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REVIEW

# DIAGNOSTIC AND THERAPEUTIC APROACHTO ACUTE PANCREATITIS DURING PREGNANCY

## ABORDAJE DIAGNÓSTICO Y TERAPÉUTICO DE LA PANCREATITIS AGUDA DURANTE EL EMBARAZO

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**ABSTRACT**

**Objective:** To determine the current diagnostic and therapeutic approaches for managing acute pancreatitis in pregnancy. **Material and methods:** We conducted a comprehensive review of journal articles and textbooks focused in pregnancy and surgery published between 2012 and 2022. We utilized databases and search engines such as BVS, PubMed, Hinari, Medline, Scielo, Scholar Google, metasearch engines, UptoDate. The review included review articles, observational studies, case reports, meta-analyses and clinical practice guidelines, both in Spanish and English. The inclusion criteria were centered on studies involving pregnant women aged 18-40 with acute pancreatitis. **Results:** The physiological changes during pregnancy increase the predisposition to experience acute pancreatitis. The therapeutic approach must be individualized and multidisciplinary. Treatment strategies may vary based on the severity of the condition, stage of pregnancy, and underlying causes. **Conclusion:** Recent advancements in the understanding of acute pancreatitis in pregnancy have led to a significant reduction in maternal-fetal mortality, reported to be less than 5%. Despite these improvements, there remains a lack of specific clinical guidelines tailored to the management of acute pancreatitis in pregnant women. Further research is needed to develop standardized treatment protocols that can optimize outcomes for both the mother and fetus.

**Key words:** Acute pancreatitis, Pregnancy, Physiological changes, Maternal-fetal mortality (Fuente: MeSH, NLM)

**RESUMEN**

**Objetivo:** Determinar el abordaje diagnóstico y terapéutico de la pancreatitis aguda durante el embarazo. **Material y métodos:** Se realizó una revisión exhaustiva de artículos de revista y libros de texto especializados en embarazo y cirugía desde el año 2012 hasta el 2022. Se utilizaron bases de datos y motores de búsqueda como BVS, PubMed, Hinari, Medline, Scielo, Google Académico, UptoDate. La revisión incluyó artículos de revisión, estudios observacionales, reportes de caso, metaanálisis y guías de práctica clínica, en español e inglés. Los criterios de inclusión se centraron en estudios sobre mujeres embarazadas de 18-40 años con pancreatitis aguda. **Resultados:** Los cambios fisiológicos durante el embarazo aumentan la predisposición a experimentar pancreatitis aguda. El enfoque terapéutico debe ser individualizado y multidisciplinario. Las estrategias de tratamiento pueden variar según la gravedad de la condición, la etapa del embarazo y las causas subyacentes. **Conclusión:** Los avances recientes en la comprensión de la pancreatitis aguda en el embarazo han llevado a una reducción significativa de menos del 5% de la mortalidad materno-fetal. A pesar de esto, faltan guías clínicas específicas. Se necesita más investigación para desarrollar protocolos de tratamiento estandarizados que puedan optimizar los resultados tanto para la madre como para el feto.

**Palabras clave:** Pancreatitis aguda, Embarazo, Cambios fisiológicos, Mortalidad materno-fetal (Fuente: DeCS, BIREME)

## INTRODUCTION

Acute pancreatitis is an inflammatory disease of the pancreas, which if not treated in a timely manner causes local injury, systemic inflammatory response syndrome, organ failure and death; and when it occurs during pregnancy, it is an important cause of morbidity and mortality. (1,2)

The incidence of acute pancreatitis in the general population is 13-45 per 100,000 inhabitants, and during pregnancy the incidence is 1 in 1000 - 1 in 12000, which is higher than in the general population, according to a study conducted at the Shengjing Hospital at China Medical University in 2022. Compared to data from a study carried out in Mexico by Saldivar-Rodríguez et al., in 2016 the same incidence is evident in this population, although it is difficult to establish an expected incidence globally, because the data vary depending on the population studied. (3-5)

Pregnant women are more predisposed to acute pancreatitis due to the physiological changes of pregnancy, such as increased lipids and variations in hormone concentrations; that is why biliary lithiasis and hypertriglyceridemia represent the main causes of acute pancreatitis in pregnant women. (3,5)

The diagnosis of acute pancreatitis in pregnant women is based on 2 of 3 criteria: clinical manifestations, laboratory tests, and imaging studies. Due to the physiological changes mentioned above, the clinical manifestations are non-specific, presenting with: acute abdominal pain, associated with vomiting, nausea, among others; and they are masked by symptoms present in pregnancy, which makes diagnosis difficult; causing delay in treatment or its inadequate management, and as a consequence an increased maternal mortality (37%) and fetal mortality (60%). (1,4-9)

Treatment is individualized, taking into account the Atlanta, APACHE II and Ranson criteria of severity, based on which medical treatment is initiated with fluid resuscitation, enteral nutrition, analgesia and antibiotics in severe cases and/or associated with cholangitis. Surgical treatment will be used if there is no improvement in 24-48 hours, and laparoscopic cholecystectomy will be deferred to the second trimester if it is of biliary origin; or discharge resolution of pregnancy if it is associated with another cause between the second and third trimester of pregnancy. (1,8,10)

Due to the scarcity of diagnostic and therapeutic guidelines for acute pancreatitis during pregnancy, this study sought to expand the available information, particularly in pregnant patients as a population at risk; It also sought to recognize the most frequent clinical characteristics, their predisposing factors and diagnostic and therapeutic approach, for a comprehensive and timely management of biliary pancreatitis; and in this way avoid maternal and fetal complications. (1,5,7,11)

## MATERIAL AND METHODS

An exhaustive review of journal articles and textbooks specialized in pregnancy and surgery from 2012 to 2022 was carried out, with the use of the metasearch engines BVS, PubMed, Hinari, Medline, Scielo, Google Scholar, UptoDate. The review included review articles, observational studies, case reports, meta-analyses, guidelines, in Spanish and English. The study unit consisted of pregnant women aged 18-40 years with acute pancreatitis.

At the end of the data search, the references that met the criteria in the construction of the topic were classified, selected and ordered using the EndNote bibliographic manager. Then, the information from each source was organized and written to facilitate its analysis.

