Cholecystectomy During the Third Trimester of Pregnancy: Proceed or Delay?

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BACKGROUND: Current guidelines suggest that cholecystectomy during the third trimester of pregnancy is safe for both the woman and the fetus. However, no population-based study has examined this issue. The aim of this analysis was to compare the results of cholecystectomy during the third trimester of pregnancy with outcomes in women operated on in the early postpartum period in a large population.

METHODS: The California Office of Statewide Health Planning and Development database was queried from 2005 to 2014. Women undergoing cholecystectomy during the third trimester of pregnancy (n = 403) were compared with those having this procedure in the 3 months post partum (n = 17,490). Patient demographics as well as maternal delivery and cholecystectomy-related outcomes were compared by standard statistics as well as after adjustments for age, race, comorbidities, insurance status, and hospital setting.

RESULTS: Women who underwent cholecystectomy during the third trimester were older (27 vs 25 years; $p < 0.001$), but did not differ in race or insurance status. Cholecystectomy during pregnancy was more likely to require hospitalization (85% vs 63%; $p < 0.001$) and more likely to be performed open (13% vs 2%; $p < 0.001$). Composite maternal outcomes (odds ratio 1.88; $p < 0.001$), including preterm delivery (odds ratio 2.05; $p < 0.001$) as well as length of hospital stay (+0.83 days; $p < 0.001$) and readmissions (odds ratio 2.05; $p = 0.002$), were all significantly increased when cholecystectomy was performed during pregnancy.

CONCLUSIONS: Maternal delivery and procedure-related outcomes were worse when cholecystectomy was performed during the third trimester of pregnancy. Preterm delivery, which is associated with multiple adverse infant outcomes, was increased in third-trimester women. Whenever possible, cholecystectomy should be delayed until the postpartum period. (J Am Coll Surg 2019;228:494–503. © 2019 by the American College of Surgeons. Published by Elsevier Inc. All rights reserved.)

Benign biliary disease represents the second most common indication for nonobstetric operations in pregnant women.[1] During pregnancy, the surge in estrogen and progesterone levels causes biliary stasis, which, in turn, increases the risk of gallstone formation.[2,3] The decision to pursue operative treatment of benign biliary disease in the pregnant woman is not trivial. Risk of the disease must be balanced against operative risks, which include

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trocar insertion injuries, the altered physiology introduced by carbon dioxide pneumoperitoneum, and biliary injuries. Current surgical guidelines suggest that cholecystectomy during the third trimester of pregnancy is safe for both the woman and the fetus.[4,5] However, the recommendation to pursue operative treatment of biliary disease during the third trimester over deferment to the postpartum period is based on case reports and small series.[6-9] All of these studies are at risk of reporting false-negative results due to underpowered analyses.[10] To date, no published population-based studies assess the differences in maternal and cholecystectomy outcomes based on the timing of the operation surrounding pregnancy.

As part of a quality improvement initiative of the state of California, the Office of Statewide Health Planning and Development (OSHPD) contracted the authors to benchmark cholecystectomy-related outcomes.[11] The state-provided OSHPD database contains a decade worth of all-capture, longitudinal data encompassing inpatient, outpatient, and emergency department visits. These data provided the authors with a valuable opportunity to examine the timing of cholecystectomy with respect to pregnancy. The aim of this analysis was to compare the results of cholecystectomy during the third trimester of pregnancy with outcomes in women operated on in the early postpartum period in a large population.

METHODS

California Office of Statewide Health Planning and Development database

Women who underwent a cholecystectomy in California from 2005 to 2014 were extracted from the California OSHPD database, which is a unique database that captures all episodes of patient care across facilities licensed by the state of California regardless of age or insurance status. Patients are assigned unique identifiers, which allows for longitudinal capture of their progression through the healthcare system over time. All inpatient, ambulatory surgery, or emergency department visits are included in the OSHPD database. The California OSHPD assembled a cholecystectomy expert panel comprising many of the coauthors. In conjunction with consultants from the Hospital Quality Institute, the expert panel determined appropriate inclusion criteria, identifiable outcomes, and definitions using ICD-9 diagnoses and procedure codes where appropriate.

