Pregnant patients undergoing cholecystectomy: nationwide assessment of clinical characteristics and outcomes

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BACKGROUND: Gallstone disease in pregnancy is one of the most common indications for nonobstetrical surgery during pregnancy. National-level data on contemporary surgical practice and outcomes are limited.

OBJECTIVE: This study aimed to assess the clinical characteristics and outcomes of patients undergoing cholecystectomy during pregnancy.

STUDY DESIGN: This cross-sectional study examined the Healthcare Cost and Utilization Project's 2 nationwide databases in the United States: the National Inpatient Sample and the Nationwide Ambulatory Surgery Sample. The study population included 18,630 patients who had cholecystectomy during pregnancy from January 2016 to December 2020. The exposure was gestational age, grouped sequentially into the following 5 groups: first trimester (<14 weeks), early second trimester (14−20 weeks), late second trimester (21−27 weeks), early third trimester (28−36 weeks), and late third trimester (≥37 weeks). The main outcomes were clinical demographics, medical comorbidities, surgical information, and pregnancy characteristics and outcomes, assessed by gestational age.

RESULTS: Cholecystectomy was most common in the early second trimester (32.1%), followed by the first trimester (25.2%), late second trimester (23.1%), early third trimester (12.4%), and late third trimester (7.2%). Patients in the first-trimester group were more likely to be aged ≥35 years, to smoke, and to have acute cholecystitis, severe hyperemesis gravidarum including metabolic disturbance, pregestational diabetes, multifetal gestation, and sepsis/shock (P<.001). Patients in the early-third-trimester group were more likely to be obese and have gestational diabetes, Charlson Comorbidity Index of ≥1, premature rupture of membranes, and intrauterine growth restriction, whereas those in the late-third-trimester group were more likely to have gallstone pancreatitis, biliary colic, chorioamnionitis, gestational hypertension, preeclampsia, and severe maternal morbidity including sepsis (P<.001). At the cohort level, a laparoscopic approach was used in most cholecystectomy procedures (97.5%), and bile duct injury was uncommon (<0.1%). Delivery during the admission occurred in 0.3%, 0%, 0.6%, 17.8%, and 60.6% in the 5 gestational age groups, respectively (P<.001). Among the cases that had delivery in the early- and late-third-trimester groups, the delivery event preceded cholecystectomy in 61.4% and 86.2%, respectively, whereas both delivery and cholecystectomy occurred on the same day in 34.3% and 13.8%, respectively.

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Details of ethics approval: The National Inpatient Sample and the Nationwide Ambulatory Surgery Sample are publicly available on the Healthcare Cost and Utilization Project website for access by researchers (available on request at https://www.hcup-us.ahrq.gov). Hence, the current study was exempted from ethics approval (ethical committee exemption: HS-16-00481).

Patient consent was not required because no personal information or details are included.

Data sharing: The data on which this study is based are publicly available upon request at Healthcare Cost and Utilization Project, Agency for Healthcare Research and Quality, https://www.hcup-us.ahrq.gov.

Transparency: The article's corresponding author (Ko.M.) affirms that the article is an honest, accurate, and transparent account of the study being reported; that no important aspects of the study have been omitted; and that any discrepancies from the study as planned (and, if relevant, registered) have been explained. The Nationwide Ambulatory Surgery Sample and the National Inpatient Sample are developed for the Healthcare Cost and Utilization Project that is sponsored by the Agency for Healthcare Research and Quality, and the program is the source of the deidentified data used. The program has not verified and is not responsible for the statistical validity of the data analysis or the conclusions derived by the study team.

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CONCLUSION: This nationwide analysis suggests that clinical and pregnancy characteristics and outcomes of patients undergoing cholecystectomy differ by pregnancy stage with a bimodal distribution. Although patients in the first and third trimesters have distinct medical conditions, more clinically significant pregnancy and maternal outcomes were found in both groups compared with patients in the second trimester.

Key words: characteristics, cholecystectomy, gestational age, morbidity, outcome, pregnancy

Introduction

Between 0.5% and 2% of women have symptomatic gallstone disease during pregnancy. In fact, cholecystectomy is the second most common nonobstetrical surgical procedure performed during pregnancy, occurring in 1 in 1600 to 10,000 pregnancies.[1–9] Pregnancy is a known risk factor for gallstone formation given the increased levels of circulating estrogen and progesterone, leading to cholestasis and supersaturation of bile with cholesterol.[8,9]

The 2019 guidelines from the American College of Obstetricians and Gynecologists recommend that medically necessary surgery not be delayed solely because of pregnancy or pregnancy stage.[10] Furthermore, the 2017 guidelines from the Society of American Gastrointestinal and Endoscopic Surgeons state that laparoscopic cholecystectomy should be the treatment of choice in pregnant patients with symptomatic gallbladder disease, regardless of pregnancy stage.[11]

These recommendations are supported by mounting evidence that nonoperative management of uncomplicated, symptomatic cholelithiasis during the antepartum period places patients at increased risk for recurrent symptoms and multiple readmissions.[2,4,8,12] Additional evidence suggests that early cholecystectomy compared with delayed operative management may be associated with lower risk of maternal and fetal complications, including preterm labor and preterm birth.[2,4,8,12]

Despite these recommendations, there are limited descriptive data to give providers insights into the general characteristics of patients requiring cholecystectomy during pregnancy and their pregnancy outcomes. This study aimed to describe the clinical characteristics of patients undergoing cholecystectomy during pregnancy and to elucidate the obstetrical outcomes at various gestational ages using national-level data.