## RESULTS

### *Epidemiology of Acute Pancreatitis in Pregnancy*

Acute pancreatitis (AP) is an acute inflammatory pathology of both pancreatic and peripancreatic tissue, which in its severe form and when not treated in a timely manner, causes local injury, significant systemic compromise, organ failure and death. (1,2,12)

Acute pancreatitis during pregnancy (ECP) is a rare cause of abdominal pain, which occurs due to gallstones, alcohol abuse, and hypertriglyceridemia, a complication that occurs most frequently during the third trimester or early postpartum. (1,6,14)

BP is a disease with various causes, broad clinical manifestations, and with a high incidence in

pregnant women; that when it occurs during pregnancy, due to its acute onset and high difficulty of diagnosis and treatment, it is a challenge for the physician, as it leads to being an important cause of morbidity and mortality both maternal and fetal. (1,2,6)

Although BP during pregnancy is a rare condition, it has a high incidence; 1 per 1 000 - 12 000 pregnant women, compared to the incidence of BP in the general population of 13 - 45 per 100 000 population. (3,7,8,15,18)

Hot S et al., in a 2019 publication of the Turkish Journal of Trauma and Emergency Surgery, identified that the incidence of ECP is between 1,000 and 5,000 pregnancies, representing a rate between 0.05-8%, with greater predominance in the third trimester and postpartum. Similar data are detailed by the French team of Ducarme et al., who reported 1 case for every 1,000 to 10,000 pregnancies, although the incidence is lower; the predominance of BP during the third trimester and postpartum is evidenced. (12,20)

*Etiology of Acute Pancreatitis During Pregnancy*

Pregnant women are more predisposed to acute pancreatitis due to the physiological changes during this stage. The increase in hormonal concentrations of progesterone produces relaxation in the smooth muscle of the gallbladder wall and partial inhibition of cholecystokinin that controls the contraction of the gallbladder, which leads to an enlarged, hypotonic gallbladder and slow and incomplete evacuation, which produces biliary stasis; associated with increased cholesterol secretion at the hepatic level, which produces biliary saturation and greater formation of cholesterol crystals that form gallstones, which obstruct the pancreatic duct. All these changes generate inflammation and release of pancreatic enzymes that induce acute pancreatitis. (1,2)

Due to the physiological changes mentioned above, it is evident that the first cause of ECP is biliary lithiasis in more than 70% of cases. (1,12,17)

ECP has several causes, similar to those reported in the general population, which listed in order of frequency are: lithiasis (70%), idiopathic (12 to 28%), alcohol abuse (0 to 10%), and hypertriglyceridemia (4%). Among the less frequent causes are: trauma, hyperparathyroidism, drugs such as: somatostatin, furosemide, N-acetyl cysteine, acetaminophen, steroids, erythromycin, among others, infections, associated with fatty liver, preeclampsia, hyperemesis gravidarum, and genetic disorders. (1,2,10,12,15,17-19,21-25)

Coto et al. in 2019 describe that in Europe and Latin America the main cause of ECP is pancreatitis of biliary origin (67%-100%), the second cause is of idiopathic origin (15%), the third is due to alcohol intake (5-10%), and the fourth cause is hypertriglyceridemia (5%). In addition, emphasis is placed on how the causes vary according to the eating habits of the populations; as an example, in China the second cause of ECP is hypertriglyceridemia. (12)

*Risk factors for acute pancreatitis during pregnancy*

Risk factors for acute pancreatitis during pregnancy should be considered, which are related to the root cause. Among these are mentioned: multiparity and the use of oral contraceptives due to the increase in stasis and formation of gallstones; other factors mentioned as risk factors are: advanced maternal age, high body mass index (BMI) and high-fat diets. (6,8,20)

According to a study carried out in Beijing by Zhang et al. in 2022, a history of gallstones and hypertriglyceridemia are risk factors that induce the development of pancreatitis during pregnancy and, therefore, recommend primary prevention in so-called high-risk patients: those who have a history of gallstones prior to or during pregnancy, hyperlipidemia or BMI ≥28kg/m2; and they recommend performing ultrasound (USG) of the abdomen prior to planning pregnancy. (8)

Obesity and the increase in leptin during pregnancy causes up to 10% of pregnant women to develop stones or bile sludge, which is why they are also considered risk factors. (22)

In 2019, Hot S et al. conducted a study in Istanbul; they demonstrated that the main risk factor for ECP is multiparity (71%), and identified other factors such as: morbid obesity, preeclampsia, diabetes mellitus, multiple pregnancy, and HELLP syndrome. (20)

*Clinical manifestations of ECP*

The clinical manifestations of acute pancreatitis are masked by the symptoms of pregnancy; therefore, the clinical manifestations are non-specific. Generally, it presents with persistent acute pain in the abdomen, specifically, in the epigastrium and/or upper hemiabdomen, poorly defined, not colic-like, progressive, which radiates in a belt to the back, relieves with flexion of the torso, is aggravated by the intake of food or liquids and the supine position. Other symptoms associated with pain are: nausea, vomiting, anorexia, fever and abdominal distension. (1,6,33-35)

Regarding the most characteristic signs and symptoms of ECP, pain prevails in the upper quadrant of the abdomen with 86.8%, vomiting in 73.6%, fever with 23.1%; and during the physical examination, sensitivity stands out with 81.8% and sensitivity to rebound in 34.7% of pregnant women. Only 6% have generalized pain. (6)

At the time of clinical examination of the abdomen, paralytic ileus, epigastric defense, and generalized contracture were present; In addition, due to the severity of the condition, shock may be clinically associated with hypotension, hyperthermia, and tachycardia. (33)

Juneja et al. in 2013 emphasize that, in addition to the classic symptoms of ECP, the presence of jaundice and pulmonary findings such as pleural effusion and basal lung collapse, present in 10% of cases, should be evaluated. (35)

In 2020, González et al. determined that, in Mexico, the mean age of presentation of ECP was 24.89 years; In addition, they revealed that it is more frequent in the third trimester (59.3%), followed by the second trimester (33.3%) and that it is infrequent during the first trimester of pregnancy (7.4%). Compared with data from Dayanand Hospital in India, similar presentation is evidenced; report that ECP is more frequent in the third trimester (62.5%). (11,35)

