

Original Article

Acute cholecystitis in pregnant women: A therapeutic challenge in a developing country center

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Backgrounds/Aims: Acute cholecystitis is a rare condition in pregnant women, potentially affecting the maternal and fetal prognosis. Our aim was to report the main clinical and paraclinical features of acute cholecystitis during pregnancy and therapeutic modalities.

Methods: We conducted a case series analysis recording pregnant patients with acute cholecystitis admitted to our surgery department over a period of 11 years. We collected clinical data, paraclinical features, and management modalities related to cholecystitis.

Results: There were 47 patients. Twenty-eight percent was in the first trimester of pregnancy, 40% in the second, and 32% in the third trimester. Abdominal pain was located in the right hypochondrium in 75% of cases. Fever was noted in 21% of cases. C-reactive protein was elevated in 39% of patients. Cholestasis markers were high in four patients. Abdominal ultrasound showed a distended gallbladder in 39 patients, with thickened wall in 34 patients, and gallbladder lithiasis in all cases. No patient had a dilated main bile duct. All patients received intravenous antibiotic therapy. Tocolysis was indicated in 32 patients. Laparoscopic cholecystectomy was performed in 32 cases (68%), and open cholecystectomy in 15 cases (32%). Postoperative course was uneventful in 42 patients, and complicated in 5 patients. Rate of complications was statistically higher after open cholecystectomy ($p = 0.003$). Morbidity rate was higher in the third trimester ($p = 0.003$).

Conclusions: Delay in the diagnosis of acute cholecystitis during pregnancy can lead to serious complications. Management is based on antibiotic therapy and cholecystectomy. Laparoscopic cholecystectomy appears to be less morbid than open cholecystectomy.

Key Words: Cholelithiasis; Cholecystectomy; Laparotomy; Laparoscopy; Pregnancy

INTRODUCTION

Despite the increasing risk of developing biliary lithiasis during pregnancy, acute cholecystitis remains a rare condition in pregnant women [1,2]. It represents a medical, surgical emergency, and often an obstetrical problem that can threaten the vital prognosis of both mother and fetus. Symptoms are often similar to cholecystitis outside of pregnancy, but sometimes

mimic those of other abdominal or obstetrical conditions. While the diagnosis is often easily confirmed, the therapeutic decision is not [3].

The purpose of our study was to report the clinical and paraclinical features of acute cholecystitis during pregnancy, as well as the therapeutic modalities. This is a retrospective study based on data from medical records granted from institutional ethical committee (grant no. 210603).

MATERIALS AND METHODS

Study design

We conducted a one-center retrospective and descriptive study over a period of 11 years from January 2009 to December 2019. This is a retrospective study based on data from medical records granted from institutional ethical committee.

Received: March 8, 2023, **Revised:** June 21, 2023,
Accepted: June 24, 2023, **Published online:** November 2, 2023

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Study population

The study included all patients admitted for acute cholecystitis during pregnancy. Patients admitted for acute cholecystitis in the postpartum period were not included. Patients with missing data on medical records or operative reports were excluded.

Data collection

The following data were collected from medical records and operative reports: socio-demographic, clinical, biological, radiological, obstetrical, and therapeutic data, as well as therapeutic outcomes.

Statistical analysis

Data entry and analysis were performed using Statistical Package for Social Sciences (SPSS) version 23.0 software (IBM Corp.).

For the statistical analyses, we calculated percentages, and means with standard deviation. We used cross-tabulation analysis for categorical data and compared means for continuous variables. The *p* was considered statistically significant when the value was less than 0.05.