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Why was this study conducted?

There is a scarcity in national-level data examining clinical characteristics and outcomes of patients undergoing cholecystectomy during pregnancy.

Key findings

An analysis of 18,630 patients who had cholecystectomy during pregnancy from 2016 to 2020 identified in the National Inpatient Sample and the Nationwide Ambulatory Surgery Sample was conducted. Patients undergoing cholecystectomy in the first trimester were more likely to be older, to smoke, and to have acute cholecystitis, severe hyperemesis gravidarum, pregestational diabetes, multifetal gestation, and sepsis/shock. Conversely, those undergoing cholecystectomy in the late third trimester were more likely to have gallstone pancreatitis, biliary colic, chorioamnionitis, gestational hypertension, preeclampsia, and severe maternal morbidity including sepsis.

What does this add to what is known?

Clinical and pregnancy characteristics and outcomes of patients undergoing cholecystectomy differ by pregnancy stage.

Materials and Methods

Data source

This retrospective cohort study examined the Healthcare Cost and Utilization Project's 2 nationwide databases: the National Inpatient Sample and the Nationwide Ambulatory Surgery Sample.[13,14] The Healthcare Cost and Utilization Project is the US health service data platform that is supported by the Agency for Healthcare Research and Quality, 1 of the 12 federal agencies within the United States Department of Health and Human Services.

The National Inpatient Sample approximates a stratified sample of 20% of discharges in each center from all the participating hospitals across 48 states and the District of Columbia.[13] Every year the data set captures >7 million inpatient admissions. In 2020, a total of 4580 hospitals participated in the program. When weighted for national survey estimates, it covers >97% of the US population.

The Nationwide Ambulatory Surgery Sample approximates a stratified sample of 67% of ambulatory surgery encounters in each hospital-owned center every year.[14] In 2020, nearly 2900 hospital-owned centers across 35 states and the District of Columbia participated in the data-capturing mechanism, collecting 7.8 million outpatient surgical encounters this year. These data sets are both publicly available and deidentified. This study was deemed exempt by the University of Southern California Institutional Review Board because of the use of publicly available, deidentified data (patient consent not required).

Study eligibility

The study population were patients who had cholecystectomy during pregnancy from January 2016 to December 2020. The starting point was based on the introduction of the Nationwide Ambulatory Surgery Sample in 2016.

The patients were identified on the basis of the World Health

Organization's International Classification of Diseases, Tenth Revision (ICD-10) Clinical Modification codes and Diagnosis Related Group (DRG) codes (Supplemental Table).

Cholecystectomy was identified on the basis of the ICD-10 Procedure Coding System codes and the American Medical Association's Current Procedural Terminology (CPT) codes (Supplemental Table).[4] Exclusion criteria included ectopic pregnancy, miscarriage, and molar pregnancy. Cases with lack of information on gestational week were also excluded.

Exposure

A previous analysis examined the characteristics and outcomes of cholecystectomy during pregnancy while dividing every trimester into 3 gestational age groups.[4] In the current study, in an attempt to further elucidate pregnancy-specific data with clinical implications and relevance, the second and third trimesters were divided into a first and second half in each trimester.

Accordingly, the gestational ages were grouped sequentially into the following 5 categories: first trimester (<14 weeks), early second trimester (14−20 weeks), late second trimester (21−27 weeks), early third trimester (28−36 weeks), and late third trimester (≥37 weeks).

Main outcome measures

Clinical demographics, medical comorbidities, surgical information, and pregnancy characteristics and outcomes were evaluated as the primary end points. These primary outcomes were assessed within each gestational age group. The secondary end point was temporal trends of cholecystectomy during the study period.

Study covariates

Clinical demographics included patient age (<25, 25−29, 30−34, 35−39, and ≥40 years), year (2016, 2017, 2018, 2019, and 2020), primary payer (Medicaid, private insurance including health maintenance organization, self-pay, and other), census-level median household income (every quarter), and patient location (large central metropolitan, large fringe metropolitan, medium metropolitan, small metropolitan, micropolitan, and neither metropolitan nor micropolitan).

Hospital parameters included regions of the United States (Northeast, Midwest, South, and West) and facility location and teaching status (rural, urban nonteaching, and teaching). These hospital parameters were determined by the programs.

Medical comorbidity included obesity, asthma, pregestational hypertension, and pregestational diabetes mellitus. The Charlson Comorbidity Index was calculated for each patient on the basis of the codes for the specified medical conditions in each category, and weighted appropriately to calculate a final score (Supplemental Table).[15]

Targeted medical comorbidities pertinent to hepatobiliary disease included acute cholecystitis, biliary colic, cholelithiasis, choledocholithiasis, gallstone pancreatitis, fatty liver disease, and viral hepatitis. These were identified according to the previous investigation (Supplemental Table).[4] Substance factors included tobacco use, alcohol use, and illicit drug use. Mental health conditions included depressive disorder and anxiety disorder.

Information on cholecystectomy included surgical modality (laparoscopic or open), identified according to the ICD-10 Procedure Coding System or CPT codes (Supplemental Table).[4] Bile duct injury was analyzed as a surgical morbidity related to cholecystectomy (Supplemental Table).[4] Among the inpatient cases, time to cholecystectomy in days after hospital admission was abstracted.