*Diagnosis of Acute Pancreatitis During Pregnancy*

Although ECP is rare, it has a wide clinical spectrum, from mild symptoms with local involvement, to significant systemic involvement, which can cause maternal and/or fetal death. It is more difficult to diagnose in the first trimester compared to the third trimester, although it is more frequent during the third trimester and puerperium, and therefore this pathology must be considered when approaching a pregnant woman with abdominal pain, which becomes a challenge for the treating physician. (1,20,22,34)

At the moment, there are no specific criteria developed for cases of acute pancreatitis during pregnancy, so the standard guidelines of the general population for this pathology in pregnant women are used. Therefore, the diagnosis of ECP is based on the Atlanta criteria, and requires the presence of 2 of the following 3 criteria: (1,6,12,36)

- Clinical picture
- Lab tests
- and/or imaging tests

As mentioned, the symptoms are not very specific and are masked by the symptoms generated by pregnancy. Therefore, in the face of clinical suspicion, laboratory tests and the imaging test of choice in pregnant women should be evaluated due to its safety: abdominal ultrasound (USG). The role of imaging studies is very important in the diagnosis of ECP, since it establishes the cause and severity of the study. (1,34,36)

Being in front of a pregnant woman with pancreatitis symptoms and with pancreatic enzymes elevated by more than 3 times the normal value, at the time of admission it is not necessary to perform a diagnostic imaging study; If they have normal laboratory tests, they should perform imaging tests, since in late presentations the levels of pancreatic enzymes may be within normal values. (6)

More than 50% of ECP cases are diagnosed in the third trimester, so it can be seen that it is more common with advancing gestational age, similar to the frequency of biliary lithiasis in pregnancy. Saldivar-Rodríguez et al. mention in their article Acute pancreatitis during pregnancy in 2016, that in the Mexican population the diagnosis occurs in the third trimester, related to the fact that the older the gestational age, the greater the risk of ECP. (2,6,8,22,37)

When the diagnosis is confirmed, the etiology of BP during pregnancy must be identified, remembering

that more than 70% of cases are due to gallstones. Due to the association of ECP with biliary pathology, it is of utmost importance to ask the pregnant woman about her medical history; which includes a history of acute pancreatitis, cholelithiasis, consumption of alcohol, drugs or drugs, among others. (1)

In 2015, Bahiyah et al. highlighted that when evaluating pregnant women with suspected AP, four questions should be answered: (38)

- Does the patient have BP (making the diagnosis and eliminating other causes)?
- What is the expected severity?
- Is there a biliary etiology?
- What is the trimester of pregnancy?

The fourth question is relevant, since the choice of diagnostic images and therapeutic approach is determined based on the answer to the question. (38)

Because of both the physiological and anatomical changes that occur during pregnancy, Parveen et al. describe that clinical evaluation is made difficult by the gravid uterus, the stretching and lifting of the anterior wall of the abdomen away from the area of inflammation, and the hindrance of movement of the omentum to an area of inflammation. (36)

Juneja et al. in 2013 detail how the mistake of underestimating the diagnosis of ECP during the first trimester can be made, confusing it with hyperemesis gravidarum, so they recommend always considering the possibility and requesting diagnostic laboratory tests for BP. They point out the importance of performing fetal well-being tests, in addition to radiological imaging studies both to evidence the cause of BP, and to rule out other pathologies and evaluate findings such as pleural effusion and lung collapse caused by the disease; and they highlight the importance of monitoring until childbirth. (35)

*Diagnostic methods of ECP*

Within the laboratory tests, amylase and lipase should be requested, whose values greater than three times their normal value confirm the diagnosis. As in the general population, lipase (>600 IU/L) has greater specificity and remains elevated for longer than amylase, and is the first to increase; in relation to amylase which is less specific and has greater sensitivity, so it increases in other diseases. Amylase peaks in the first 14 hours and then declines after 3-5 days, while lipase remains elevated for up to 2 weeks. (1,6,22,39)

Padmavathi Mali (2016) in his article Pancreatitis in pregnancy: etiology, diagnosis, treatment, and outcomes, refers to the sensitivity of amylase and lipase in the diagnosis of ECP; the elevation of both laboratory tests raises the sensitivity to 94%, and only the elevation of one of these has 81% diagnostic sensitivity, in addition, it refers to the levels of alkaline phosphatase; Also, they can be increased up to 3 times their normal value during pregnancy, so this data must always be considered. Ducarme et al. compare the sensitivity of serum lipase in relation to amylase, which shows the highest sensitivity (94% versus 83%) and specificity (96% versus 88%) of lipase in the diagnosis of BP. (12,18)

After the confirmation of the condition, complementary tests should be requested that will be a guide to evidence the etiology and severity of the condition; Among the tests requested are; blood count, C-reactive protein (CRP), calcium, lipid profile, and liver function tests. (1)

In 2019, Coto et al. detailed that clinical presentation and diagnostic suspicion must be considered to request laboratories, and mention the most commonly used due to the most frequent causes of ECP, which are: (6)

- Amylase and lipase: which specifically evaluate acute pancreatitis.
- Liver function tests: aspartate aminotransferase and alanine aminotransferase, total bilirubin, alkaline phosphatase, and blood count; useful for evaluating complicated biliary disease, HELLP syndrome, and severe preeclampsia.
- Proteinuria: to rule out preeclampsia. (6)

Regarding the diagnosis of ECP due to hypertriglyceridemia, it is based on triglyceride levels greater than 1 000 mg/dl, or serum triglycerides with a cloudy appearance; since levels above this value are at risk of PAE in 4-56%. Most pregnant women have transient hypertriglyceridemia, which returns to <150 mg/dl after 2-3 days. However, in severe (1 000 - 1 999

mg/dl) or very severe (>2 000 mg/dl) cases associated with elevated lipase levels (three times the upper limit value); They are associated with high levels of fatty acids and can lead to systemic inflammation. In addition, Gupta et al. in 2022 recommend performing a triglyceride test once every trimester in high-risk pregnant women. (6,18,31,41)

Regarding idiopathic pancreatitis, the diagnosis of this is by imaging test, after having ruled out lithiasic pancreatitis, alcoholic, trauma, hypertriglyceridemia, drugs, autoimmune and surgical factors. (6,15)

