

# Acute biliary pancreatitis during pregnancy and in the post-delivery period

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## ABSTRACT

**BACKGROUND:** Acute pancreatitis has an incidence of approximately 1 in 1000 to 5000 pregnancies, and is most often seen in the third trimester or the postpartum period. The most common cause of pregnancy-related acute pancreatitis is cholelithiasis, which accounts for more than 65% of cases. The aim of this study was to present a detailed analysis of 4 years of experience with cases of acute biliary pancreatitis related to pregnancy from a single center.

**METHODS:** The medical records of 55 consecutive patients who were hospitalized in the emergency surgery clinic for acute biliary pancreatitis related to pregnancy between January 1, 2014 and January 1, 2018 were examined in this single-center, retrospective study.

**RESULTS:** Fifty-five patients with acute biliary pancreatitis related to pregnancy were included in the study. Of the 55 women, 13 (24%) were in the pregnant group, 28 (51%) in the postpartum (6 weeks) group, and 14 (25%) were in the 1-year (6 weeks-1 year) group. There was no statistically significant difference between the 3 groups. The most appropriate treatment for each patient was targeted. Six (10%) patients had recurrent acute pancreatitis. There was no maternal or fetal mortality or morbidity.

**CONCLUSION:** Acute biliary pancreatitis related to pregnancy is not limited to pregnant women, and the incidence of these cases was greater than expected. Acute biliary pancreatitis related to pregnancy can be successfully managed with conservative treatment because it usually has a mild to moderate clinical course. However, the surgeon should keep an early cholecystectomy in mind for patients other than those in the first trimester.

**Keywords:** Acute pancreatitis; management; pregnancy; prognosis.

## INTRODUCTION

The physiological changes that usually occur during pregnancy may change the process, symptoms, and signs of many diseases. It also affects the accuracy and reliability of many diagnostic tests. While early diagnosis of diseases becomes more challenging, the results and prognosis can also worsen. Also, serious emergency surgical conditions, such as acute pancreatitis (AP), are difficult to diagnose during pregnancy and in the postpartum period. The symptoms may be misleading and considered normal in pregnancy.<sup>[1]</sup> Also, pregnancy is an exclusion criterion in some AP studies.<sup>[2]</sup>

The incidence rate of pregnancy-related biliary colic, acute cholecystitis, acute biliary pancreatitis, or acute cholangitis is between 0.05% and 8%.<sup>[1]</sup> AP usually occurs with an incidence of approximately one in 1000–5000 pregnancies, particularly in the third trimester or the postpartum period.<sup>[1,3,4]</sup> During pregnancy, changes in the bile composition and gall bladder mobility lead to the formation of gall bladder stones.<sup>[5]</sup> Cholelithiasis is the most common cause of pregnancy-related AP, which accounts for more than 65% of cases.<sup>[6]</sup> A gallstone passing through the ampulla of Vater leads to AP.

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If AP is not correctly diagnosed and treated, it can lead to pancreatic necrosis, abscess, and multiple organ dysfunction and subsequently maternal and fetal morbidity and mortality.<sup>[7–9]</sup> Despite the issues, there are no guidelines currently available for AP diagnosis and management in pregnant women. In addition, a gallstone disease (acute cholecystitis, choledocholithiasis, cholangitis, or gallstone pancreatitis) is the most common cause of maternal hospitalization in the first year after delivery.<sup>[10]</sup> Particularly, acute biliary pancreatitis related to pregnancy (ABPP) has a relatively high recurrence rate of 70% in pregnant women compared to the general population (20–30%).<sup>[2,6]</sup>

For the management of ABPP, the physician should consider maternal and fetal risks associated with irradiation using endoscopic retrograde cholangiopancreatography (ERCP), imaging methods, medical treatment, general anesthesia, and surgery. Laparoscopic cholecystectomy (LC) reduces the morbidity of surgical treatment in ABPP patients. In this study, medical data, management, and outcomes of women with ABPP were examined.

## MATERIALS AND METHODS

### Study Ethics

The clinical study protocol was approved by the Institutional Ethics Committee of University of Health Sciences, Okmeydanı Training and Research Hospital. The study was performed according to the principles of the Helsinki Declaration. All the patients were routinely informed about the procedures and provided their written informed consent (no: 09.01.2018/806).