Inclusion criteria

Women who had childbirth around the time of undergoing a cholecystectomy (from 3 months before delivery to 3 months after delivery) with a benign pathology diagnosis, including acute cholecystitis, biliary colic, choledocholithiasis, or gallstone pancreatitis, were included in the analysis. Patients undergoing a laparoscopic or open cholecystectomy were identified by ICD-9 procedure codes of 51.21, 51.22, 51.23, or 51.24 as a primary procedure in the inpatient database. Patients with CPT codes of 47562-64, 47600, 47605, 47610, 47612, 47620, 49310, 49311, and 56340-42 as a primary procedure in the ambulatory surgery database also were identified. The benign pathology diagnoses were identified with primary ICD-9 diagnosis codes of 574.0-574.2,575.0-575.8, 789.0, and 789.01. Childbirth was identified with ICD-9 diagnosis and procedure codes as listed in eTable 1. For patients with multiple deliveries within the study period, the childbirth closest to the time of cholecystectomy was identified. Gestational age at the time of cholecystectomy was then determined a priori backwards from the date of delivery. For the purpose of the study, patients were then divided into 2 groups: cholecystectomy in the third trimester (operation performed within 90 days before date of childbirth) and cholecystectomy during the 0 to 3 months post partum (operation performed within 90 days after the date of childbirth).

Exclusion criteria

Men who underwent a cholecystectomy were excluded. Women who underwent any other abdominal surgical procedures, with the exception of cesarean section at the same time as the cholecystectomy; had an earlier cholecystostomy tube; or had a diagnosis of gallbladder, liver, bile duct, pancreatic, ampullary, or duodenal cancer at the time of or after cholecystectomy were excluded. Additionally, patients who underwent cholecystectomy for initially presumed benign gallbladder neoplasms, but returned with malignancy on the final pathology and subsequently underwent cancer treatments within a year of cholecystectomy were also excluded.

Variable definitions

Patient comorbidities were measured using the Charlson Comorbidity Index score[12] and captured with validated ICD-9 coding techniques for administrative databases.[13] Hospital teaching status was categorized 3 three groups: facilities with a surgical residency, facilities affiliated with a surgical residency, or those not affiliated with a surgical residency. Cost data were obtained by first applying inflation adjustment of charges based on 2015 dollars, then converted to cost estimates by comparing Net Patient Revenue, as reported by California Hospital Annual Financial Data vs total hospital charges for all patients that year. Readmissions were defined as unscheduled inpatient admissions after the date of cholecystectomy,

censoring for obstetric-related causes of readmission. Bile leaks and bile duct injuries were defined using techniques described previously.[11,14]

Women with a preterm delivery were defined as those with ICD-9 codes 644.20 and 644.21 before the childbirth episode. Other pregnancy outcomes, such as eclampsia and antepartum hemorrhage, were defined as patients with ICD-9 codes (as listed in eTable 1) within 270 days before the date of childbirth. Composite adverse maternal end point was defined as women who developed eclampsia, antepartum hemorrhage, or preterm delivery.

Women who had an earlier inpatient hospitalization for benign biliary disease before cholecystectomy or childbirth were identified and adjusted for in the multivariate regression models. Also, a separate analysis was done to eliminate confounding variables. In this analysis 2 types of patients were eliminated. Women who had a cholecystectomy in the third trimester and who also had an earlier hospital admission from biliary disease were eliminated to avoid patients who failed nonoperative management. These women were those in whom cholecystectomy in the third trimester could not be avoided. Additionally, in the postpartum group, only women with an inpatient hospitalization for biliary disease before childbirth were included in this analysis to avoid including patients who did not have problems during pregnancy. This subset analysis provided for a more conservative approach to only include women who were more likely to have biliary disease in the third trimester and had the option to either receive upfront cholecystectomy or deferment of operation to after the delivery. This analysis also helped to control for difficulties in accurately diagnosing acute cholecystectomy and severe gallstone pancreatitis in the California administrative database.

Statistical analysis

Categorical variables were expressed as frequency or proportions and were analyzed comparatively with Fisher's exact test. Continuous variables were expressed as medians with interquartile ranges and were compared with the Kruskal-Wallis test. Adjusted analyses of cholecystectomy-related outcomes were performed using multivariate regression models controlling for patient's age, race, payer status, Charlson Comorbidity Index score, earlier hospitalization for benign biliary disease, cholecystectomy setting, and urban and hospital teaching status. Adjusted analyses of adverse maternal delivery outcomes were performed using multivariate regression models controlling for the variables mentioned, with the addition of a diagnosis of obesity or a history of preterm delivery. All regression analyses were performed clustering on individual hospitals to account for intraclass correlation. All tests were performed 2-sided, and $p < 0.05$ was considered to indicate statistical significance. All statistical analyses were performed using Intercooled Stata software, version 15.0 (Stata Corp).