*Diagnostic imaging studies*

The imaging study to evidence acute pancreatitis during pregnancy is abdominal ultrasound, this because it is harmless to the fetus, it is cheap and highly available; in addition, it allows to rule out other pathologies that cause abdominal pain, and evidences the presence of gallstones, the main cause of PAE. When in doubt, experts suggest using methods with greater sensitivity such as computerized axial tomography and magnetic resonance imaging. (1,6,35)

In 2013, Juneja et al. reported that at Dayanand Hospital and Medical College, India, endoscopic ultrasound, MR cholangiopancreatography (MRCP), endoscopic retrograde cholangiopancreatography (ERCP), and therapeutic options including endoscopic sphincterotomy, biliary stent placement, gallstone removal, and laparoscopic cholecystectomies are fundamental options for both the diagnosis and the appropriate management of ECP. and with this the forecast has improved compared to the past. (35, 42)

Abdominal ultrasound

Imaging study of choice for ECP, this because it is harmless for both the mother and the fetus; because it does not use radiation, is non-invasive, is highly available and low cost. Its sensitivity is 90%-100% in ECPs of biliary etiology, as it identifies gallstones >3 mm and the presence of dilation of the bile duct, making it the first-line study to be used when the etiology is suspected to be of lithiasic origin. (1,6,20,35)

With the abdominal USG, the pancreas can be visualized in 30%-40%, so it is a disadvantage of this; and has low sensitivity (<60%) to detect choledocholithiasis and biliary sludge. (1,6)

Computed tomography (CT) scan

This non-invasive imaging study allows the presence of inflammation, collections and/or necrosis present in the pancreas to be evaluated, in addition to being useful for diagnosis, determines the prognosis and severity of ECP, and is used 48 hours after the onset of the clinical picture. (1,6,20)

The need to use intravenous (IV) contrast dye which crosses the placenta, ionizing radiation, the higher cost, and the underestimation of necrosis and severity are all of its disadvantages. (1,6,35)

By means of abdominal CT, a score and grade is provided according to the characteristics of the pancreas through the Balthazar classification: grade A reports a normal pancreas and a score of 0 is given, in grade B there is an increase in the size either local or diffuse of the pancreas, but there is no evidence of peripancreatic pathology, so 1 point is awarded, grade C with a score of 2; presents intrinsic pancreatic changes, increased peripancreatic density, and inflammatory changes in fat, if they report a collection it is grade D and score of 3, while the presence of more than two collections or gas in or adjacent to the pancreas defines grade E with a score of 4. (1,6)

The fetal exposure to radiation emitted by the CT scan of the abdomen ranges from 0.8 to 4 rads, due to this variable fetal exposure to ionizing radiation, Fernández et al. in 2017 suggest that it be performed in pregnant women who present severe acute pancreatitis after 72 hours, APACHE II ≥8, RANSON >3, organ failure, or significant clinical deterioration. (1.34)

Magnetic resonance imaging (MRI)

This study is non-invasive, does not require anesthesia, does not use radiation, does not require IV contrast medium since it uses gadolinium which is not toxic to the fetus, and achieves a good visualization of the pancreas. Its disadvantages are high cost, longer time to perform, less access, and it is not standardized in prognostic evaluation. (1,6,18,43)

It is not recommended before 18 weeks of gestation due to the increase in temperature exerted by radiofrequency pulses on fetal tissues. (1,18,35,43)

Other advantages of MRI are that it provides information on complications of AP: edema, pseudocysts and hemorrhagic pancreatitis; in cases of persistent cholestasis it is useful to determine if the bile duct is clear; In addition, the evaluation of the pancreatic parenchyma, the reliable detection of pancreatic and peripancreatic necrosis, and the discrimination between necrosis and collections are superior with this method. (18,33,43)

Endoscopic ultrasound

It is a semi-invasive study, which has better sensitivity and predictive value compared to MRI in the case of choledocholithiasis; in addition, the pregnant woman is not exposed to radiation, so it can be used in any trimester, but its use is limited because it requires experience and IV sedation. (18,25,35)

Parveen et al. (2015) reserve the use of endoscopic ultrasound when there is suspicion of stones in the common bile duct, since it has a high positive predictive value (100%) even for microlithiasis (≤2 mm) or sludge in the common bile duct. (25,36)

Diagnostic endoscopic retrograde cholangiopancreatography (ERCP)

ERCP is used in the diagnosis and treatment of choledocholithiasis and its complications: cholangitis, biliary stenosis, etc., both in the general population and in pregnant women, although in these it is a challenge for the physician, due to the complications associated with the procedure, fetal exposure to radiation and the duration of the procedure and fluoroscopy. (44)

The risks of ERCP should always be considered, including: perforation, hemorrhage, ERCP pancreatitis, and fetal radiation. Juneja et al. indicate that when this is the diagnostic and therapeutic method to use, fetal shielding should be used and the use of fluoroscopy should be limited to less than 1 minute; In addition, it is preferred to use this method in the second trimester, and prior to the procedure, prophylactic antibiotic coverage and tocolytic medications are initiated. (42)

*Severity criteria*

The severity of ECP is classified into 3 categories according to the ATLANTA consensus in 2012:

*Mild:* pancreatitis without organ dysfunction or generalized complications, evolves towards recovery, with improvement in 48 to 72 hours, APACHE II ≤8 points, only conservative treatment is provided.

*Moderate to severe or moderately severe:* Pancreatitis with transient organ dysfunction or localized or generalized complication within 48 hours after treatment.

*Severe or severe:* Pancreatitis with persistent organ dysfunction or localized or generalized complication for more than 48 hours after treatment. (1,6,10,13)

The criteria of Ranson (Table 4), Balthazar and APACHE II are also used to evaluate the severity of ECP, since there are no specific criteria for this population. It has been shown that both CT and MRI are effective in evaluating the Balthazar criteria, as this study is performed 48 hours after the onset of symptoms, since early imaging tests may underestimate the severity of BP. In addition, cases of severe ECP (score ≥3) are mainly due to gallstone migration or hypertriglyceridemia. (6, 10, 12, 17, 33)

With respect to Ranson's criteria for the prognosis of BP, it shows whether pancreatitis is severe with a score greater than or equal to 3; and a score lower than this shows that severe pancreatitis is unlikely (6,12,33).