RESULTS

Clinical features

There were 47 patients. The mean age was 29.8 ± 5.7 years, with ages ranging 18 to 45 years. Seven patients were diabetic, and one patient had had an appendectomy. Fifty-five percent of patients had multiple gestations, and 49% were multiparous. The mean term of pregnancy was 20.9 ± 8.8 weeks, with terms ranging 8 to 34 weeks. Twenty-eight percent was in the first trimester of pregnancy, 40% in the second trimester, and 32% in the third trimester. Abdominal pain was the main symptom in all cases. This pain was located in the right hypochondrium in 75% of cases, and in the epigastrium in 25% of cases. Fever was noted in 2.1% of patients. Thirty per cent of patients presented nausea or vomiting. There was no icterus. Right hypochondrium or epigastrium guarding was noted in 3 patients. A palpable mass in the right hypochondrium was noted in only one patient.

Biological findings

The mean white blood cell count was $10,338 \pm 2,926$ elements per mm^3 . Seven patients had hyperleukocytosis. The mean hemoglobin was 12.47 ± 1 g/dL. Two patients were anemic. No patient had thrombocytopenia. The mean C-reactive protein (CRP) was 13.05 ± 13.94 g/L, and CRP was elevated in 39% of patients. No patient had liver cytolysis. Cholestasis markers were high in four patients. No patient had hyperbilirubinemia. Table 1 presents the laboratory findings.

Radiological findings

Abdominal ultrasound was conducted in all patients, showed gallbladder lithiasis in all cases, gallbladder distension in 39 patients (83%), and a thickened wall in 34 patients (72%). No patient had a dilated main bile duct. The mean main bile duct diameter was 4.8 ± 0.7 mm. Peri-vesicular effusion was noted in 6 patients (13%). Hepatic and pancreas parenchyma were normal in all cases. No abdominal scan or magnetic resonance imaging was performed.

Obstetrical findings

On admission, all patients had a gynecological examination with obstetric ultrasound, which examinations were normal in all cases.

Therapeutic management

On admission, all patients were initiated on a broad spectrum intravenous antibiotic therapy. The most commonly used molecule was Cefotaxime in 85% of cases. Average duration of antibiotic therapy was 6.3 ± 1 days with duration ranging 4 to 10 days. Antispasmodics were used in 41 patients (87%). Tocolysis was indicated in 32 patients (68%).

The approach technique, open or laparoscopic, was decided after collegial discussion, on a case-by-case basis, and after consensus between the surgeon and patient. Cholecystectomy was performed by laparoscopy in 32 cases (68%), and by laparotomy in 15 cases (32%). Two cases of conversion from laparoscopic to open cholecystectomy were noted in 32 cases, due to dissection difficulties.

Subcostal incision was used in all cases of open surgery. Four trocars were used in all cases of laparoscopy, which was the department's standard method in all cases of acute cholecystitis.

Of 13 patients operated on during the first trimester of pregnancy, only one patient underwent an open cholecystectomy; this was a conversion case from laparoscopic to open approach.

Table 1. Laboratory assessment of pregnant women with acute cholecystitis

Biologic parameter	Mean \pm standard deviation	Extremes
WBC (elements/ mm^3)	$10,338 \pm 2,926$	6,800–16,500
Hb (g/dL)	12.5 ± 1	10–14.3
CRP (mg/L)	13.1 ± 13.9	2–80
AST (UI/L)	21.7 ± 6.6	14–33
ALT (UI/L)	14.1 ± 5.4	1–26
GGT (UI/L)	70.6 ± 123.8	10–292
ALP (UI/L)	92.5 ± 51	44–163
Total bilirubine ($\mu\text{mol/L}$)	6.1 ± 2.5	4–17

WBC, white blood cells; Hb, hemoglobin, CRP, C-reactive protein; AST, aspartate aminotransferase; ALT, alanine aminotransferase; GGT, gamma-glutamyl transferase; ALP, alkaline phosphatase.

Table 2. Postoperative outcome according to the surgical approach

	Laparoscopy (n = 30)	Laparotomy (n = 17)	<i>p</i> -value
Complications	0 (0)	5 (31)	0.003
Premature delivery		2	
Biloma		1	
Surgical site infection		1	
Iliac vein thrombosis		1	
Average stay (day)	7.8 ± 2.5	10.1 ± 6	0.160

Values are presented as number (%), number only, or mean ± standard deviation.

p-value: statistical significance.