RESULTS

Patient demographics

The search identified 316,242 women of childbearing age who underwent cholecystectomy from 2005 to 2014, of whom 3,409 (1.1%) were pregnant at the time of cholecystectomy. Of these pregnant women, 403 (11.8%) underwent operations during their third trimester. This third-trimester group was compared with 17,490 (5.6%) patients who had a cholecystectomy within 3 months of delivery. Patients who had their cholecystectomy in their third trimester were slightly older (27 years vs 25 years; $p < 0.001$) and had higher Charlson Comorbidity Index scores than the postpartum group (0.7% vs 0.1% having scores ≥ 2; $p < 0.001$) (Table 1). In the prepartum group 177 of the 403 (44%) women had an inpatient admission for benign biliary disease before the cholecystectomy hospitalization. Only 955 of the 17,690 (5.4%) postpartum women had an inpatient admission before delivery. Third-trimester cholecystectomy patients were less likely to have operations performed as an outpatient (14.9% vs 37.3%; $p < 0.001$) (Table 1) compared with patients who had the cholecystectomy post partum. Additionally, women in the third-trimester group were more likely to have the cholecystectomy performed at a teaching hospital (23.6% vs 18.5%) or an affiliated teaching hospital (7.7% vs 4.8%; $p < 0.001$).

Maternal cholecystectomy outcomes

Women who underwent cholecystectomy in the third trimester had a longer hospital length of stay (3 days vs 1 day; $p < 0.001$), higher cost of cholecystectomy index hospitalization ($19,918 vs $17,461; $p < 0.001$) and higher 30-day nonpregnancy, nondelivery readmission rates (10.2% vs 4.0%; $p < 0.001$) (Table 2 and Fig. 1) compared with women who underwent the procedure within 3 months of delivery. Bile leak and bile duct injury rates did not differ between the groups. On adjusted analyses, cost was not significantly different, but the third-trimester group was still associated with longer hospital length of stay (+0.83 days; $p < 0.001$) and higher 30-day readmission rates (odds ratio [OR] 2.05; $p = 0.002$) (Table 3, Fig. 1) compared with the postpartum group.

Maternal delivery outcomes

Women who underwent cholecystectomy in the third trimester had higher rates of the composite adverse

Table 1. Demographics of Patients Who Underwent Cholecystectomy in the Third Trimester and 0 to 3 Months Postpartum

Variable	CCY in third trimester (n = 403)	CCY 0 to 3 mo postpartum (n = 17,490)	p Value
Age, median (interquartile range)	27.0 (23.0–32.0)	25.0 (21.0–30.0)	<0.001
Race/ethnicity, n (%)			0.13
Hispanic	220 (55.4)	10,368 (59.6)	—
Non-Hispanic white	128 (32.2)	5,293 (30.4)	—
Black	23 (5.8)	675 (3.9)	—
Asian	17 (4.3)	561 (3.2)	—
Native American/other	9 (2.3)	510 (2.9)	—
Payer status, n (%)			0.43
Private	200 (49.6)	8,848 (50.6)	—
MediCal	176 (43.7)	7,663 (43.8)	—
Self-pay	22 (5.5)	782 (4.5)	—
Medicare	5 (1.2)	129 (0.7)	—
Other	0 (0.0)	67 (0.4)	—
Charlson Comorbidity Index score ≥2, n (%)	3 (0.7)	23 (0.1)	0.001
Obesity, n (%)	51 (12.7)	2,838 (16.2)	0.054
History of preterm delivery, n (%)	11 (2.7)	393 (2.2)	0.52
Earlier hospitalization for benign biliary disease, n (%)	177 (43.9)	955 (5.5)	<0.001
CCY setting, n (%)			<0.001
Inpatient, unscheduled, laparoscopic	238 (59.1)	10,025 (57.3)	—
Outpatient	60 (14.9)	6,524 (37.3)	—
Inpatient, scheduled, laparoscopic	46 (11.4)	617 (3.5)	—
Inpatient, scheduled, open	4 (1.0)	28 (0.2)	—
Inpatient, unscheduled, open	55 (13.6)	294 (1.7)	—
Urban hospital, n (%)	396 (98.3)	16,692 (95.4)	0.007
Hospital teaching status, n (%)			<0.001
Nonteaching	277 (68.7)	13,410 (76.7)	—
Primary teaching	95 (23.6)	3,244 (18.5)	—
Affiliate teaching	31 (7.7)	836 (4.8)	—

CCY, cholecystectomy.