*Therapeutic approach*

The initial measures in pregnant women are the same management for non-pregnant women, which includes: the use of analgesics, intravenous hydration and avoiding oral feeding to reduce pancreatic secretion. Other useful medications for ECP are application of aprotinin, ochreotide and antispasmodics, the latter 3 are controversial, so they are not recommended during pregnancy. Antibiotic treatment may be initiated in specific cases. (2,50)

In patients who are in the first trimester of pregnancy, the medical treatment is the one of choice, without the need for surgery or any

additional treatment. Even in patients who have mild BP, it is the treatment of choice. (38)

Patients with ECP caused by hypertriglyceridemia, hierarchical management should be considered, of which the basis is a multidisciplinary management with: obstetrician-gynecologists, nutritionists, nursing, endocrinologist, among others; followed by the corresponding diet. If treatment is refractory, supervised fasting, parenteral nutrition, or intravenous insulin therapy should be initiated. Hospitalization is important to perform these treatments because of better maternal-fetal monitoring. After the first trimester, you can continue to the next step, which is fibrate therapy, and finally: plasmapheresis. (48)

Having the diagnosis of BP as well as having identified the cause: after the physical examination, laboratory tests and imaging studies; it will be classified according to the severity of the condition, for which the criteria of APACHE II, Ranson, Atlanta, organ failure or presence of local or systemic complications must be identified. (1)

Patients should be hospitalized for maternal and fetal monitoring, oxygen placement if necessary, and initial resuscitation and support measures. The peripheral route should be channeled for the administration of intravenous fluid and the corresponding gastrointestinal rest. If you have persistent vomiting or prolonged ileus, a nasogastric tube should be placed, which is also useful for gastric decompression. In this regard, there are no differences in the in-hospital evolution of nasogastric tube placement vs. nasojejunal tube, so for more practical purposes, the nasogastric tube is recommended. (1,2,51)

Fluid replacement is a fundamental basis for the treatment of acute pancreatitis of any etiology, whether pregnant or non-pregnant, since it reduces the incidence of SIRS, organ failure and mortality. (1)

This treatment should be started immediately, and initially with crystalloids such as saline or Ringer's lactate, of which the latter is recommended the most. It should be administered at 5-10 cc/kg/hr in the first 24 hours; then the contribution is reduced to 80 cc/hr in the remaining hours, for a total infused of 2 500 to 4 000 cc in 24 hrs. (1)

Another measure of great importance after fluid resuscitation is fasting for no more than 48 hours, and early enteral feeding. Because there may be greater protein catabolism due to BP, altered glucose metabolism, alteration in the absorption and digestion of nutrients, which can cause a nutritional deficit, which should not happen in a pregnant woman. (1)

Early enteral nutrition is preferable due to its multiple benefits such as: maintenance of normal intestinal bacterial flora, immunity and integrity of the intestinal mucosa, prevents bacterial translocation and endotoxins; this avoids severe complications such as multiple organ failure, sepsis, local complications, hospitalization time and even death according to Fernández C. et al during 2017. (1)

When abdominal pain, nausea and vomiting disappear; when appetite is restored and when it is observed that inflammatory markers and pancreatic enzymes begin to normalize, with an emphasis on clinical improvement; enteral feeding can be initiated. (1,52)

Various studies argue that although the patient should initially have gastrointestinal rest, enteral feeding should be started earlier.

If there is an indication to start parenteral feeding, the use of a central venous catheter (CVC) should be avoided in pregnant patients due to a higher risk of infection and thrombosis, so it should preferably be started with the use of a peripheral catheter, the patient should be observed carefully and the use of CVC should be determined, taking into account the maternal-fetal benefit risk. (52,53)

Among the indications for parenteral feeding, the following are mentioned: (53)

- In patients who do not tolerate the oral route
- Prolonged ileus
- Complicated pancreatic fistula
- Compartment syndrome

In the case of diagnosis it was PAE due to hypertriglyceridemia, treatment is mainly based on diet as the first line and symptomatic. The diet should be planned in conjunction with the nutrition department, taking into account the balance of maternal and fetal needs. It should have fat

restriction in less than 20% of the caloric requirements, and can be even less than 10% depending on triglyceride levels. (48)

The consumption of carbohydrates with a low glycemic index and proteins is recommended, which should generally be 45-65% and 10-35% of the caloric requirements; without avoiding essential fatty acids, with ethyl esters and omega-3 acids (3-4/day): which decrease the synthesis of triglycerides (TG), enhance the beta-oxidation of fatty acids and increase the activity of lipoprotein lipase (LPL).; Also, the use of nutritional supplements such as folic acid, iron and calcium should be continued. After the acute phase, a lifestyle change and long-term diet adjustments should be made to avoid recurrences. (18,48, 52,54)

Pain management is another fundamental pillar of ECP and BP treatment in non-pregnant women. In the management of pregnant women, opioids can be used as the first line, despite their effects causing spasms in the sphincter of Oddi. (1)

A systematic review called Opioids for acute pancreatitis pain in 2013 by Basurto Ona X et al. mention that opioids compared to other analgesics, reduce the need to add more analgesics to the treatment, so there is no difference in risk of complications or adverse effects. Therefore, the pregnant woman is given analgesia, using the least possible amount of medication. (1,55)

Among the options are: (1)

Tramadol + antiemetic + paracetamol with schedule and with intravenous rescue morphine. 1 If the response is not favorable, an intravenous morphine analgesic infusion pump may be used, monitoring the patient's response to pain to modify the dose accordingly. (1)

Antibiotics

Antibiotic prophylaxis is not recommended in patients with AP and is not recommended for use in PA. Several studies describe that antibiotic prophylaxis can be used in severe forms of AP, however, they have not shown benefits with its use. (34)

Antibiotic treatment is initiated in case of fever or bacterial superinfection of PAG, necrotizing pancreatitis, peritoneal exudates, pseudocysts, sepsis or cholangitis. (34)

Broad-spectrum antibiotics should be administered in the first line. It is recommended to start with third-generation cephalosporins associated with antibiotics against anaerobic microorganisms, which are safe in pregnancy, such as ceftriaxone 1-2 g/day intravenously + metronidazole 500mg c/8 hrs. (1)

