).

17 Interventional treatment of APP

Usually, if gallstones result pancreatitis, the removal of the gallbladder is delayed until the end of the pregnancy. Often, a stent placed in the bile duct can correct the situation until operative resection is required [32]. However, if waiting until the end of pregnancy is not possible, surgical resection can usually be performed safely, especially before 28-30 weeks of gestation [34].

In stable patients with infected necrosis, surgery should be delayed for more than 4 weeks from the onset of symptoms so that the lesions can be organized into a more specific shape [26].

Treatment of stones in the biliary tract can be Xray surgical-antegradetranshepatic access to the ducts (limited during pregnancy), as well as endoscopic retrograde access through an endoscope in duodenum. Both of these approaches can mechanically destroy the stones, then they will independently enter the intestinal lumen, or remove them. Bile duct stenting is not required in this situation.

Acute biliary pancreatitis in pregnant women requires surgical treatment only when there is: However, in necrotizing acute biliary pancreatitis, cholecystectomy must wait until active inflammation subsides, fluid accumulations dissolve and stabilize in order to avoid contamination of necrotic tissue regardless of the severity of the disease [23].

18 Obstetric procedure

The data in Tables 2-4 provide strong evidence of the relationship between the severity of APP, hyperlipidemia, and maternal and fetal outcome [35,36].

Hyperlipidemia (hypertriglyceredemia) is an extremely dangerous symptom and is mainly combined with moderate severity and severe course of APP, leading to fetal distress and fetal loss [37,38]. The severe course of APP is extremely dangerous for the fetus and leads in all cases to its distress and in 60.0% of cases to fetal loss (Table 4). The moderate severity of pancreatitis is also unfavorable for the fetus and is accompanied by its loss in every fourth case (25%) [26].

If fetal distress occurs in the period of gestation from 22 to 26 weeks and there are no conditions for high professional resuscitation of the newborn (a favorable perinatal outcome is extremely doubtful), the decision on the strategy of pregnancy management and/or its termination, first of all, is made in favor of saving the health and life of the pregnant woman. If triglycerides are the cause of acute pancreatitis, urgent termination of pregnancy is indicated. Before 30 weeks of gestation, and in the presence of professional newborn resuscitation, urgent delivery is preferred, as this will lead to an immediate decrease in triglyceride levels [39,40].

When the cervix is ready for childbirth, it is advisable to deliver through the natural birth canal. During childbirth after 28 weeks (approximately at this time), monitoring of the intrauterine state of the fetus is indicated.

At the same time, the outcome of delivery largely depends on the severity of acute pancreatitis (Table 5), and does not always depend on the method of delivery. A cesarean section performed in conjunction with a surgeon allows immediate delivery of a pregnant woman with APP, increases the likelihood of a favorable perinatal outcome, creates conditions for performing the necessary amount of surgical interventions for pancreatitis, but increases the risk of septic complications. Delivery through the natural birth canal reduces the risk of purulent-septic complications, but somewhat delays the time of delivery. Therefore, the decision on the method of delivery is made by the council after considering all risk factors. During a cesarean section, the decision whether the surgical intervention due to pancreatitis should be extended or not should meet a surgeon (preferably a council of surgeons).

19 Indications for immediate pregnancy termination:

1. Moderate and severe acute pancreatitis; 2. Pancreatic necrosis (or reasonable suspicion of it); 3. The presence of organ failure -acute renal failure, ARDS 4. Hypertriglyceridemia; 5. Hypocalcemia; 6. Complications of pancreatitis: shock, consumption coagulopathy, abscess, sepsis, extensive necrosis and hemorrhage, paralytic ileus.

II.

20 Conclusion

The management of pregnant women with acute pancreatitis is an extremely difficult task, despite the achievements of recent years, and is accompanied by high perinatal and maternal mortality, the level of which depends, first of all, on the severity of acute pancreatitis.