maternal outcomes (eclampsia, hemorrhage, and preterm delivery) compared with patients who underwent the procedure post partum (25.8% vs 12.9%; $p < 0.001$) (Table 2 and Fig. 2). The third-trimester women were associated with increased rates of eclampsia (2.2% vs 1.1%; $p = 0.023$), antepartum hemorrhage (6.7% vs 3.7%; $p = 0.002$), and preterm delivery (21.6% vs 9.6%; $p < 0.001$, Table 2) compared with the postpartum group. On multivariate regression, women operated in the third trimester were associated with greater abnormal composite maternal outcomes (OR 1.88; $p < 0.001$) (Table 3, Fig. 2A). The increased preterm delivery risk in the third-trimester group was primarily driving the composite outcomes (OR 2.05; $p < 0.001$) (Table 3 and Fig. 2B); no difference was observed between groups in the adjusted risk of eclampsia and antepartum hemorrhage.

Subset analysis

A subset analysis described here was then performed comparing third-trimester women with no earlier inpatient hospitalization before cholecystectomy (n = 226) and postpartum women with an inpatient hospitalization before childbirth (n = 955). On this subset analysis, the demographic trends of patients in both groups were similar to those of the overall study population. On univariate analysis, the third-trimester group was similarly associated with longer hospital length of stay, higher cost, readmission, and preterm delivery rates (Table 2). On adjusted analysis, the third-trimester group was still associated with longer length of stay (+0.84 days; $p < 0.001$) and cost of cholecystectomy hospitalization (+$4,972; $p = 0.013$), but not 30-day readmission rates (OR 1.56; $p = 0.153$). The third-trimester group was also still associated with higher composite adverse maternal

Table 2. Demographics of Patients Who Underwent Cholecystectomy in the Third Trimester and 0 to 3 Months Postpartum

Patient group	CCY in third trimester	CCY 0 to 3 mo postpartum	p Value
Entire cohort, n	403	17,490	—
CCY-related outcome			
LOS, d, median (IQR)	3.0 (1.0–5.0)	1.0 (0.0–3.0)	<0.001
Cost, $, median (IQR)	19,918 (14,660–31,191)	17,461 (12,730–24,677)	<0.001
30-d nonpregnancy, nondelivery readmission, n (%)	38 (10.2)	676 (4.0)	<0.001
Bile leak, n (%)	1 (0.2)	136 (0.8)	0.23
Bile duct injury, n (%)	2 (0.5)	29 (0.2)	0.11
Maternal delivery outcome, n (%)			
Composite maternal outcome*	104 (25.8)	2,247 (12.9)	<0.001
Eclampsia	9 (2.2)	184 (1.1)	0.023
Antepartum hemorrhage	27 (6.7)	645 (3.7)	0.002
Preterm delivery	87 (21.6)	1,684 (9.6)	<0.001
Cesarean section	173 (42.9)	6,997 (40.0)	0.237
Patient subset,† n	226	955	
CCY-related outcome			
LOS, d, median (IQR)	3.0 (1.0, 5.0)	1.0 (0.0, 3.0)	<0.001
Cost, $, median (IQR)	19,661 (14,694–30,801)	17,676 (12,969–24,361)	0.002
30-d non-pregnancy, nondelivery readmission, n (%)	20 (9.7)	50 (5.4)	0.022
Bile leak, n (%)	0 (0.0)	7 (0.7)	0.34
Bile duct injury, n (%)	2 (0.9)	6 (0.6)	0.67
Maternal delivery outcome, n (%)			
Composite maternal outcome*	62 (27.4)	170 (17.8)	0.001
Eclampsia	5 (2.2)	13 (1.4)	0.35
Antepartum hemorrhage	12 (5.3)	42 (4.4)	0.56
Preterm delivery	53 (23.5)	133 (13.9)	<0.001
Cesarean section	100 (44.3)	392 (41.1)	0.380

*Eclampsia, antepartum hemorrhage, and preterm delivery.
†Subset of patients who were hospitalized for gallbladder disease during the third trimester who had their cholecystectomy during pregnancy or were delayed until postpartum.
CCY, cholecystectomy; IQR, interquartile range; LOS, length of stay.

outcomes (OR 1.89; $p < 0.001$), mainly driven by the higher adjusted risk of preterm delivery (OR 2.12; $p < 0.001$) compared with the postpartum group.