Of 19 patients operated on during the second trimester of pregnancy, seven patients underwent an open cholecystectomy (37%). There was one conversion case from laparoscopic to open approach.

Of 15 patients operated on during the third trimester of pregnancy, nine patients underwent an open cholecystectomy (60%).

The most common macroscopic form of cholecystitis was gallbladder hydrops in 23 cases (49%), followed by suppurative gallbladder in 16 cases (34%), then gangrenous cholecystitis in 8 cases (17%). Retrograde cholecystectomy was performed in 64% of cases, and antegrade in 36%.

A peri-vesicular abscess was found and drained in three cases (6%). No cases of hepatic abscesses, or purulent or biliary peritonitis were reported. Intraoperative cholangiography via a trans-cystic drain was performed in four patients (8%), for cholestasis on liver biological assessment, and was normal in all cases. The number of images was limited to two in all cases, with protective measures for the fetus being taken with a lead gown. No trans-cystic drain was kept. No cases of intraoperative incidents were reported.

Postoperative outcomes

Postoperative course was simple in 42 patients (92%). Postoperative antibiotic therapy was noted in 31 patients. The main indication was the gallbladder intraoperative local condition in 24 cases. In 7 cases, postoperative antibiotic therapy was not justified. Postoperative complications were noted in five patients (8%), all after open cholecystectomy. There were 3 medical/surgical complications: A biloma in one case, surgical site infection on a right sub-costal wound in one patient, and iliac vein thrombosis in one patient.

There were 2 obstetrical complications: Premature delivery by cesarean section in two patients with fetal distress: the first patient delivered at 33 weeks. The cholecystitis diagnosis was made 72 hours after the symptoms onset that it had been evolving for more. The initial biological assessment was normal. A gallbladder hydrops was found intraoperatively. The second patient delivered at 34 weeks. Her symptoms had also been

Table 3. Postoperative outcome according to trimester

	First trimester (n = 13)	Second trimester (n = 19)	Third trimester (n = 15)	<i>p</i> -value
Complications	0 (0)	0 (0)	5 (33)	0.003
Average stay (day)	7.3 ± 2.6	9.6 ± 2.3	10.4 ± 6	0.110

Values are presented as number (%) or mean ± standard deviation.

p-value: statistical significance.

evolving for more than 72 hours. Hyperleukocytosis and a high CRP level were noted in the biological assessment. A suppurative gallbladder was found intraoperatively.

There were no complications after laparoscopic cholecystectomy. Postoperative obstetrical examination follow-up did not reveal any abnormality, and pregnancy was carried to term in 45 patients.

Analyzing the association between surgical approach and complications (Table 2), it appears that open cholecystectomy was statistically related to the occurrence of complications ($p = 0.003$), taking into consideration that the two conversion cases were assigned to open cholecystectomy group. Also, postoperative morbidity was higher in the third trimester of pregnancy ($p = 0.003$) (Table 3).

All the complication cases occurred in the third trimester of pregnancy. Five cases of complications were observed after open surgery (56%). There were no reported complications after laparoscopic cholecystectomy. The comparison between laparoscopic and open approach in terms of postoperative morbidity in the third trimester revealed a statistically significant morbidity rate after open surgery ($p = 0.02$).

The average hospital stay was 9.2 ± 4 days, with stays ranging 4 to 30 days. The average intensive care unit stay was 1.2 ± 0.6 days, with stays ranging 1 to 4 days.

DISCUSSION

Our work is of considerable importance for several reasons: the rarity of acute cholecystitis during pregnancy (the average is 4 cases per year in our center); the management particularities requiring cooperation between the surgeon, radiologist, and obstetricians; and the absence of any management consensus of acute cholecystitis in pregnant women.