The management of such pregnant women with acute pancreatitis requires a multidisciplinary approach to predict the course of pancreatitis, to determine the [1]

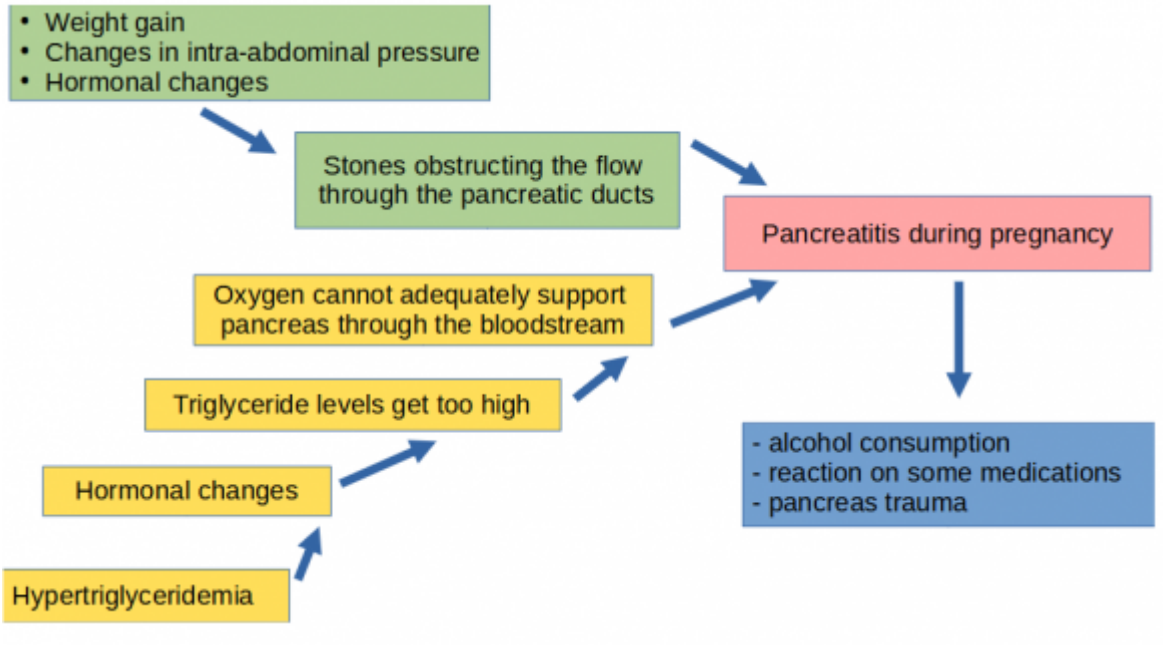
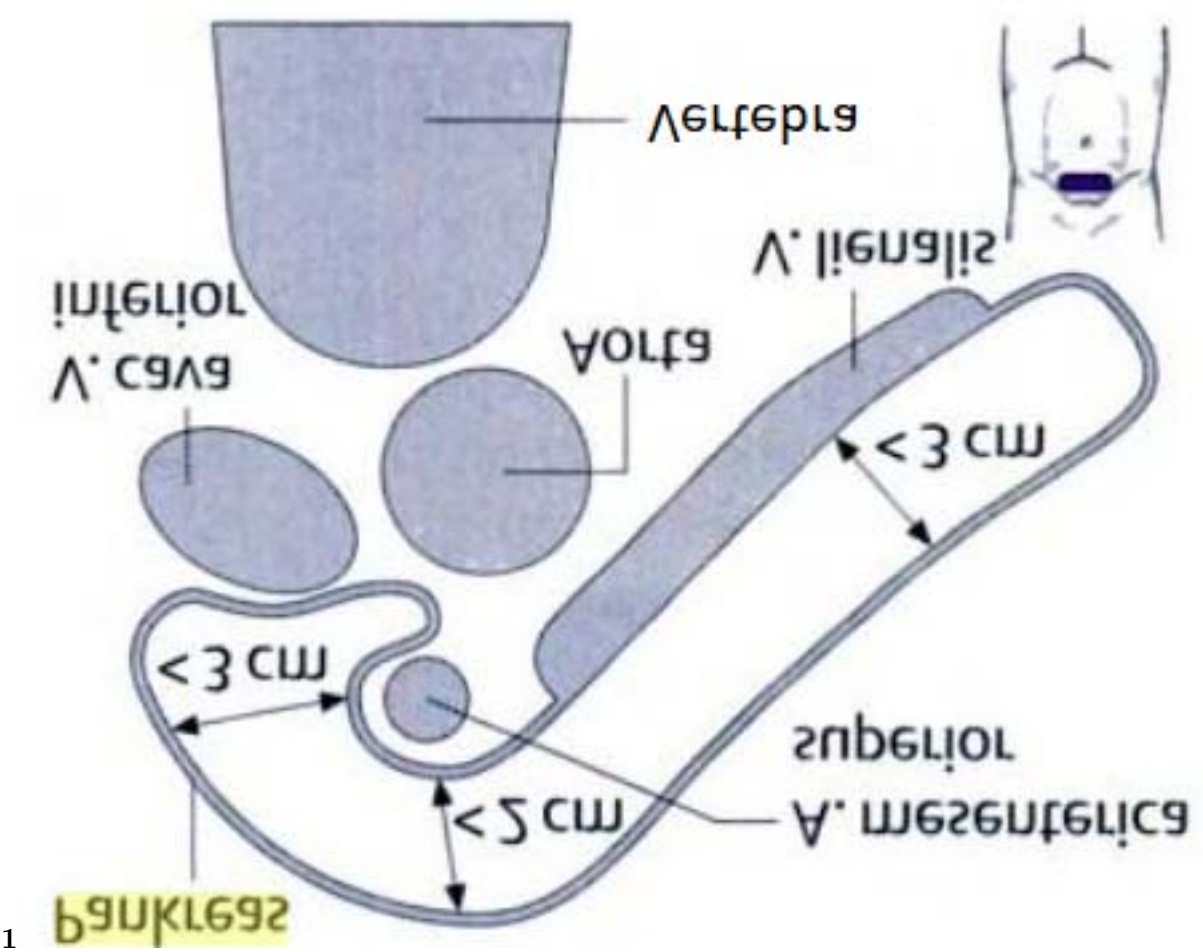