### Study Design

In this single center retrospective study, medical records of the patients who were hospitalized in the Emergency Surgery Clinic for ABPP between January 1, 2014, and January 1, 2018 were examined. The patients were divided into three groups: (1) pregnancy; (2) postpartum; and (3) the first year after delivery. Patients with non-biliary AP and those with acute cholecystitis, choledocholithiasis, or acute cholangitis were excluded from the study. Pregnancy was grouped as the first (0–13 weeks), second (14–26), and third (27–40 weeks) trimesters. Infants who were born before the end of week 37 were considered premature, while a pregnancy was considered full term at 40 weeks. For an AP diagnosis, at least two of the following three criteria were stipulated: (1) acute abdominal pain; (2) serum lipase activity (or amylase activity) at least three-fold greater than the upper limit of the normal reference range; and (3) radiological AP findings. The ABPP severity was determined using the 0- and 48 h Ranson scores. Abdominal ultrasonography (USG) was performed on all patients by radiologists. Magnetic resonance cholangiopancreatography (MRCP) was performed in patients with high bilirubin levels or in those who had abnormal biliary channel signs detected in USG.

ERCP was performed in patients with the evidence of stones in the common bile duct (CBD). The following parameters were reviewed: the patient's age, pregnancy trimester, AP severity, risk factors such as hormonal therapy, *in vitro* fertilization (IVF) procedure, multiparity, obesity and diabetes mellitus, imaging modalities, results of biochemical tests, treatment methods, length of hospital stay (LOS), and maternal or fetal morbidity and mortality.

The medical data from maternal and fetal obstetric evaluations that were performed on a monthly basis by the gynecologist were reviewed. The infant's height and weight at birth, gestational week, and physical examination findings were evaluated.

The mainstay of management in ABPP patients consisted of conservative treatment in the first trimester; LC in the second trimester; conservative treatment or endoscopic sphincterotomy (ES) via ERCP in the third trimester, and LC in the postpartum period in our clinic. The follow-up of the patients was continued until the first year after delivery.

### Statistical Analysis

The data analysis was carried out using the Statistical Package for Social Sciences (SPSS®) software, version 15.0 (IBM® Corp., Armonk, NY, USA). All values were expressed as mean ± standard deviation or number (percentage). The data were compared between subgroups using ANOVA (SPSS software, version 15). A p value of <0.05 was considered statistically significant.

## RESULTS

In total, 55 patients with ABPP were included in the study, of which 13 (24%) were in the pregnant group, 28 (51%) in the postpartum (6 weeks) group, and 14 (25%) in the 1 year (6 weeks–1 year) group. During the same 4-year period, 15,229 deliveries were reported at our center. The incidence of ABPP was one case per 1171 pregnancies during pregnancy, and if the total patients in the three groups were considered, the incidence of ABPP was calculated as one case per 277 pregnancies. Overall, 86% of the patients in the 1 year group had ABPP within the first 6 months after birth. Epigastric pain was the main complaint in all patients and 43 (78%) patients had nausea and vomiting. All the patients had high serum lipase and amylase activity (at least three-fold greater than the upper limit of the normal reference range) and biliary pathology detected in abdominal USG.

Seven of 13 pregnant patients were in the third trimester and five were in the second trimester. There was only one woman in the first trimester. The mean age of the patients was 28.93±6.3 (range, 18–45) years, with no significant difference between the pregnancy, postpartum, and the first-year groups (31.8±6.2, 28.1±6.5, and 27.9±5.6 days, respectively,  $p>0.05$ ).

**Table 1.** Characteristics of the patients with ABPP

Groups	Pregnant	Postpartum	One year	Total
Patients, n (%)	13 (24)	28 (51)	14 (25)	55 (100)
Maternal age, years (Mean±SD)	31.8±6.2	28.1±6.5	27.9±5.6	28.93±6.3
Multiparity, n (%)	13 (100)	18 (64)	8 (57)	39 (71)
Parity (Mean±SD)	3.5±2.2	1.9±1.1	2.1±1.1	2.4±1.6
Ranson score (Mean±SD)	0.3±0.5	0.6±0.9	0.9±0.9	0.62±0.8
Recurrence, n (%)	3 (23)	3 (10)	–	6 (11)
Length of the hospital stay, days (Mean±SD)	5.0±1.0	4.5±1.3	4.5±0.9	4.6±1.1

ABPP: Acute biliary pancreatitis related to pregnancy; SD: Standard deviation.