Pregnancy characteristics included maternal factors (hyperemesis gravidarum including the severe form with metabolic disturbance, gestational hypertension, preeclampsia, and gestational diabetes), fetal factors (multifetal gestation, intrauterine demise, intrauterine growth restriction), and membranous and amniotic fluid factors (premature rupture of membranes and chorioamnionitis) (Supplemental Table). These were preselected according to study relevance.

Pregnancy outcomes included the occurrence of delivery during the hospital admission. Both vaginal and cesarean deliveries were evaluated (Supplemental Table). Among the cases that had delivery events during the hospital admission, chronology in days between the cholecystectomy and delivery was assessed (delivery before cholecystectomy, delivery and cholecystectomy on the same date, delivery after cholecystectomy).

Severe maternal morbidity data were abstracted according to the Centers for Disease Control and Prevention criteria.[16] of the following 21 morbidity indicators were assessed (A−Z)[16]: acute myocardial infarction, acute renal failure, adult respiratory distress syndrome, air and thrombotic embolism, amniotic fluid embolism, aneurysm, blood product transfusion, cardiac arrest/ventricular fibrillation, cardiac rhythm conversion, disseminated intravascular coagulation, eclampsia, heart failure/arrest during surgery or procedure, hysterectomy, puerperal cerebrovascular disorders, pulmonary edema/acute heart failure, severe anesthesia complications, sepsis, shock, sickle cell disease with crisis, temporary tracheostomy, and ventilation. Maternal mortality during the inpatient admission was also evaluated.

Statistical analysis

The analytical approach in the current study followed the previous studies using both the National Inpatient Sample and the Nationwide Ambulatory Surgery Sample to assess the national estimates.[17,18] Frequency tables for the exposure−outcome analysis were generated in the weighted model for national estimates in each database separately. Summation was then performed to aggregate the outputs for the 2 data sets. The chi-square test was used to assess the statistical significance.

Distribution of cholecystectomy was plotted by gestational age in weeks to visualize the peak of surgical intervention. The ratio of inpatient to ambulatory surgery settings was also plotted by gestational age.

Temporal trends of cholecystectomy timing from 2016 to 2020 were assessed for the 5 gestational age groups with the Cochran−Armitage trend test with 1-year time increments. Temporal trends were also assessed for surgery modality and surgical setting during the study period. Gestational age−specific trends were assessed by fitting a linear segmented regression model with log transformation.

All statistical analyses were based on 2-tailed hypotheses, and a *P* value of <.05 was considered statistically significant. The weighted values for national estimates provided by the programs were used for the analysis in each database. Missing values in each study covariate were grouped for analysis. IBM SPSS Statistics, Version 28.0 (IBM Corp, Armonk, NY) and R statistical software, Version 3.5.3 (R Foundation for Statistical Computing, Vienna, Austria) were used for the analysis. The STROBE (STrengthening the Reporting of OBservational studies in Epidemiology) guidelines were followed in the performance of this study.[19]