Indeed, acute cholecystitis is a relatively rare emergency in pregnancy. Its incidence has been estimated at 0.2 to 0.5/1,000 pregnancies [1]. The incidence may be higher in some countries, as in Saudi Arabia (0.39%). This may be attributed to a high number of repeat pregnancies and genetic predisposition [1]. Additionally, quiescent gallstones may become active during pregnancy [4].

Symptoms of acute cholecystitis during pregnancy are not different from the general population [5]. Presentation usually

begins with abdominal pain localized commonly in the right hypochondrium, or in the epigastrium. Hepatic colic may radiate to the right scapula. Fatty or large meal after fasting may precipitate acute cholangitis. One in two patients may have nausea and vomiting. Moreover, 70%–80% of patients may report a history of vesicular lithiasis and/or liver colic attacks [6].

Findings on physical examination vary according to the gravity of cholecystitis. Fever is above 38°C in 30% of cases [7]. Many signs may be noted, such as abdominal guarding in the right upper quadrant, Murphy's sign that is rarely observed in pregnant women, or fever, and tachycardia [8].

There are no specific biological elements for diagnosis. If cholecystitis is suspected, the patient must be hospitalized. The difficulty in making the diagnosis lies in the fact that there is a physiological hyperleukocytosis reaching 20,000 elements/mL, especially in late pregnancy. CRP is significantly elevated, with suspected bacterial infection when its value is above 40 IU/L [9].

Serum bilirubin and transaminases may be elevated, as in non-pregnant women. Bilirubin elevation above 4 mg/dL may be found in the absence of any complications. Serum alkaline phosphatase is less useful, because it can be falsely elevated by estrogen [10]. Abdominal ultrasound is the first line investigation for suspected acute cholecystitis. It has a sensitivity of 50% to 88%, and a specificity of 80% to 88% [9].

Gallbladder morphology can be studied by ultrasound in 95% to 98% of cases during pregnancy. Sludge or gallstones are visible on ultrasound in 30% of pregnant patients [11]. The most suggestive ultrasound signs are thickening of the wall thickening (5 mm or more), peri-vesicular effusion, and ultrasound Murphy's sign (sensitivity: 63%; specificity: 93%) [12]. Other signs are vesicular distension, identification of stones, and the presence of air bubbles [9]. The use of Doppler would increase the performance of abdominal ultrasound in the diagnosis of acute cholecystitis [13]. Another element that should be looked for and excluded is obstruction of the main biliary duct, as this changes the therapeutic approach. Abdominal Scan should not be performed because of its lower sensitivity and specificity than ultrasound, with an unnecessary risk of radiation in pregnant women [14].

Magnetic resonance cholangiopancreatography can be particularly useful in the differentiation of biliary main duct stones from intrahepatic cholestasis in pregnancy [15]. It can also differentiate between stones in the biliary main duct, and external compression second to Mirizzi's syndrome [15].

Colic pain may increase premature contractions, then causing miscarriage and in utero fetal death [16].

In our series, the diagnosis was made easily in 43 patients, involving a combination of clinical, biological, and especially ultrasound findings. In the 4 cases where there was cholestasis in the biological assessment, the ultrasound did not show bile duct dilatation. Biliary MRI was not performed, because it was not available. The decision was to perform cholecystectomy with intraoperative cholangiography.

The medical component of management is based on rest, hydration, correction of possible fluid disorders, antibiotics, and antispasmodics. Antibiotic therapy must target an optimal infection control, while taking into account the exposure of the fetus [17].

With medical treatment, cholecystectomy may be delayed to the second trimester, which is characterized by a lower rate of spontaneous abortion (12% in the first trimester, 5.6% in the second trimester) [18]. In addition, the risk of preterm delivery is none in the second trimester. However, this risk can raise to 40% in the third trimester [18].