When all patients were considered, 39 (71%) women were multiparous and two had undergone IVF treatment for pregnancy. Other risk factors in the total patients with ABPP included morbid obesity (n=2), preeclampsia (n=2), diabetes mellitus (n=2), multiple (twin) pregnancies (n=1), and hemolysis, elevated liver enzymes, and low platelet count (HELLP) syndrome (n=1).

When the patients were evaluated according to the Ranson system, they usually had mild pancreatitis. Thirty-one (56%) patients had a Ranson score level (RSL) of 0, 15 (27%) patients had 1, eight (15%) patients had 2, and one (2%) patient had 3. No significant differences were found between the groups in terms of age, multiparity, parity, and RSL. The characteristics of patients with ABPP are presented in Table 1. However, pregnant women with ABPP were older, and more number of parities but lower mean RSL than women with ABPP in the postpartum and 1-year groups was observed. The mean RSL was 0.62±0.8 (3–9) days with no significant differences between the three groups (pregnancy, 0.3±0.5; postpartum, 0.6±0.9, and first year after delivery, 0.9±0.9,  $p>0.05$ ). The mean LOS was 4.6±1.1 (range, 3–9) days with no significant differences between the pregnancy, postpartum, and the 1-year groups (5.0±1.0, 4.5±1.3, and 4.5±0.9 days, respectively,  $p>0.05$ ). A total of six (10%) patients (three in the pregnant group and three in the postpartum group had recurrent ABPP.

LC was used for three pregnant women in their second trimesters. ES via ERCP was applied to four women in their third trimesters. Two of these patients had had previous cholecystectomies, and three patients had recurrent ABPP. Eight patients in the pregnant group underwent planned LC in the first 6 months after birth.

Only a 44-year-old female in the postpartum group had acute necrotizing pancreatitis. There were stones in the CBD, as detected in the MRCP imaging. This patient underwent percutaneous drainage, and stones were removed by standard techniques using ERCP. A 36 year-old multiparous (three children) patient with preeclampsia and Class II HELLP syn-

drome had ABPP in the postpartum period. This patient underwent conservative treatment and ES via ERCP followed by LC. LC was performed in 21 (75%) of the 28 patients in the postpartum group and 11 (78.5%) of the 14 patients in the 1-year group. ES via ERCP and LC were performed in three patients with recurrent ABPP in the postpartum group. There were no postoperative or post-ERCP procedural complications.

Of the 13 patients who were pregnant, 10 (77%) had normal vaginal delivery and three (27%) had cesarean delivery. There was no fetal or maternal mortality. Seven (54%) patients with ABPP in the pregnant group had high risk pregnancies because of advanced age (>35 years, n=4), morbid obesity (n=1), twin pregnancy (n=1), and preeclampsia (n=1). Eleven patients had full-term births, while two patients had premature labor. One of them was a 45-year-old woman who was morbidly obese and multiparous (six children and one abortion) and the other was a 25-year-old multiparous woman (three children) with preeclampsia.

## DISCUSSION

Studies have shown that the use of oral contraceptives and multiparity increase the risk of biliary stasis and therefore leads to gallstones formation.<sup>[11,12]</sup> The gallbladder motility disorder continues for about 1 year after delivery. The frequency of pregnancy and multiparity are the major risk factors for cholesterol gallstones. As the number of pregnancies increased, gallstone-related diseases also increased.<sup>[11,13]</sup> In this study, multiparity was detected in most of the patients (71%). Furthermore, all patients in the pregnant group were multiparous.

ABPP has a high likelihood of recurrence. However, it is possible to prevent the recurrence by the early diagnosis and optimal treatment. For this reason, the etiology should be prioritized in the management of ABPP patients.<sup>[8,14]</sup> In the present study, six (10%) patients had recurrent ABPP. Five patients with recurrent ABPP were multiparous, and a primiparous patient had undergone IVF to induce pregnancy.

USG is a highly reliable modality with approximately 100% sensitivity and specificity to diagnose gallbladder diseases in pregnant women.<sup>[15]</sup> Therefore, USG is the first-referenced imaging method to elucidate the etiology of biliary pancreatitis and confirm it in patients whose diagnosis was compatible with pancreatitis based on the clinical signs and laboratory parameters. In the present study, USG proved to be reliable once again by detecting biliary pathology in all patients.