Avoid aminoglycosides, ampicillin, first-generation cephalosporins due to low penetration into the pancreas. Fluoroquinolones are contraindicated during pregnancy due to the fetal complications that this pharmacological group can cause. (34)

Surgical treatment

Surgical treatment is divided into 2 pathways in ECP. For treatment of cholelithiasis by cholecystectomy or ERCP with sphincterotomy, and for treatment not associated with lithiasis, to local complications of PA. (51)

Surgical treatment in the presence of multiple lithiasis with risk of recurrence is assessed. However, this treatment should be delayed until the second trimester; early surgical intervention is also indicated if ECP is associated with acute cholecystitis. (51)

Indications not associated with biliary causes are: pancreatic abscess, infected effusion or pancreatic necrosis, association with serious complications such as intestinal perforation, or deterioration after active treatment for 2-3 days. (57)

Among the general considerations, maternal and fetal needs must be taken into account prior to entering the operating room, so in the perioperative stage fetal heart rate monitoring, uterine contractions, take into account gestational age and if there are indications for intervention. (58)

The approach should be in the lateral decubitus position to prevent supine hypotension syndrome, due to decreased pressure on the vena cava, which decreases venous return, where there is a drop in blood pressure and uterine blood flow. Also, the use of oxygen, constant monitoring of maternal and fetal

hemodynamics should be considered. Monitor for the presence of nausea or vomiting during the procedure due to delayed gastric emptying of the pregnant woman. (58)

ERCP with sphincterotomy

This is a method that is preferably used in the third trimester and immediate postpartum in patients with biliary ECP with/without association with choledocholithiasis, prevention of recurrences and indicated in patients in whom there is a contraindication to surgery. However, the risk benefit of the fetus and the mother should always be evaluated. (35,38)

The ERCP should be performed if there are stones in the bile duct, a procedure that is safe during pregnancy, as long as the fluoroscopy time is reduced and with protection of the pelvic region, protecting the fetus. It can also be performed after endoscopic ultrasound (EUS) and magnetic resonance cholangiopancreatography (MRCP). These procedures allow the identification of patients who are candidates for therapeutic ERCP (Table 6). After ERCP, sphincterotomy can be performed without the need to repeat sedation because there is a greater risk of persistent biliary pathology associated with obstruction, and this increases the severity of acute pancreatitis and predisposes to cholangitis. (33,58)

Cholecystectomy

It is considered in case the cause of PAE is cholelithiasis and can be performed preferably in the second trimester laparoscopically, with a risk of fetal loss of 0-5% and without malformations associated with the procedure. According to the ARS MEDICA article by Fernández et al. entitled Management of acute lithiasic pancreatitis in pregnant women in 2017; This trimester is ideal because the organogenesis has ended, there is a lower incidence of miscarriages and better visualization of the surgical field since there is no interference by the uterus, thus reducing the risks. The use of ERCP with sphincterotomy is also recommended in the immediate postpartum period when pancreatitis occurs in the third trimester of pregnancy. It is emphasized that in cases during the third trimester, the case should be individualized and the best time for surgery should be decided. However, there are studies that support the performance of videolaparoscopic cholecystectomy in any trimester, since, if patients have AP in the first trimester, there is a probability of recurrence, as well as an increase in hospital costs and reduces the quality of life of patients. (1,34,40)

According to the study *Changing management of gallstone-related disease in pregnancy – a retrospective cohort analysis* carried out in 2015 by Ríos-Cruz et al., many women with conservative treatment during pregnancy report having undergone surgery 2 years after pregnancy resolution. (18.59)

When patients with cholelithiasis present asymptomatically, they can be managed expectantly. However, when there are symptoms and to avoid complications such as biliary tract obstruction, ascending cholangitis, pancreatitis or acute abdomen; The procedure should be performed as soon as possible and provided that complications are not reached. When pancreatitis occurs, cholecystectomy is necessary and it is considered after the inflammation subsides, since women may have recurrent pancreatitis. The risk of recurrence in the first 6 weeks has been shown to reach 30%, and this risk increases the earlier the first case of biliary BP occurs during pregnancy. (18,50)

The approach can be open, although it is currently being performed laparoscopically more frequently, whose benefits are: faster postoperative recovery, shorter hospitalization time, less postoperative pain, early refeeding, less uterine manipulation and less risk of deep vein thrombosis due to early mobilization. 18,58 There will be cases in which laparoscopic surgery will be converted to open surgery due to adhesions associated with cholecystitis. (34)

Pancreas surgery

According to Cheng Q et al. (2012), incision of the capsule of the pancreas, partial pancreatectomy, and peripancreatic and peritoneal drainage can be performed. It is used in cases of: severe infection, necrosis, and peripancreatic and peritoneal effusion. (14)

Pseudocyst-jejunostomy

It can also be pseudocystocyst-gastrostomy or pseudocyst-duodenostomy. Treatment is based on incision of the cyst surface and resection. Drainage should be performed at the deepest point of the cyst and anastomosed. This procedure causes morbidity of 16% and mortality of 2.5%. (60)

Indications for surgical treatment are: (60)

- Pressure of the great vessels
- Stomach or duodenum that produce clinical symptoms
- Bile duct stenosis or impaired bile flow with cholestasis
- Infection or bleeding from the cyst
- Bloating, vomiting, pain, and gastrointestinal bleeding

The relative indications are: (60)

- Pseudocysts larger than 4cm with change in size or shape
- Presence of pseudocysts for more than 6 weeks
- Percutaneous drainage

Only as an emergency procedure for acute fluid retention or infected cysts, with recurrence of 70%, its most frequent complication is percutaneous fistulas. This procedure may be performed in case of necrotizing pancreatitis to determine if it is sterile or infected. (10,60)

Endoscopy

In this approach, stenting is performed (transmural or transpapillary, transgastric or transduodenal). With an 80% success rate. The rate of mortality, recurrence and complications is 0.2-7 and 13%. Its main complication is stent occlusion. (60)

Laparoscopy

It presents better results than the endoscopic approach. However, it should not be performed in patients who are not suitable for general anesthesia and previous abdominal surgery. (60)

Necrosectomy

According to Bernal Hernández (2014), necrosectomy and empirical antibiotic treatment are indicated in the case of necrotizing AP. To take gram and culture from the sample, a percutaneous puncture is performed and it is defined if the sample is infected. At the same time, an antibiogram should be requested to treat the specific microorganism. If sterile, conservative treatment should be continued. Endoscopic necrosectomy is the recommended surgical approach, which offers better results than endoscopic transmural necrosectomy. (11)