Figure 1:

[1] © 2021 Global JournalsFrom Acute Pancreatitis to Pancreonekrosis during Pregnancy



1

Figure 2: Figure 1 :

1

		Mild	Moderate	Severe
Number of cases		59	44	18
Hyperglycemia	10 (16.9)		13 (29.5)	7 (38.9)
Hypertriglyceredemia	10 (16.9)		13 (29.5)	7 (38.9)
Hypocalcemia		3 (5.1)	7 (15.9)	8 (44.4)
Increased white blood cell count	45 (76.3)		36 (81.8)	15 (83.3)

Program of acute pancreatitis monitoring J.M. Hahn, G.Adler 2012 [22]

Monitoring interval	Criteria for evalu
Several times a day	Health condition (degree of abdominal pain), palpation and auscul of the abdomen, blood pressure, pulse, fluid balance, CVP/ultraso control of the inferior vena cava, body temperature
At least daily (depending on individual parameters also more often)	Laboratory parameters: ? Blood count ? Creatinine, Na +, K +, Ca ++ ? AP , ?GT, AST ? Bilirubin ? Coagulation parameters Quick/INR, PTT) ? CRP and LDH ? protein/albumin ? daily sugar profile ? BGA Abdominal sonography
With clinical deterioration	Rö-Đ?”?????? ??????/??????? ???????, ??Đ?” ?????????? Đ?”?????????????: ??/??? ??? ????-??? ???????? ????Đ?”, ????????????? ?????????? Rö Thorax/Abdominal, ECG Monitoring Optional: CT/MRI or endo-ultrasound possibly ERCP, surgical observation

Figure 3: Table 1 :

2

Etiology	Mild N=23	Moderate N=24	Severe N=7	Number of Pat. N=54
Biliary	9 (39.1%)	5 (20.8%)	0	14 (25.9%)
Hyperlipidemia	1 (4.2%)	14 (58.4%)	7 (100%)	22 (40.7%)
Other	13 (56.6%)	5 (20.8%)	0	18 (33.4%)

Figure 4: Table 2 :

3

	Biliary (n=14)	Hyperlipidemia (n=22)	Other (n=18)	P value
fetal distress	2	14	4	<.01
fetal loss	1	7	3	.203

Figure 5: Table 3 :

4

	Mild N=23	Moderate N=24	Severe N=7	Number N=54	P value
Spontaneous delivery on term	20 (87.0%)	11 (45.8%)	0 (0.0%)	31 (57.4%)	<.001
Pregnancy termination due to maternal and/or fetal complications	2 (8.7%)	3 (12.5%)	0 (0.0%)	5 (9.26%)	>.999
Premature birth	0 (0.0%)	7 (29.2%)	5 (71.4%)	12 (22.2%)	<.001
Abortion (spontaneous or med. indicated)	1 (4.3%)	3 (12.5%)	2 (26.6%)	6 (11.1%)	.211
Fetal distress	2 (8.7%)	11 (45.8%)	7 (100%)	20 (37.0%)	<.001
Fetal loss	1 (4.3%)	6 (25.0%)	4 (57.1%)	11 (20.4%)	.007

Figure 6: Table 4 :

5

Mild N=23	Moderate N=24	Severe N=7

Figure 7: Table 5 :

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