DISCUSSION

In an analysis of an all-capture statewide database, more than 400 women underwent a cholecystectomy in the third trimester of pregnancy, and another 17,490 had operations in the first 2 months post partum. Women who had a cholecystectomy performed in the third trimester were associated with a longer hospital length of stay, a higher cost of the cholecystectomy admission episode, increased 30-day nonobstetric readmissions, and elevated preterm delivery rates compared with women undergoing an operation in the 3 months post partum. A subset analysis was performed that only included women who were most likely to have biliary disease in the third trimester with the options of upfront treatment or deferment. This analysis demonstrated similar unfavorable outcomes in the third-trimester group compared with the postpartum cholecystectomy women. This subset analysis was rigorous because many patients with biliary symptoms during pregnancy were not hospitalized, and those requiring admission were more likely to have severe disease.

When reviewing the demographics of the pregnant patients and the setting of the cholecystectomies, some qualitative differences existed between the general California population receiving cholecystectomy from our previous report.[11] As expected, the postpartum population was younger than the general population (median 25 vs 47 years old) receiving cholecystectomy. They also were more likely to be Hispanic (60% vs 37% in the overall population), which might be due to more Hispanic women being of childbearing age. Cholecystectomies also were less likely to be performed on an outpatient basis for the postpartum population (37% vs 53% for the

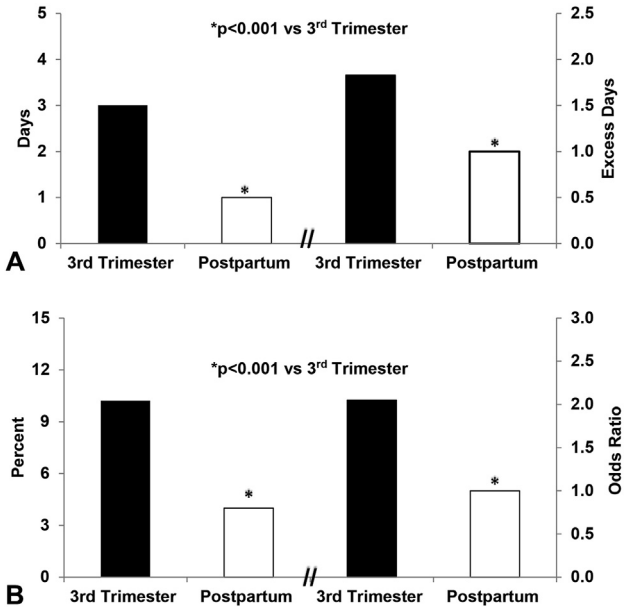

Figure 1. Unadjusted and adjusted comparisons of cholecystectomy outcomes between women who underwent a cholecystectomy during their third trimester and those having operation 0 to 3 months postpartum for (A) length of stay and (B) 30-day readmissions.

general population), but more likely to be performed in a primary teaching hospital (19% vs 5%).

No differences were observed in the rates of bile leaks and bile duct injuries when comparing the third trimester and 0 to 3 months postpartum groups. However, the incidences of both injuries were very low, and the study might be underpowered to detect a difference between groups. However, the overall hospital length of stay and readmission rates were longer and higher for patients in the third-trimester group vs the postpartum group on univariate and adjusted analyses. These observations can be explained by a combination of the need for additional fetal surveillance and more conservative approaches by healthcare providers surrounding pregnant patients.

Kuy and colleagues[1] used the Nationwide Inpatient Sample and were the first to assess maternal outcomes after cholecystectomy at a population level. They reported higher cost and rates of complications when pregnant and nonpregnant patients were compared. Our analysis goes beyond this assessment of outcomes after cholecystectomy, and also reports bile leaks, bile duct injuries, and adverse maternal outcomes with comparison to a postpartum group. Women who underwent cholecystectomy in the third trimester demonstrated a 2-fold increase in the risk of preterm delivery compared with the 0- to 3-month postpartum group. This finding was one of the most statistically significant differences throughout the univariate, multivariate, and subset analyses. This observation is also in line with the literature of general laparoscopy during pregnancy.

A Swedish Health Registry analyzed 2,181 laparoscopic procedures reporting a 2- to 3-fold increase in preterm delivery in third-trimester patients.[15] This finding in the Swedish registry and the current analysis is significant because neonatal brain, lung, and liver development occur during the final weeks of pregnancy. As such, preterm delivery has been associated with increased risks of bronchopulmonary dysplasia, retinopathy of prematurity, and several other long-term issues, such as respiratory problems and learning disabilities.[16-18] Importantly, preterm delivery also leads to higher perinatal mortality, accounting for 85% of early neonatal deaths not due to lethal congenital deformities.[19,20] The risk of eclampsia also was higher in the third-trimester group in the current study on unadjusted analysis. This maternal complication lost statistical significance on adjusted analysis due to its relatively low incidence rate. However, eclampsia is a life-threatening complication of pregnancy that predisposes both the women (seizures, coagulopathy, renal and pulmonary failure) and the newborn (low birth weight, birth asphyxia, and prematurity) to major risks.[21-23]