Pregnancy resolution

Resolution of pregnancy as well as conservative management of pancreatitis are effective, most recommended in PAG and the procedure is performed by decompression of the organ without taking into account the fetus. In PAM, termination of pregnancy is not recommended. (57)

The principles of treatment in a pregnant patient follow the therapeutic guidelines for the general population. However, treatment decisions can be influenced by the timing and pathway of pregnancy resolution. (52)

In hypertriglyceridemia in pregnancy, continuous vigilance should be maintained, glycemia tests should be performed and the patient's management should be planned, since counseling is necessary. In the case of ECP and hypertriglyceridemia is refractory, early induction of labor or discharge resolution should be considered. (48)

The evidence suggests that there is no specific time for induction and resolution of labor, this should be taken into account in conjunction with endocrinologist, obstetrician and anesthesiologist, based on fetal development and maternal risk; preferably after the middle of the third trimester and as soon as possible after fetal maturity has been reached after 37 weeks. In case of the presence of hemorrhagic-necrotizing pancreatitis or BP due to hypertriglyceridemia, the pregnancy should end as soon as possible because it can cause maternal and fetal mortality. (2,5,48)

The indications for pregnancy resolution are: (7)

- Full-term pregnancy
- Deterioration of general clinical status after 24-48 hours of treatment.
- Paralytic ileus without improvement
- Stillbirth
- Fetal malformations
- Severe pancreatitis

- Severe fetal distress
- Increased intra-abdominal pressure refractory to treatment

*Vaginal*

Although the route of resolution of labor is a matter of controversy, according to Gonzalo et al., several studies establish that PAE does not affect the indication of the route of labor, and if there are no contraindications, vaginal delivery is preferred. (61)

According to a study carried out in 2014 by Bernal Hernández RG, there is a predominance of vaginal resolution of pregnancy, since there is a decrease in maternal morbidity due to a lower risk of infection or necrosis associated with laparotomy. But this decision must be made in conjunction with gastroenterologists, surgeons and obstetricians to avoid fetal loss. (4,41)

*Caesarean section*

Transperitoneal segmental cesarean section is the method of choice for resolution of labor. Currently, there is no defined consensus on the appropriate time for discharge resolution, since the patient must be individualized and the severity of pancreatitis and fetal maturation must be taken into account. In this case, cesarean section reduces perinatal mortality in patients with hypertriglyceridemia. According to a study entitled Multidisciplinary diagnosis and treatment of severe acute pancreatitis associated with hypertriglyceridemia in pregnancy: a case report in 2022 by Zheng et al., if there are 1 or more indications, cesarean section can prevent the clinical deterioration of the pregnant woman, and avoid maternal-fetal mortality and morbidity. If the fetus is of gestational age at term, the cesarean section should be performed as soon as possible. (7, 52)

Postpartum

In the study carried out in 2016 by Vishnu Priya KMN, the patients were followed for a year, and ERCP was performed on 2 patients, which had no complications. In cases of ALP, it is recommended to prolong the pregnancy and give conservative treatment. In biliary lithiasis, the picture can be resolved conservatively and in the postpartum period biliary pathology can be resolved and BP recurrences can be avoided in the future. (62)

In the case of presenting symptoms after the end of pregnancy, it is necessary to perform intensive support therapy, due to the physiological changes and the possible deterioration in this period of the mother. Among the conditions that can affect the mother are: rapid deterioration, accompanied by insufficient organ perfusion, excess inflammatory mediators and endotoxins. Therefore, to reduce autoimmune damage, blood therapy should be considered. (52)

## DISCUSSION

Acute pancreatitis is defined as acute inflammation of the pancreatic and peripancreatic tissue; which during pregnancy is a cause of abdominal pain and leads to local and systemic complications that affect fetal viability, and in its severe form leads to organ failure and death. (1,2,4,5,14-17)

Within the generalities of ECP, acute pancreatitis in pregnant women is a rare entity, but with a high incidence (1 per 1,000-12,000 pregnant women) compared to the general population, and is the cause of maternal-fetal morbidity and mortality. (3,5,8,15,18)

During pregnancy, there is a predisposition to BP linked to the eating behaviors that pregnant women present, even prior to pregnancy; as well as the increase in lipids and hormonal changes presented in the normal physiology of pregnancy. Therefore, pregnancy itself is a risk factor for developing PA; and as evidenced in the different studies, the main causes of this are biliary BP and hypertriglyceridemia. (3,4,5,11,49)

Several authors state that other causes of ECP should be considered, which, although less frequent, have also been reported as causing this pathology. Among these, cases of ECP associated with: hyperparathyroidism, trauma, drugs, infections, preeclampsia, fatty liver, hyperemesis gravidarum, among others, are reported. (1,2,10,12,15,17-19,21,22,25,36)

The risk factors for ECP are related to its origin, mainly associated with stasis and increased triglyceride and cholesterol concentrations, which predispose to the formation of gallstones. Hot et al. (2019) list several factors, including: multiparity, morbid obesity, preeclampsia, diabetes mellitus,

multiple pregnancy, and HELLP syndrome. Other authors also mention the use of oral contraceptives, high-fat diets, and a history of gallstones and hypertriglyceridemia as risk factors. (6,8,11,20)

According to the generalities of the ECP, the importance of recognizing it as a cause of morbidity and mortality is evident; due to the high incidence and association with the physiological changes of pregnancy, since it predisposes to the formation of gallstones and increased triglycerides, the main most frequent triggers of ECP.

The difficulty of the approach is due to the lack of diagnostic guidelines for acute pancreatitis during pregnancy, since the same guidelines and scales of the general population are used so far. Therefore, the diagnosis of ECP is based on the presence of 2 of 3 Atlanta criteria: clinical manifestations, laboratory tests, and imaging studies.