Results

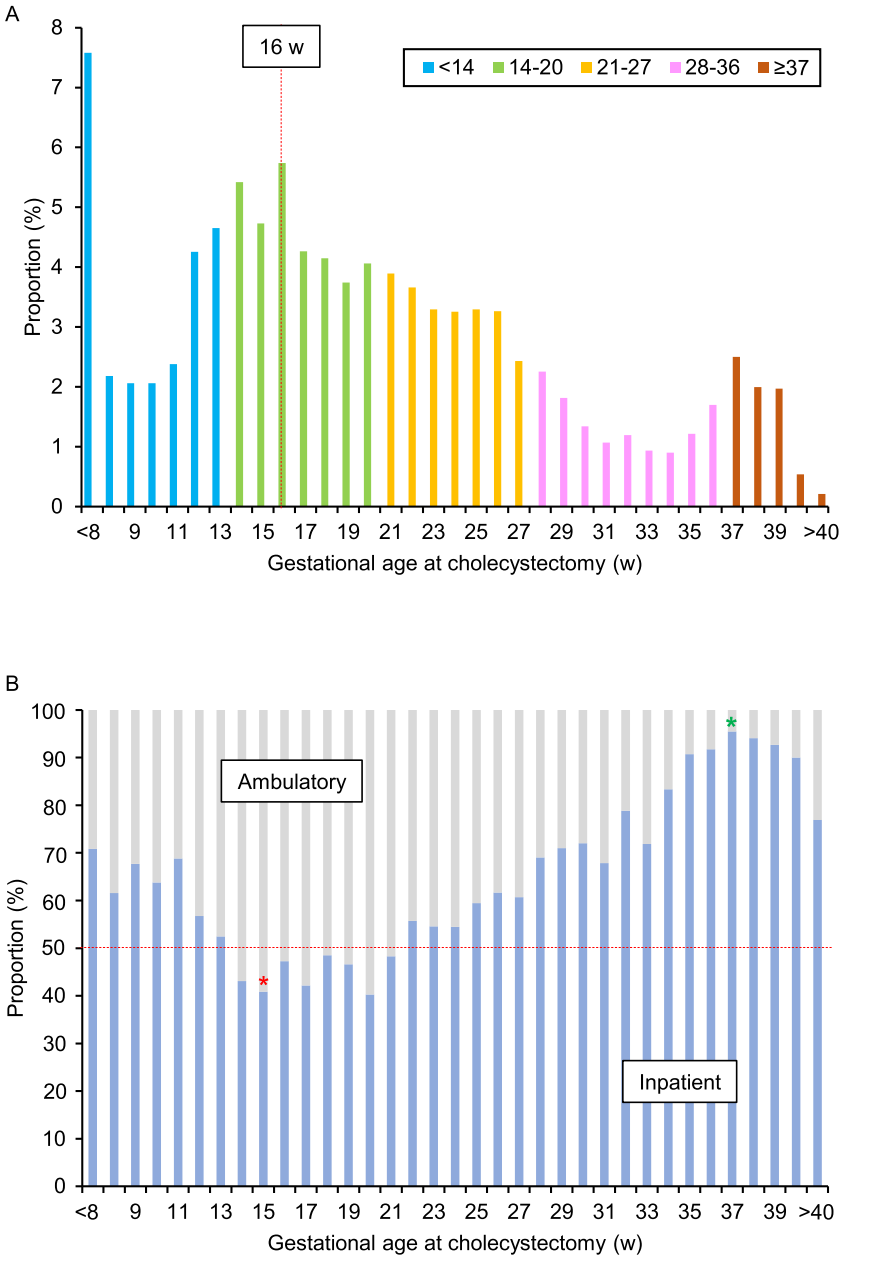
Timing of cholecystectomy

A total of 18,630 patients met the inclusion criteria. Cholecystectomy was performed most commonly in the early second trimester (n=5980; 32.1%), followed by the first trimester (n=4690; 25.2%), the late second trimester (n=4303; 23.1%), the early third trimester (n=2313; 12.4%), and the late third trimester (n=1344; 7.2%) (Figure 1).

When gestational age was trisected, it was found that more than half of cholecystectomies were performed during the second trimester (n=10,283; 55.2%), followed by the first trimester (n=4690; 25.2%) and the third trimester (n=3657; 19.6%).

When gestational age was examined by week (Figure 1), the first peak of cholecystectomy was at 16 weeks of gestation (5.7%), followed by 14 weeks of gestation (5.4%). Thereafter, the number of cholecystectomies steadily decreased until 34 weeks of gestation (0.9%), followed by a slight resurge to another peak at 37 weeks of gestation (2.5%).

FIGURE 1
Gestational age at cholecystectomy



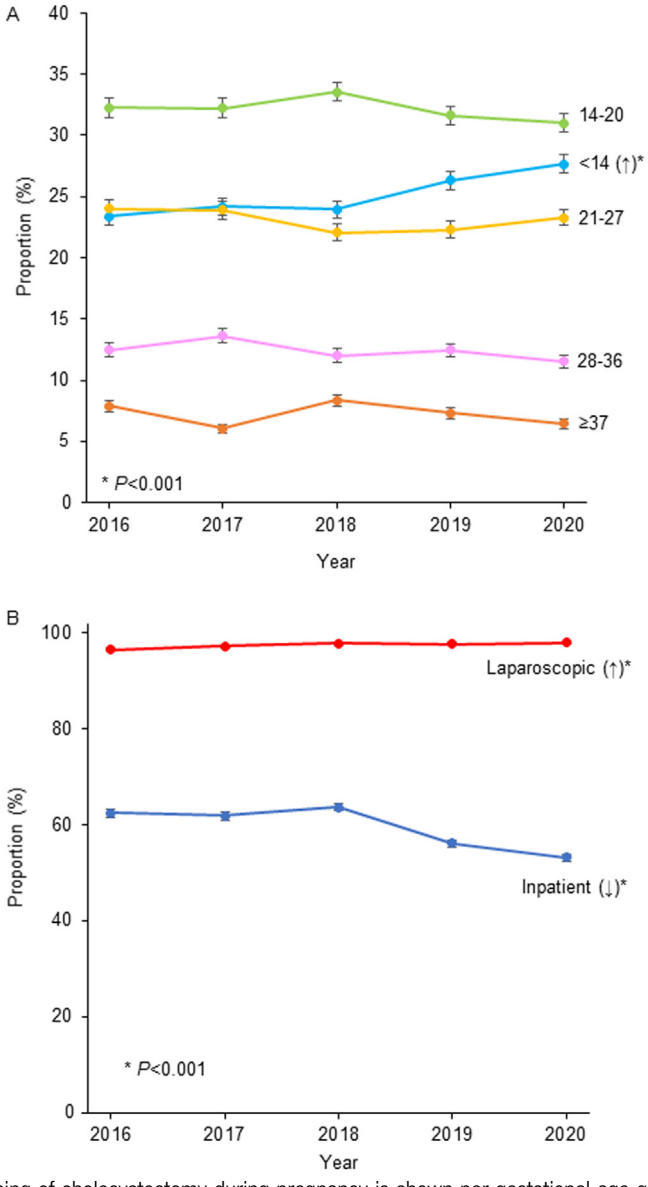
A, Percentage proportion of cholecystectomy is shown per gestational age. Light blue color indicates the first trimester (<14 weeks), light green the early second trimester (14−20 weeks), yellow the late second trimester (21−27 weeks), pink the early third trimester (28−36 weeks), and light brown the late third trimester (≥37 weeks). The vertical red dashed line indicates the peak gestational age at cholecystectomy of 16 weeks. **B,** Distribution of surgical setting (inpatient and ambulatory) is shown per gestational age. The horizontal red dashed line indicates an equal 1-to-1 ratio between the 2 surgical settings. *Asterisk* denotes inflection points (red at 15 weeks; *P* trend=.007; green at 37 weeks; *P* trend<.001).

