



## Association of complicated gallstone disease in pregnancy and adverse birth outcomes



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### ARTICLE INFO

#### Article history:

Received 16 October 2019

Received in revised form

20 January 2020

Accepted 20 January 2020

#### Keywords:

Gallstone disease

Pregnancy

Adverse birth outcome

Surgical intervention

### ABSTRACT

**Background:** Complicated gallstone disease (CGD) is a common condition requiring intervention during pregnancy to avert adverse birth outcomes (ABO).

**Methods:** Cohort study using the California OSHPD 2007–2014 database. Records of pregnant patients were analyzed for gallbladder calculus within four months of delivery. Biliary system interventions were evaluated as the primary exposure.

**Results:** Of 7,597 patients, those with CGD had a greater likelihood of biliary system procedures than those with uncomplicated gallstone disease (36.6% vs. 2.5%,  $p < 0.001$ ). Patients with CGD also had increased odds of ABO (OR 2.02, 95% CI, 1.48–2.76). Compared to patients without biliary system procedures, those with interventions for gallstones had an OR of 3.46 (95% CI, 2.48–4.82) for ABO. After adjustment, biliary system intervention for CGD had an even greater risk of ABO (OR 4.26, 95% CI, 2.86–6.35).

**Conclusions:** The risk of ABO is significantly increased in women with CGD and intervention for gallstones.

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### Introduction

Complicated gallstone disease (CGD) is the second most common non-gynecologic condition requiring surgical intervention during pregnancy, occurring in 0.05–0.8% of pregnancies.<sup>1–4</sup> Multiple physiologic and hormonal changes taking place during pregnancy increase the likelihood of biliary sludge and stone formation and associated CGD.<sup>5–7</sup> Selecting an approach to the management of CGD that optimizes outcomes for mother and fetus is therefore an important task for general surgeons and obstetricians. The majority of current literature suggests that prompt surgical treatment of CGD be recommended to patients at their first presentation due to high rates of readmission and increased frequency of emergency department visits in patients treated nonoperatively.<sup>2,8–10</sup> Nonoperative management has also been associated with increased rates of preterm delivery.<sup>2,8–10</sup> However, the incidence of maternal complications and adverse birth outcomes related to the surgical

management of CGD ranges from 1.2% to 12.0%.<sup>1,3,4,10–13</sup> Additionally, in contrast to prior studies, recent evidence suggests that surgical management of gallstone disease during pregnancy is associated with increased risk of preterm delivery and antepartum hemorrhage.<sup>14</sup>

To assess birth outcomes in women with CGD comprehensively, we evaluated a population of pregnant patients with gallstones hospitalized in California over an eight-year period and analyzed the association between gallstone disease status and intervention on the biliary system with adverse birth outcomes. We hypothesized that pregnant patients with CGD treated without an intervention have fewer adverse birth outcomes compared with those patients treated with surgical or endoscopic interventions.

### Materials and methods

We conducted a historical cohort study of patients hospitalized in California between January 1, 2007 and December 31, 2014. Data originated from the California Office of Statewide Health Planning and Development (OSHPD) patient discharge database that contains patient records from all licensed, nonfederal California

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hospitals that are mandated to report all hospitalizations. Patients in the OSHPD database are provided record linkage numbers that allow for prior and subsequent admissions to be ‘traced back’ to unique patients for the evaluation of temporally distant outcomes, such as the birth of a child. Data contained patient demographics, admission factors, discharge disposition, diagnoses, and procedures. This study was approved by the Committee for the Protection of Human Subjects of the California Health and Human Services Agency and the Scripps Institutional Review Board, which waived the requirement to obtain informed consent.