The first diagnostic criterion is based on the clinical presentation of BP, which is nonspecific and masked by the physiological changes of pregnancy. It is characterized by acute and persistent, progressive abdominal pain, located in the epigastrium and/or upper hemiabdomen; associated with vomiting, nausea, among others. (1,6,33-35)

In a retrospective study, they showed that ECP was more frequent during the third trimester (59.3%), followed by the second trimester (33.3%), and was less frequent in the first trimester (7.4%). These results are similar to the study carried out in India, with a predominance in the third quarter with 62.5%; therefore, it is concluded that it is more frequent as pregnancy progresses. (2,11,35)

Diagnosis is more difficult during the first trimester, because the symptoms of pregnancy are similar to the symptoms of ECP. Both the physiological and anatomical changes of pregnancy hinder the doctor's clinical evaluation. (36)

The second diagnostic criterion is laboratory tests, specifically elevation of amylase and/or lipase greater than or equal to 3 times their normal value; of which, the highest specificity is lipase, which remains elevated for up to 2 weeks; compared to amylase. (36)

To determine the etiology and severity of ECP, complementary tests should be requested; among them are mentioned: blood count, C-reactive protein (CRP), calcium, lipid profile and liver function tests. (1)

The third diagnostic criterion is imaging studies which, during pregnancy, the study of choice is abdominal ultrasound for the safety of the fetus. In addition, this method allows to rule out other causes of acute abdomen and evidences gallstones that are the main cause of ECP. (1,6,35)

Other imaging studies are indicated in specific situations. Fernández et al. (2017) suggest performing abdominal CT scans in pregnant women with PAG after 72 hours, APACHE II ≥8, RANSON>3, organ failure, or significant clinical deterioration. Because it has the Balthazar classification standardized by CT, this method is preferred in cases of greater severity. (1.34)

Another diagnostic alternative is MRI, which is performed in case of ECP due to choledocholithiasis, and is useful for persistent cholestasis, and to identify if there is obstruction of the bile duct. However, it is not recommended before 18 weeks of gestation. (1,18,33,35,43)

ERCP is used in the diagnosis and treatment of choledocholithiasis and its complications such as cholangitis, biliary stenosis, among others. (25,36,44)

In addition, in the diagnosis of ECP, the severity of the ECP must be taken into account, for this, the ATLANTA criteria are used, which categorizes BP as: mild if there is no organ dysfunction or generalized complications, moderate to severe or moderately severe in cases of pancreatitis with transient organ dysfunction or localized or generalized complication, and severe or severe if there is persistent organ dysfunction. (1,6,10,13)

The diagnosis of ECP is a challenge, therefore, a thorough diagnostic approach must be carried out. Several authors mention that other possible diagnoses must be considered, such as acute appendicitis and cholecystitis, hyperemesis gravidarum, gestational fatty liver, preeclampsia with severity data, uterine contractions, HELLP syndrome, among others. (16,32,42,45)

PAE is a multidisciplinary and individualized management entity that requires immediate hospitalization. According to the Atlanta, APACHE II and Ranson criteria of severity, medical treatment is initiated. The basic ECP measures of any etiology are summarized as IV hydration, gastric rest, and analgesia; broad-spectrum antibiotic treatment is only initiated in specific cases, especially associated with bacterial superinfection of PAG, necrotizing pancreatitis, peritoneal exudates, pseudocysts, abscesses, sepsis or cholangitis. (1,2,34,50)

Surgical treatment is used if there is no improvement in 24-48 hours, and delayed laparoscopic cholecystectomy is performed until the second trimester if it is of biliary origin; or discharge resolution of pregnancy if it is associated with another cause between the second and third trimester of pregnancy. (1,8,10)

During admission, maternal-fetal monitoring should be performed, fetal well-being should be evaluated, and the approach of both patients should be planned. To do this, it is necessary to consider the cause of ECP, the severity, the trimester of pregnancy, comorbidities, the presence of cholangitis and whether or not there is dilation of the bile duct. This guides the treating physician in the therapeutic approach to be performed, whether conservative, surgical or if there is fetal viability for resolution of the pregnancy. (18,50)

In pregnant women with PA, it is necessary to start early enteral feeding (before 48 h), as it can cause nutritional deficit in the mother and, therefore, in the fetus. If the patient presents clinical improvement and decreased inflammatory markers and pancreatic enzymes, it is considered to restart enteral feeding, emphasizing the disappearance of abdominal pain. (1,52)

In pregnant women with ECP due to hypertriglyceridemia, the treatment of choice is conservative. It is diet-based and symptomatic. Subsequently, a low-fat diet with a low glycemic index and omega-3 acids is followed. If the patient has refractory BP or severe cases, fibrates, low molecular weight heparin and insulin infusion are considered, and in more severe cases, after considering maternal-fetal risk, plasmapheresis. If the condition continues despite all these measures, it is considered to terminate the pregnancy. (48,52,54)

ECP of biliary origin can be addressed by surgical treatment. It is indicated at risk of recurrence due to multiple lithiasis and associated with acute cholecystitis. Surgery is recommended when there are symptoms and to avoid obstruction of the biliary tract, ascending cholangitis, acute abdomen or recurrence. It can be performed in all trimesters, but preferably it should be delayed to the second trimester and in the immediate postpartum period in case of BP in the third trimester, by laparoscopic cholecystectomy at the time of the swelling subside. (1,18,34,40,50,51)

Patients with asymptomatic cholelithiasis can be reserved for expectant management, although according to a study by Ríos-Cruz et al. in 2015, they show that after 2 years of diagnosis, patients have undergone surgery. (18,59)

In case there is a contraindication to surgery, cholangitis, jaundice or choledocholithiasis; as an alternative approach to biliary BP, ERCP with sphincterotomy can be performed in the second and third trimesters. (1,34,40)

The other type of surgical approach is associated with the management of local complications of PA, which are: hemorrhage, abscess, pseudocyst, and sterile or infected necrosis. According to Cheng Q et al. in 2012, it can be addressed by incision of the pancreas capsule, partial pancreatectomy, and peripancreatic and peritoneal drainage. Other surgical options are laparoscopic and endoscopic. Surgery is reserved in cases of severe infection, necrosis, and peripancreatic and peritoneal effusion. (10,14,60)

## CONCLUSION

Recent advances in understanding acute pancreatitis in pregnancy have led to a significant reduction of less than 5% in maternal-fetal mortality. Despite this, specific clinical guidelines are lacking. More research is needed to develop standardized treatment protocols that can optimize outcomes for both mother and fetus.

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**Contributions:**

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