Abdominal computed tomography (CT) is the most commonly used imaging modality to determine the severity of AP. However, it is not recommended in all trimesters, particularly to prevent the fetus from being exposed to radiation.<sup>[8]</sup> A CT scan was used for only one patient with an increase in the 48-h Ranson score to level 3. A 27-year-old postpartum patient who had single peripancreatic fluid collection seen in the CT scan underwent LC. The effects of non-contrast MRCP on the fetus during pregnancy are unknown. However, it is not recommended to use this method in the first trimester. Data in the fetal safety are limited during this period. The administration of gadolinium during pregnancy is controversial, and the physician should be aware of the fact that it is not used unless absolutely necessary.<sup>[16,17]</sup> However, MRCP is useful for detecting gallstones in the CBD, while CT and USG modalities have low sensitivities in this regard.<sup>[18]</sup>

ERCP is used for diagnostic and therapeutic purposes. This method is particularly useful for detecting the presence of small gallstones in the CBD. In addition, many studies have reported that ERCP and ES can be safely performed in pregnant women.<sup>[19]</sup> In the present study, ES via ERCP were successfully carried out in 13 (24%) patients without any complications. The Ranson criteria comprise one of the oldest scoring systems for assessing the severity and mortality of AP. However, it is still used safely today.<sup>[20,21]</sup> While the criteria with 11 parameters are used to score acute alcoholic pancreatitis, the modified Ranson criteria with 10 parameters are used to score acute biliary pancreatitis. In the present study, the AP severity was evaluated according to the Ranson scoring system, and most of the patients had mild ABPP. The absence of mortality and morbidity in the patients supported the accuracy of the Ranson scoring system.

Hospitalization, supportive treatment, intravenous fluid therapy, and nutritional supplements such as probiotics, glutamine, omega-3 fatty acids, and vitamins are preferred for the initial ABPP management. Most patients recovered well with the appropriate treatment and support.<sup>[22]</sup> In addition, the components of conservative treatment include pain control and antibiotic therapy (depending on the clinical picture). Antibiotic therapy is recommended when there is a biliary infection or infected necrotizing pancreatitis accompanied by ABPP.<sup>[23]</sup>

However, the management was difficult in patients with comorbid factors, such as morbid obesity, diabetes mellitus,

preeclampsia, and HELLP syndrome. These patients should be managed by a multidisciplinary team with experienced surgeons working at high-volume centers. There was no significant difference in the maternal mortality when conservative and surgical treatments were compared, but fetal mortality was significantly higher in patients who did not rapidly benefit from the supportive treatment.<sup>[24]</sup> ERCP and ES, biliary stent placement, or cholecystectomy should be performed in patients who do not respond quickly to supportive therapy and in those with acute cholangitis during follow-up. To avoid recurrences and reduce costs, cholecystectomy can be performed in patients with mild ABPP who recover during the hospital stay.<sup>[25]</sup> Cholecystectomy may be performed safely, focusing on pregnant patients' changing anatomy and not harming the fetus, although this technique can be challenging in pregnant patients, particularly in the last weeks of the third trimester.<sup>[26]</sup> Undoubtedly, the surgical treatment by experienced surgeons working at high-volume centers is associated with less maternal and fetal complications compared to the surgical treatment by less experienced surgeons.<sup>[27]</sup> LC is the gold standard for gallbladder-associated surgical treatment and should also be preferred in pregnant women.<sup>[28]</sup> Although LC seems to be a reliable surgical treatment in pregnancy, it is ideally performed in the second trimester because the uterus is not very large and the organogenesis has been achieved in the fetus. LC may be advised as soon as possible, without maternal and fetal morbidity.<sup>[6]</sup> The best choice in the treatment of ABPP can be summarized as follows: (1) conservative treatment and planned LC in the second trimester for patients in the first trimester; (2) LC for patients in the second trimester; and (3) conservative treatment or ES via ERCP and early postpartum planned LC for patients in the third trimester.<sup>[6]</sup>

Hypertension, the essential sign of preeclampsia, is common in patients with the HELLP syndrome. Thrombocytopenia is one of the criteria for the HELLP syndrome and is common in preeclampsia. Hypertension and thrombocytopenia may occur after the twentieth week of pregnancy. Pregnant women with preeclampsia or the HELLP syndrome may have high levels of liver enzymes.<sup>[29]</sup> HELLP syndrome may cause placental abruption, uterine rupture, intra-amniotic infections, and pulmonary and cerebral edema.<sup>[30]</sup> There are microvascular abnormalities in preeclampsia. If the splanchnic circulation is affected, preeclampsia can cause the HELLP syndrome, AP, and cholecystitis. In the present study, ABPP was observed in a 36-year-old woman with preeclampsia and class II HELLP syndrome in the postpartum period. Initially, the patient underwent conservative treatment. Later, ES via ERCP and LC were performed.