Mazza. Cholecystectomy during pregnancy. Am J Obstet Gynecol Glob Rep 2024.

Temporal trends

The annual number of cholecystectomies performed during pregnancy gradually increased from 3519 in 2016 to 3920 in 2020 (11.3% relative increase). Across the study period, the

FIGURE 2
Temporal trends of cholecystectomy per gestational age



A, Annual timing of cholecystectomy during pregnancy is shown per gestational age group: first trimester (<14 weeks; light-blue; *P* trend<.001), early second trimester (14–20 weeks; light-green; *P* trend=.178), late second trimester (21–27 weeks; yellow; *P* trend=.177), early third trimester (28–36 weeks; pink; *P* trend=.073), and late third trimester (≥37 weeks; light-brown; *P* trend=.234). **B,** Surgical approach with cholecystectomy (red line; *P* trend<.001) and surgical setting with inpatient admission (blue line; *P* trend<.001) are shown. (*Arrows*) indicate statistically significant increase (↑) or decrease (↓) with *P*<.001 level assessed in the Cochran–Armitage trend test. Dots represent the observed value and bars represent standard error.

Mazza. Cholecystectomy during pregnancy. Am J Obstet Gynecol Glob Rep 2024.

most common cholecystectomy timing was the early second trimester (31.0%–33.6%) (Figure 2).

Over time, the number of patients who had a cholecystectomy in the first trimester increased by 18.5%, from 23.4% in 2016 to 25.2% in 2020 (*P* trend<.001). The first trimester was the third most frequent timing in 2016 but became the second most frequent timing in 2018 (Figure 2).

Clinical characteristics

Patient baseline demographics including hospital parameters by gestational age are shown in Table 1. Patients in the first-trimester group were more likely to be aged ≥35 years (14.7% vs 10.8%–12.5%), have lowest-quartile household income (36.5% vs 32.6%–34.7%), and reside in large central metropolitan areas (34.1% vs 26.9%–29.2%) (all, *P*<.001).

Medical comorbidity

Gestational age–specific medical comorbidity profiles are shown in Table 2. Notably, patients undergoing cholecystectomy in the first trimester were more likely to be smokers (10.9% vs 6.3%–8.0%) and have pregestational diabetes (1.9% vs 0%–1.5%) (both, *P*<.001). Patients in the early-third-trimester group were more likely to be obese (21.6% vs 14.1%–18.6%), have Charlson Comorbidity Index of ≥1 (18.4% vs 15.3%–17.1%), and have a diagnosis of depressive disorder (6.7% vs 4.3%–5.1%), whereas those in the late-third-trimester group were more likely to have anxiety disorder (8.6% vs 5.9%–7.8%) (all, *P*<.001).

Hepatobiliary disease characteristics differed across the gestational age groups (Table 2). Diagnosis of acute cholecystitis was more prevalent among patients in the first-trimester group (52.2% vs 37.0%–46.6%; *P*<.001). Conversely, diagnosis of gallstone pancreatitis was more prevalent among patients in the third-trimester group (18.3% vs 8.5%–13.5%; *P*<.001). Diagnosis of biliary colic was more prevalent in later pregnancy stages (7.1%, 9.5%, 11.0%, 10.9%, and 16.4% in the 5 gestational age groups, respectively; *P*<.001).

Cholecystectomy characteristics

Information on cholecystectomy is shown in Table 3. Most cases at this cohort level were laparoscopic (97.5%), and the use of this approach continued to increase over time (96.7% to 97.9%; *P* trend<.001) (Figure 2). When examined for gestational age, cholecystectomy in the early third trimester had the lowest rate of laparoscopic approach use

TABLE 1
Patient demographics

Characteristic	Gestational age at cholecystectomy (wk)					*P* value
No.	<14 n=4690	14–20 n=5980	21–27 n=4303	28–36 n=2313	≥37 n=1344	
Age (y)						<.001
<25	33.4	30.8	35.2	36.3	27.5	
25–29	29.5	32.7	31.4	30.9	39.6	
30–34	22.5	24.1	22.1	21.8	21.1	
35–39	12.4	10.2	9.9	7.5	9.8	
≥40	2.3	2.3	1.4	3.5	2.1	
Primary payer						<.001
Medicaid	52.2	49.2	48.3	57.1	52.1	
Private	36.3	42.9	44.5	37.0	41.7	
Self-pay	7.1	3.9	2.9	1.7	1.9	
Other	4.3	4.0	4.0	3.9	4.1	
Unknown	—[a]	—[a]	0.3	—[a]	—[a]	
Household income						<.001
QT1 (lowest)	36.5	34.7	32.6	33.0	33.7	
QT2	28.6	27.8	27.2	29.4	29.5	
QT3	21.5	22.3	24.5	21.9	21.1	
QT4 (highest)	12.3	14.3	14.9	14.9	15.3	
Unknown	1.1	0.9	0.7	0.9	—[a]	
Patient location						<.001
Large central metropolitan	34.1	26.9	27.5	29.2	29.2	
Large fringe metropolitan	19.6	21.6	20.7	21.5	20.8	
Medium metropolitan	21.6	22.4	22.8	22.1	21.1	
Small metropolitan	8.6	10.5	10.8	9.6	10.7	
Micropolitan	9.7	10.9	11.9	12.1	11.4	
Not metropolitan or micropolitan	6.3	7.8	6.2	5.1	6.8	
Unknown	—[a]	0	—[a]	—[a]	0	
Region						<.001
Northeast	9.0	9.7	10.9	9.9	7.9	
Midwest	19.7	23.3	21.8	20.9	20.6	
South	43.9	45.7	42.5	41.5	43.8	
West	27.3	21.3	24.8	27.7	27.7	
Teaching status						<.001
Rural	8.6	11.7	8.7	5.1	12.9	
Urban nonteaching	21.8	20.8	20.0	18.9	22.2	
Urban teaching	69.6	67.5	71.3	76.0	64.9	

Chi-square test was used for *P* values.