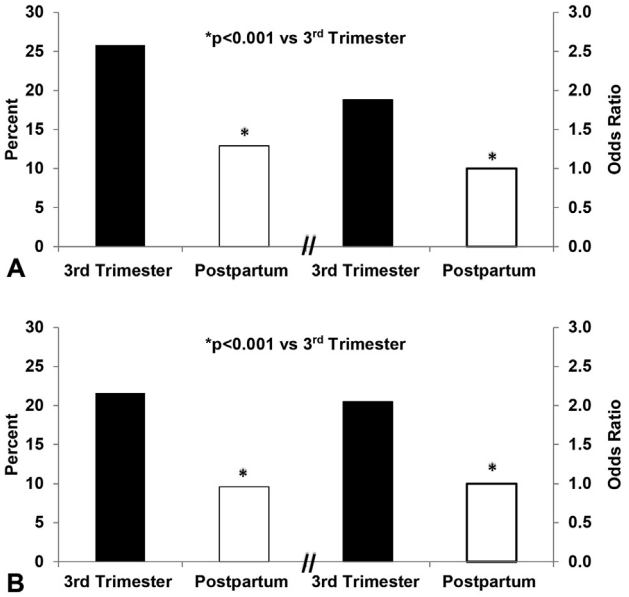

Figure 2. Unadjusted and adjusted comparisons of maternal outcomes between women who underwent a cholecystectomy during their third trimester and those having operation 0 to 3 months postpartum for (A) composite maternal outcomes* and (B) preterm delivery. *Composite maternal outcomes consist of eclampsia, antepartum hemorrhage, and preterm delivery.

Table 3. Adjusted Maternal Cholecystectomy-Related and Maternal Delivery Outcomes after Cholecystectomy for the Entire Cohort of Cholecystectomy During the Third Trimester or 0 to 3 Months Postpartum

Outcome	Data	95% CI	p Value
CCY-related outcome			
Length of stay, d, coefficient			
Third trimester	0.83	0.53 to 1.13	<0.001
0 to 3 mo postpartum	Reference	—	—
Cost, $, coefficient			
Third trimester	3,917	-307 to 8,140	0.069
0 to 3 mo postpartum	Reference	—	—
30-day nonpregnancy, nondelivery readmission, OR			
Third trimester	2.05	1.29 to 3.26	0.002
0 to 3 mo postpartum	Reference	—	—
Maternal delivery outcome, OR			
Composite maternal outcome*			
Third trimester	1.88	1.48 to 2.38	<0.001
0 to 3 mo postpartum	Reference	—	—
Eclampsia			
Third trimester	1.73	0.74 to 4.06	0.21
0 to 3 mo postpartum	Reference	—	—
Antepartum hemorrhage			
Third trimester	1.56	0.97 to 2.50	0.06
0 to 3 mo postpartum	Reference	—	—
Preterm delivery			
Third trimester	2.05	1.56 to 2.69	<0.001
0 to 3 mo postpartum	Reference	—	—

*Eclampsia+ antepartum hemorrhage + preterm delivery.
CCY, cholecystectomy; OR, odds ratio.

Currently, surgical guidelines recommend proceeding with operative intervention for biliary disease during pregnancy, irrespective of gestational age. The Society of American Gastrointestinal and Endoscopic Surgeons guidelines for the use of laparoscopy during pregnancy states that "given the low risk of laparoscopic cholecystectomy to the pregnant woman and fetus, the procedure should be considered for all gravid women with symptomatic gallstones."[4] The Italian Surgical Societies Working Group consensus guidelines on laparoscopic cholecystectomy states that operative intervention is indicated in pregnant patients as long as "extreme caution" is exercised, and performed by an "expert surgeon."[5] However, these recommendations are based on case reports and small series demonstrating no statistical significance in outcomes, which might represent false negatives in underpowered studies.[6-10] Based on current findings, revisions of these surgical guidelines might be warranted.[24]

Concerns about risk of recurrent symptoms pertain more to women with biliary disease in the first and second trimesters. Based on the findings of an increased incidence of both cholecystectomy-related and maternal delivery outcomes in the third trimester, the authors recommend delaying cholecystectomy, if at all possible, to the early postpartum period. In an analysis of 29 patients with complicated gallstone disease initially presenting during pregnancy with operation delayed to the postpartum period, 35% recurred within 1 month, and 82% within 3 months of delivery.[25] This study suggests that early intervention in the postpartum period is warranted when cholecystectomy can be delayed.