In the present study, 10% (n=6) of the conservatively treated patients were accepted for recurrent ABPP and re-hospitalized. It is unpredictable to determine when and how severe ABPP can be in case of relapses; therefore, cholecystectomy should be performed at the earliest. The incidence of ABPP

during pregnancy was calculated as one case per 1171 pregnancies. However, when ABPP cases observed during the first year after delivery were added to the total number, the incidence of ABPP was determined as one case per 277 pregnancies. Considering that the physiological changes during pregnancy are normalized within 1 year after delivery, this study showed that the incidence of ABPP cases was actually higher than that originally presumed. This awareness was accepted as the novelty of our research.

There are certain limitations to the present study. The first limitation was the retrospective nature of this study. The results of the retrospective study are limited to change existing practices in the management of diseases. However, this limitation could be ignored because the medical records were evaluated very cautiously. In addition, such a study is difficult to perform prospectively due to ethical concerns related to very close maternal and fetal follow up. Another limitation of the present study was the small size of patients used for analysis, a reflection of the low incidence of ABPP.

In conclusion, ABPP remains a difficult clinical problem today to overcome with a comparatively limited evidence base. ABPP does not only include pregnant women, but the incidence of these cases is actually higher than expected. ABPP can be successfully managed with conservative treatment because it usually has a mild to moderate clinical course. However, the surgeon should consider early cholecystectomy in patients except in the first trimester. ES via ERCP should be performed if necessary. In addition, patients with high risks for maternal and fetal mortality and morbidity should be managed by a multidisciplinary team consisting of an obstetrician, radiologist, gastroenterologist, and experienced surgeons working at high-volume centers

Conflict of interest: None declared.

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## ORIJİNAL ÇALIŞMA - ÖZET

### Gebelikte ve doğum sonrası dönemde akut biliyer pankreatit

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**AMAÇ:** Akut pankreatit, özellikle üçüncü trimesterde veya doğum sonrası dönemde, 1000–5000 gebelikte yaklaşık bir oranında görülür. Gebeliğe bağlı akut pankreatitin en yaygın nedeni, olguların %65'inden fazlasını oluşturan kolelitiazistir. Bu çalışma, gebeliğe bağlı akut biliyer pankreatit olgularında tek bir merkezin dört yıllık deneyiminin detaylı bir analizini sunmayı amaçlamıştır.

**GEREÇ VE YÖNTEM:** Bu tek merkez geriye dönük çalışmada, acil cerrahi kliniğinde 1 Ocak 2014–1 Ocak 2018 tarihleri arasında gebeliğe bağlı akut biliyer pankreatit nedeniyle hastaneye yatırılan 55 ardışık hastanın tıbbi kayıtları incelendi.

**BULGULAR:** Çalışmaya gebeliğe bağlı akut biliyer pankreatitli elli beş hasta dahil edildi. Elli beş kadından 13'ü (%24) hamile, 28'i (%51) doğum sonrası (altı hafta), 14'ü (%25) bir yıl (6 hafta–1) grubuydu. Üç grup arasında istatistik olarak anlamlı fark yoktu. Her hasta için en uygun tedavi hedef alındı. Altı hastada (%10) tekrarlayan akut pankreatit vardı. Anne veya fetal mortalite ve morbidite yoktu.

**TARTIŞMA:** Gebeliğe bağlı akut biliyer pankreatit sadece hamile kadınları içermez ve bu olguların görülme sıklığı beklenenden daha yüksektir. Gebeliğe bağlı akut biliyer pankreatit konservatif tedavi ile başarılı bir şekilde tedavi edilebilir, çünkü genellikle hafif-orta şiddette bir klinik ile seyredir. Ancak, cerrah ilk trimester dışındaki hastalar için erken kolesistektomiye akılda tutulmalıdır.

**Anahtar sözcükler:** Akut pankreatit; gebelik; prognoz; yönetim.

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