Few antibiotics are approved during pregnancy [19]. Third generation cephalosporins have a real advantage in that their use can be envisaged whatever the term of the pregnancy. An antibiotic that is active against Gram-negative germs and has good biliary distribution must be administered to all acute lithiasis cholecystitis before surgical management, except for the paucisymptomatic cholecystitis forms [13]. In all cases, and especially in severe forms, it is necessary to have, a bacteriology by blood culture or bile sample [13]. Postoperative antibiotic treatment is not necessary, except in cholecystitis in high-risk individuals or severe forms [13]. Medical treatment alone is often ineffective: in Swisher et al. [18], it resulted in failure in 44% of cases.

All elements in the recent literature show that a non-surgical approach for acute cholecystitis may be responsible for preterm recurrence risk requiring one or more re-hospitalizations, in addition to spontaneous abortion and premature delivery, in comparison with patients who had cholecystectomy [14,20]. In our series, there was no patient who had exclusive medical treatment.

Concerning the surgical components of management, it is difficult to recommend a surgical approach. In the literature, the outcomes for mother and fetus seem to be similar for laparoscopic cholecystectomy and open cholecystectomy. Therefore, there were no significant increasing morbidity and mortality rates with laparoscopic cholecystectomy, which constitutes a good prognostic element [21].

Our center's attitude was to operate on all patients after conditioning and antibiotic therapy targeting biliary tropic germs.

According to the literature, the advantages of laparoscopy are a significantly reduced hospital stay (3.7 vs. 6.2 days for conventional surgery), reduced consumption of narcotics, and a quicker return to enteral feeding [22]. In addition, there is less manipulation of the uterus. It also reduces deep vein thrombosis in the postoperative period and reduces the risk of abortion in the first trimester and prematurity in the third trimester [23,24].

In our series, the surgical approach was decided after consensus between the surgeon and the patient, with a tendency to perform an open cholecystectomy in patients with an advanced pregnancy term.

In our series, the maternal-fetal morbidity rate was higher in

the laparotomy group ($p = 0.003$). However, this result may be related to a selection bias, as the average term of patients who had open cholecystectomy was higher than the average term of patients who had laparoscopic cholecystectomy.

Considering our series' findings, as well as our center's particularities, abdominal ultrasonography remains the main morphological examination to make the positive diagnosis of acute cholecystitis in pregnant women, and to eliminate differential diagnoses, such as HELLP syndrome. A well-conducted ultrasound examination might substitute for an irradiated abdominal CT scan or an MRI examination, which is often not available. The conservative attitude, which consists of antibiotic therapy associated with intensive abdominal and obstetrical surveillance, aiming to delay cholecystectomy to the postpartum period, currently has a limited place. It requires long hospitalization with frequent monitoring and observation, which is sometimes difficult to provide by some centers in developing countries. The failure rate of this approach is quite high. The surgical approach combined with obstetrical assistance is the most preferred approach, as it has proven to be efficient. Cholangiography is an accessible and low-irradiation examination that could be performed in the case of suspected main bile duct lithiasis associated with acute cholecystitis. Laparoscopic cholecystectomy seems to be as safe as open cholecystectomy, but it may need expertise to be performed in a late pregnancy term. Our study results may present a confusion bias: are the higher complications related to the surgical approach, or to the late term of pregnancy?

Good cooperation between surgeons and obstetricians is crucial to avoid obstetrical complications and/or to rapidly diagnose them to optimize their management.

Conclusion

Acute cholecystitis occurs rarely during pregnancy. Diagnosis is often easy considering the typical clinical presentation, but delay in the diagnosis can lead to serious complications for both mother and fetus. Therapeutic modalities are based on antibiotic therapy and urgent cholecystectomy. The laparoscopic approach seems to be safe to perform cholecystectomy in pregnant women. However, this approach may be less easy to achieve in the third trimester of pregnancy and necessitates a certain level of expertise.

FUNDING

None.

CONFLICT OF INTEREST

No potential conflict of interest relevant to this article was reported.

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AUTHOR CONTRIBUTIONS

Conceptualization: MFM. Data curation: ABD. Methodology: BR, YK. Visualization: NE. Writing - original draft: MM. Writing - review & editing: MBM.

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