QT, quartile.

[a] Small numbers suppressed per the Healthcare Cost and Utilization Project guidelines.

Mazza. Cholecystectomy during pregnancy. Am J Obstet Gynecol Glob Rep 2024.

(90.9% vs 96.9%–99.1%; *P*<.001) (Table 3).

Most cholecystectomies were conducted in inpatient settings at the cohort level (n=11,050; 59.3%). Cholecystectomies in the early second trimester were commonly performed in the ambulatory setting, whereas most cases in both the first and third trimesters were conducted in the inpatient setting (Figure 1). There was a peak in outpatient cholecystectomies at the gestational age of 15 weeks (59.1%; *P* trend=.007), with a nadir at 37 weeks (4.5%; *P* trend<.001). Notably, the number of inpatient-setting cholecystectomies gradually decreased over time (62.5% to 53.2%; *P* trend<.001) (Figure 2).

Among the inpatient-setting cases, time from hospital admission to cholecystectomy was longer in the third-trimester groups than in the first- and second-trimester groups (median, 2 vs 1; *P*<.001) (Table 3). Bile duct injury was uncommon in this study cohort (<0.1%).

Pregnancy characteristics

Gestational age–specific pregnancy characteristics are shown in Table 4. Patients in the first-trimester group were more likely to have severe hyperemesis gravidarum including metabolic disturbance (5.2% vs 0%–2.6%) and multifetal gestation (1.8% vs 0.6%–1.5%) (both, *P*<.001).

Patients in the early-third-trimester group were more likely to have premature rupture of membranes (1.7% vs 0%–1.1%) and intrauterine growth restriction (2.7% vs 0%–2.2%); those in the late-third-trimester group were more likely to have chorioamnionitis (1.5% vs 0%–0.4%), gestational hypertension (6.3% vs 0.4%–3.6%), and preeclampsia (8.6% vs 0%–5.3%) (all, *P*<.001).

Pregnancy outcomes

Delivery during the admission occurred in 0.3%, 0%, 0.6%, 17.8%, and 60.6% in the 5 gestational age groups, respectively (*P*<.001) (Table 4). This included cesarean delivery in 10.0% and 22.7% of patients in the early- and late-third-trimester groups, respectively.

TABLE 2
Medical comorbidity

Characteristic	Gestational age at cholecystectomy (wk)					*P* value
No.	<14 n=4690	14–20 n=5980	21–27 n=4303	28–36 n=2313	≥37 n=1344	
Medical comorbidity						
Obesity	18.0	14.1	17.0	21.6	18.6	<.001
Asthma	7.6	8.9	8.6	8.5	5.1	<.001
Pregestational hypertension	2.9	3.0	2.7	1.6	2.6	.012
Pregestational diabetes	1.9	1.5	1.5	1.1	0	<.001
Charlson Comorbidity Index ≥1	15.3	15.9	17.1	18.4	15.8	<.001
Substance use						
Tobacco	10.9	7.3	7.3	8.0	6.3	<.001
Alcohol	0.4	0.3	—[a]	—[a]	—[a]	.025
Illicit drug	3.0	1.8	2.3	2.8	2.8	<.001
Mental health condition						
Depressive disorder	4.3	4.5	4.3	6.7	5.1	<.001
Anxiety disorder	6.5	6.3	5.9	7.8	8.6	<.001
Hepatobiliary diagnosis						
Acute cholecystitis	52.2	37.0	38.8	46.6	37.3	<.001
Biliary colic	7.1	9.5	11.0	10.9	16.4	<.001
Cholelithiasis	85.6	84.0	84.6	82.2	83.0	.003
Choledocholithiasis	18.2	11.5	13.0	17.4	19.3	<.001
Gallstone pancreatitis	11.7	8.5	9.6	13.5	18.3	<.001
Fatty liver disease	3.0	1.4	1.2	3.3	1.9	<.001
Viral hepatitis	0.7	0.6	1.2	—[a]	0	<.001

Chi-square test was used for *P* values.

[a] Small numbers suppressed per the Healthcare Cost and Utilization Project guidelines.

Mazza. Cholecystectomy during pregnancy. Am J Obstet Gynecol Glob Rep 2024.

Among the cases that had delivery in the early- and late-third-trimester groups, the delivery event preceded the cholecystectomy in 61.4% and 86.2%, respectively, whereas both delivery and cholecystectomy occurred on the same day in 34.3% and 13.8%, respectively.

Maternal morbidity

There was a bimodal distribution in severe maternal morbidity per gestational age (Table 4). Patients in the first- and third-trimester groups had higher rates compared with the second-trimester groups (2.9%–5.6% vs 1.4%–1.5%; *P*<.001). Specifically, the severe maternal morbidity rate exceeded 5% in the late-third-trimester group (5.6%).