The current analysis should be interpreted in the context of its study design. First, a composite adverse maternal end point was used to assess the influence of cholecystectomy on pregnant women. However, recent reports suggest that composite outcomes are more meaningful than individual low-incidence outcomes.[26,27] Second, gestational age at the time of cholecystectomy was determined by means of backward calculation from the date of delivery. Despite the low incidence of preterm delivery, the calculation that was used might have overestimated the gestational age for patients with this condition. Additionally, given the method of gestational age calculation, identification of patients who had

a spontaneous abortion was not possible. However, given that our analysis focuses on the third trimester of pregnancy, the proportion of these patients is likely very small. Third, accurate identification of patients with acute cholecystitis or severe gallstone pancreatitis also was difficult with the OSHPD data. However, the subset analysis was performed to mitigate this limitation and, in general, confirmed the larger analyses. Fourth, given the low incidence of bile leaks and bile duct injuries, meaningful assessment of whether the pregnant state and gravid abdomen predisposes women to a higher risk of these injuries also was not possible. Finally, although the added risk on the newborn can be extrapolated from maternal conditions, such as preterm delivery, direct assessment of neonatal outcomes was not available.

CONCLUSIONS

Women with benign biliary disease experience longer hospital length of stay, more 30-day readmissions, and higher preterm delivery rates when cholecystectomy is performed during the third trimester of pregnancy compared with those undergoing the operation in the first 3 months post partum. Importantly, preterm delivery is associated with increased neonatal mortality and multiple adverse infant outcomes. Whenever possible, women presenting with benign biliary disease in the third trimester of pregnancy should have their cholecystectomy delayed until the postpartum period.

Author Contributions

Study conception and design: Fong, Pitt, Loehrer, Sicklick, Talamini, Lillemoe, Chang
Acquisition of data: Fong, Talamini, Chang
Analysis and interpretation of data: Fong, Pitt, Molina, Perez, Kelleher, Chang
Drafting of manuscript: Fong, Pitt, Chang
Critical revision: Pitt, Strasberg, Loehrer, Sicklick, Chang

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Discussion

DR DAVID T EFRON (Baltimore, MD): Pregnancy clearly adds angst to virtually any superimposed medical urgency. Gallbladder disease is no exception. While not common, when the situation arises, there has been a paucity of good data to guide management. The authors present retrospective evidence that when performed in the postpartum period, patients undergoing cholecystectomy do better than those who have the procedure during the third trimester. This is seen in terms of better composite maternal outcomes including eclampsia, antepartum hemorrhage, and preterm labor. It is also reflected in shorter lengths of stay, lower cost, and 30-day nonpregnancy, nondelivery readmission rates. Further, this holds up under subgroup sensitivity analysis and multivariate analysis.

These are truly attention-grabbing data, as conventional recommendation currently seems to encourage expeditious cholecystectomy in the third trimester for symptomatic gallbladder disease because the procedure is technically feasible and is believed to be safe. An odds ratio associated with experiencing preterm labor of 2.05 after cholecystectomy in the third trimester is particularly troubling. It is interesting that, even with current societal recommendations, the majority of patients analyzed had the procedure postpartum and very few had them in the third trimester. Perhaps the surgeon's proclivity is prescient.

First, with regard to inclusion and exclusion criteria, were there many patients who underwent cholecystectomy at the same time as the caesarean section? How were these treated in the analysis? Also, were there many patients managed with cholecystostomy, presumably used for patients with severe cholecystitis not amenable to expeditious cholecystectomy? In our practice, it remains very common. Second, are there any data on patients who failed initial laparoscopic cholecystectomy and were converted to open procedure? If known, was the rate comparable in the pre- and postpartum groups? Third trimester cholecystectomy was associated with a higher incidence of open procedure. Does this account for the longer inpatient stay and cost seen in that group? Was this accounted for in the multivariate analysis? Third, although preterm labor and hemorrhage would or could be considered pregnancy term indicators, that is, likely to follow the cholecystectomy intervention, does the same hold true for eclampsia? That is, was the eclampsia identified after or before the intervention or managed as both in your analysis?

Fourth, although the caesarean section percentage seems to be similar, are there any data on the subsequent mode of delivery after third trimester cholecystectomy, especially with respect to open gallbladder removal, as preservation of spontaneous vaginal delivery may be an additional theoretical advantage to delayed cholecystectomy, especially if it were an open procedure?