Regarding individual morbidity indicators (Table 4), the late-third-trimester group had the highest rate of sepsis (1.9%), followed by the first-trimester group (1.7%). Shock was reported in 0.3% of patients in the first-trimester group.

Comments

Principal findings

The key results of this study are as follows. There were distinct differences in clinical and pregnancy characteristics and outcomes of cholecystectomy according to pregnancy stage. Furthermore, there was a bimodal distribution of disease acuity and adverse medical and obstetrical outcomes, with patients in the first and third trimesters demonstrating more medical comorbidity compared with those in the second trimester.

Insights for results

Cholecystectomy trends. As noted in previous studies,[5,20–22] in this nationwide analysis, most cholecystectomies were performed in the second trimester, particularly in the first half. The current analysis further demonstrated a gradual increase over time in first-trimester cholecystectomy rates. This could be due to many factors, including response to the 2017 Society of American Gastrointestinal and Endoscopic Surgeons guidelines, increased surgeon comfort with first-trimester cholecystectomy, or medical indication.

Existing literature suggests the safety of first-trimester cholecystectomy, which may contribute to increased surgeon comfort with surgical intervention.[4,21–24] Larger sample sizes (18,630 vs single-center reviews of 22–31 patients),[21,23] contemporaneous time period (2016–2019 vs 1996–2007, 1998–2002),[20,23] and inclusion of outpatient cases[4,24] in the current study compared with previous investigations provide more reassuring data for first-trimester cholecystectomy.

With regard to outpatient management, there is scant literature on ambulatory gallbladder surgery in pregnancy. Few studies queried databases that include outpatient data[25,26]; however, their study populations were limited to late pregnancy cases and to certain regions (California or New York State). The current study included all pregnancy stages in a nationwide cohort that provides a more broad and global view of gestational cholecystectomy.

A slight 37-week peak in cholecystectomy rates was also observed. This likely represents patients who had earlier surgery deferred and failed conservative treatment or underwent planned postpartum cholecystectomy. Because most patients at ≥37 weeks underwent delivery before cholecystectomy, this 37-week peak may represent surgeon preference to deliver the fetus before cholecystectomy, making a laparoscopic approach

TABLE 3
Cholecystectomy characteristics

Characteristic	Gestational age at cholecystectomy (wk)					*P* value
No.	<14 n=4690	14–20 n=5980	21–27 n=4303	28–36 n=2313	≥37 n=1344	
Surgery setting						<.001
Inpatient	63.2	44.1	56.0	77.0	93.4	
Ambulatory	36.8	55.9	44.0	23.0	6.6	
Surgery timing[a]	1 (1–3)	1 (0–2)	1 (0–2)	2 (1–3)	2 (2–4)	<.001
Surgery type						<.001
Laparoscopic	98.6	99.1	97.7	90.9	96.9	
Open	1.4	0.9	2.3	9.1	3.1	
Bile duct injury	—[b]	0	0	0	0	.005

Chi-square test was used for *P* values.

[a] Median time (interquartile range) in days from admission to cholecystectomy among the inpatient cases; [b] Small numbers suppressed per the Healthcare Cost and Utilization Project guidelines.

Mazza. Cholecystectomy during pregnancy. Am J Obstet Gynecol Glob Rep 2024.

more feasible. This is supported by the slight decrease in laparoscopic cases and increase in open cases between weeks 28 and 36, followed by increase in laparoscopic cases at ≥37 weeks.

Clinical characteristics and pregnancy outcomes. There was a bimodal distribution regarding severe maternal morbidity. Patients in the first and third trimesters had higher rates of severe maternal morbidity compared with those in the second trimester. The first and late third trimesters also had increased rates of sepsis. Patients in the first trimester were more likely to have severe hyperemesis gravidarum with metabolic disturbance. Third-trimester patients had a higher Charlson Comorbidity Index, consistent with a previous population-based study from California.[25] These findings suggest medical indication for surgery in the first and third trimesters, whereas second-trimester surgery was more likely elective.

Delivery occurred during the index admission for cholecystectomy in 17.8% of patients in the early-third-trimester group. Most of these deliveries (61.4%) occurred before cholecystectomy. Previous studies noted increased preterm birth rates with third-trimester cholecystectomy relative to the second-trimester or postpartum period,[4,25,26] whereas other studies did not note a significant difference in preterm birth rates between conservative and surgical management.[20,23,24,27] Thus, the association between preterm birth and third-trimester cholecystectomy is controversial. Third-trimester cholecystectomy may instead be an indication of disease severity, an independent risk factor for preterm delivery.[26]

There were no cases of maternal mortality and very low rates of fetal demise at any gestational age, similar to findings from a large 2021 systematic review and meta-analysis.[7] Whether obstetricians are electively delivering late preterm patients to facilitate having the surgeons perform the cholecystectomy warrants further investigation.

Hepatobiliary perspective. The current study found acute cholecystitis to be the most common indication for surgical intervention across all gestational ages. Although overall frequency was low, gallstone pancreatitis was most commonly observed in the third trimester compared with earlier trimesters. A 2016 systematic review that included 590 patients in 51 studies also found acute cholecystitis to be the most common indication for surgery,[28] whereas a population-based Australian study found it to be acute biliary pancreatitis.[22] However, further gestational age comparisons within these studies were limited. Thus, the findings of the current study make important contributions to the existing literature regarding the interplay between hepatobiliary etiology and antepartum cholecystectomy timing.

Strengths and limitations

Nationwide data capturing, a contemporaneous study period, and large sample size enhanced the reliability of this study's findings. Given that previous studies examined the inpatient setting only,[4,6] combining both inpatient and ambulatory data output enabled more robust analysis.

This study has several limitations. Unmeasured bias is inherent to retrospective studies. The details of cholecystectomy and delivery data are important factors that may impact the cohort selection, exposure assignment, and outcome measures, but these details were not available in the programs. Accuracy of exposure assignment and outcome measures was also unavailable because this study solely relied on administrative codes without medical record review, having possible misclassification in a small number of cases. For example, there were few cases with gestational diabetes and preeclampsia in the early pregnancy groups, and it is unknown if these were miscoded or if these diagnoses were made later during the prolonged hospital stays.

Furthermore, information on race and ethnicity and neonate and postdischarge data (including readmission for inpatient delivery following outpatient cholecystectomy) were not available. Because the 2 databases were not linked, possibility of duplicated counts was not assessable. Ascertainment bias due to the data capturing schema limits the study quality. Finally, the generalizability of the study results to other populations was not assessed.

Clinical implications

Management of gallstone disease in pregnancy can be complex. Because of

TABLE 4
Pregnancy characteristics and outcomes

Characteristic	Gestational age at cholecystectomy (wk)					*P* value
No.	<14 n=4690	14–20 n=5980	21–27 n=4303	28–36 n=2313	≥37 n=1344	
Hyperemesis gravidarum	10.7	5.9	1.3	1.0	0.8	<.001
Severe[a]	5.2	2.6	0.6	0	—[b]	<.001
Multifetal gestation	1.8	1.5	0.6	0.8	—[b]	<.001
Intrauterine demise	—[b]	—[b]	—[b]	—[b]	—[b]	.071
Intrauterine growth restriction	0	0	0.7	2.7	2.2	<.001
Premature rupture of membranes	0	0	—[b]	1.7	1.1	<.001
Chorioamnionitis	0	0	0	0.4	1.5	<.001
Gestational hypertension	[b]	0.4	1.2	3.6	6.3	<.001
Preeclampsia	0	0.4	0.8	5.3	8.6	<.001
Gestational diabetes	0.6	1.3	2.9	8.5	6.6	<.001
Delivery during admission	0.3	0	0.6	17.8	60.6	<.001
Cesarean delivery	0	0	—[b]	10.0	22.7	<.001
Delivery timing[c]						<.001
Before cholecystectomy	0	n/a	0	61.4	86.2	
Same day as cholecystectomy	—[b]	n/a	0	34.3	13.8	
After cholecystectomy	0	n/a	—[b]	—[b]	0	
Severe maternal morbidity (any)[d]	2.9	1.4	1.5	3.7	5.6	<.001
Sepsis	1.7	0.3	0.5	—[b]	1.9	
Shock	0.3	0	0	0	0	
Multiple morbidities	0.3	—[b]	—[b]	1.1	1.5	
Maternal mortality[e]	0	0	0	0	0	n/a

Chi-square test was used for *P* values.

[a] Hyperemesis gravidarum with metabolic disturbance; [b] Small numbers suppressed per the Healthcare Cost and Utilization Project guidelines; [c] Analysis among the cases that had delivery; [d] Defined according to the Centers for Disease Control and Prevention definition; [e] Among inpatient cases.

Mazza. Cholecystectomy during pregnancy. Am J Obstet Gynecol Glob Rep 2024.

the variability in clinical presentation, gestational age, disease severity, and patient-specific factors, establishing universal guidelines can be challenging. The findings of this study, specifically regarding the bimodal distribution in maternal morbidity, underscore the need for better risk stratification tools to identify patients at highest risk for severe disease and who may optimally benefit from surgical intervention during pregnancy. With enhanced ability to identify the highest-risk patients, surgical counseling can be individualized, and more specific clinical practice guidelines can be developed.

Conclusion

This national-level assessment provides an overview of when and in which circumstances cholecystectomy is performed during pregnancy in the United States. Distinct differences in patient demographics and obstetrical outcomes of gestational cholecystectomy in the early and late stages of pregnancy are observed. Although mid-pregnancy is commonly set for the timing of gestational cholecystectomy in the ambulatory setting, the increasing trend of conducting this surgery in the first trimester is noteworthy. Further investigations are warranted for individual-level analysis of demographic, medical, or obstetrical factors that predict higher morbidity or adverse outcomes for mothers and fetuses. ■

CRediT authorship contribution statement

Genevieve R. Mazza: Conceptualization, Investigation, Methodology, Writing – original draft. **Ariane C. Youssefzadeh:** Investigation, Resources, Writing – review & editing. **Laurel S. Aberle:** Investigation, Writing – review & editing. **Zachary S. Anderson:** Investigation, Writing – review & editing. **Rachel S. Mandelbaum:** Data curation, Investigation, Resources, Software, Writing – review & editing. **Joseph G. Ouzounian:** Investigation, Resources, Supervision, Writing – review & editing. **Kazuhide Matsushima:** Conceptualization, Investigation, Methodology, Resources, Supervision, Writing – review & editing. **Koji Matsuo:** Conceptualization, Formal analysis, Funding acquisition, Investigation, Methodology, Project administration, Resources, Software, Supervision, Validation, Visualization, Writing – original draft. ■

Supplementary materials

Supplementary material associated with this article can be found in the online version at doi:10.1016/j.xagr.2024.100310.

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