DR WILLIAM G HAWKINS (St Louis, MO): In summary, the question that they addressed is should cholecystectomy be performed in the third trimester of pregnancy when we encounter a patient with symptoms, or should it be delayed whenever possible? This is a really important question that surgeons are faced with on occasion in part because there are 2 patients at risk, both the mom and the baby, and there are very few good data to guide us in making this decision. So I think that trying to address this using a large prospective database is a significant contribution.

One of the things the authors analyzed and discussed, which I must admit I have not considered when I have faced this decision, is the cost differential. In this situation, when faced with this high-stakes decision, a few thousand dollars one way or the other was never really that important to me and would not drive my decision.

The authors found that only 2% of patients were receiving their cholecystectomy during the third trimester, and 98% were postponed until after delivery. Somehow, as a surgeon who evaluates a lot of people and indications for cholecystectomy, this 2% number (people needing an urgent cholecystectomy) felt right to me. I have several questions. Given the limitations of the information available in the data set, we do see that the operative group was different, perhaps sicker than the delayed group. Do you believe the surgeons in California are mostly getting this right or are we still operating on too many patients too early?

Were you able to see evidence where delay was attempted and nonoperative intervention failed? I saw that you excluded those who had a cholecystostomy tube and ERCP previously. How did this group compare with the operative treatment group? Did they do better or worse?

Did you try to break down your recommendations to specific indications? So cholecystectomy can be needed for acute gallbladder; it can be needed for biliary colic; it can be needed for pancreatitis. Was there any evidence that a certain indication was more likely to require a cholecystectomy compared with another indication? In closing, I would like to say that as a surgeon I appreciate the thoughtful guidance when faced with cholecystectomy in pregnancy. I think much of the existing literature is underpowered and as a result, inconclusive.

DR STEVEN STAIN (Albany, NY): During my training in Los Angeles, we were never allowed to operate on third-trimester cholecystitis. Dr Pitt, what would you advise if we have a patient who

eTable 1. ICD-9 and CPT Codes Used to Define Procedures and Diagnosis

ICD-9	Code
Procedure	
Open cholecystectomy	51.21,51.22
Laparoscopic cholecystectomy	51.23, 51.24
Choledochoenterostomy	51.94, 51.36, 51.37, 51.39, 51.72, 51.79
Simple suture of common bile duct	51.71, 51.72
Endoscopic stent insertion into bile duct	57.87
ERCP	51.10, 51.11, 51.81, 51.82, 51.84, 51.85, 51.89
Percutaneous transhepatic cholangiogram	87.51
Childbirth	72.0, 72.1, 72.2, 72.21, 72.29, 72.3, 72.31, 72.39, 72.4, 72.5, 72.51, 72.52, 72.53, 72.54, 72.6, 72.7, 72.71, 72.79, 72.8, 72.9, 73.0, 73.2, 73.22, 73.5, 73.59, 73.8, 73.9, 73.91, 73.93, 73.94, 73.99
Cesarean section	73.3, 74.0, 74.1, 74.2, 74.3, 74.4, 74.9, 74.91, 74.99
Diagnosis	
Cholecystitis	574.0, 574.1, 575.0–575.4
Biliary colic	574.2, 789.0, 574.5–574.7, 575.8
Gallstone pancreatitis	577.0, 577.8
Maternal	
Childbirth	650.0, 651.01, 651.11, 651.21, 651.91, 651.81, 652.01, 652.11, 652.21, 652.31, 652.41, 652.51, 652.61, 652.71, 652.81, 652.91, 653.01, 653.11, 653.21, 653.31, 653.41, 653.51, 653.61, 653.71, 653.81, 653.91, 659.21, 659.31, 659.41, 659.51, 659.61, 659.71, 659.81, 659.91
Eclampsia	642.6, 642.60, 642.61, 642.62, 642.63, 642.64, 642.70, 642.71, 642.72, 642.73, 642.74
Antepartum hemorrhage	641.0, 641.01, 641.03, 641.1, 641.11, 641.13, 641.20, 641.21, 641.23, 641.30, 641.31, 641.33, 641.80, 641.81, 641.83,
Preterm delivery	641.90, 641.91, 641.93 644.20, 644.21
CPT	
Procedure	
Open cholecystectomy	47600, 47605, 47610, 47612, 47620, 47605
Laparoscopic cholecystetomy	49310, 49311, 47562–47564, 56340–56342, 47563