The study population consisted of pregnant patients diagnosed with gallstones within 4 months of delivery. Pregnant patients were identified by scanning *International Classification for Diseases, Ninth Revision, Clinical Modification* (ICD-9-CM) diagnosis codes for evidence of pregnancy using the following: supervision of pregnancy (V22), supervision of high-risk pregnancy (V23), postpartum care and examinations (V24), outcomes of delivery (V27), antenatal screening (V28), perinatal conditions (760–779), and complications and outcomes experienced during pregnancy, childbirth, and the puerperium (630–679). The records of these patients were then analyzed for diagnosis codes related to calculus of the gallbladder and classified as either CGD (acute cholecystitis [574.0, 574.3, 574.6, 574.8, 575.0, 575.12], acute cholangitis [576.1], gallstone pancreatitis [577.0]) or uncomplicated gallstone disease (cholelithiasis without cholecystitis [574.2], calculus of the bile duct without cholecystitis [574.5], calculus of the gallbladder and bile duct without cholecystitis [574.5]). Among patients with multiple pregnancies, each birth outcome was considered a unique event. Records without a valid record linkage number were excluded. Pregnant patients without a birth outcome in the OSHPD database were also excluded. We further excluded patients who had a birth outcome of hydatidiform mole (630), ectopic pregnancy (633), or other abnormal products of conception (631) as these were deemed nonviable pregnancies.

Interventions on the biliary system were categorized as either present or absent and classified using ICD-9-CM procedure codes. Biliary system procedures were defined as cholecystectomy (51.2, 51.22), partial cholecystectomy (51.21), laparoscopic cholecystectomy (51.23), laparoscopic partial cholecystectomy (51.24), cholecystostomy (51.02, 51.03), percutaneous aspiration of the gallbladder (51.01), cholecystotomy (51.0, 51.04), endoscopic retrograde cholangiopancreatography (ERCP) (51.1, 51.10), or endoscopic retrograde cholangiography (ERC) (51.11). Cholecystectomy was further dichotomized for sub-analyses as either open (51.21, 51.22) or laparoscopic (51.23, 51.24). Patients without any of the foregoing procedure codes were categorized as nonprocedural.

Other variables evaluated included age at admission, race and ethnicity, admission year, hospital length of stay, and characteristics of the admitting hospital including unique code, type, county, and US zip code. Pregnancy-related complications specifically evaluated included hypertension complicating pregnancy (642), hyperemesis (643.00, 643.03, 643.1, 643.10, 643.13), diabetes complicating pregnancy (648.0, 648.00, 648.03, 648.04), thyroid dysfunction complicating pregnancy (648.1, 648.10, 648.13, 648.14), anemia complicating pregnancy (648.2, 648.20, 648.23, 648.24), drug dependence complicating pregnancy (648.3, 648.30, 648.33, 648.34), tobacco use complicating pregnancy (649.0, 649.00, 649.03, 649.04), and epilepsy complicating pregnancy (649.4, 649.40, 649.43, 649.44).

The primary outcome of interest was the pregnancy outcome, classified as either normal or adverse. A normal outcome was defined as any delivery resulting in a live birth based on diagnosis codes V27.0, V27.2, or V27.5. An adverse outcome was defined as any delivery resulting in a stillborn (V27.1, V27.3, V27.4, V27.6, V27.7), miscarriage (632, 634), induced abortion (635, 637, 638), or

other abnormal product of conception (631). The secondary outcome of interest was preterm delivery (before 37 weeks of gestation) (644.2).

Descriptive statistics for covariates and outcomes were calculated using the *t*-test, rank sum test, and chi-square test by the gallstone disease status. Logistic regression was used to evaluate the crude and adjusted association between gallstone disease status and intervention status with adverse birth outcomes after adjusting for relevant covariates. Logistic regression was also used for stratified sub-analyses of biliary system procedures by gallstone disease status, and on preterm delivery among all live births. Covariates were initially selected for inclusion in models based on their crude relationship with the outcome and reviewed for clinical plausibility. The sequential addition of covariates into each model was performed to evaluate the robustness of associations. Highly skewed variables were log-transformed before inclusion in the models. Statistical significance was defined as a *p*-value < 0.05. For variables that were not statistically significant at the *p* < 0.05 cutoff, Akaike’s Information Criterion values were used to evaluate whether their exclusion affected model fitness. These variables were retained if model fitness was affected. Data were managed and analyzed using Stata MP, version 13.1 (StataCorp LLP, College Station, TX).

## Results

Among over 18 million records in the OSHPD database, we identified 3,563,258 records with evidence of a pregnancy. Of these, 75,438 had a record of a birth event and 7,653 had a diagnosis of gallstones in the previous four months. After exclusion of nonviable pregnancies, there were 7,597 unique birth events that satisfied our inclusion criteria.

A total of 5,868 (77.2%) involved uncomplicated gallstone disease and 1,729 (22.8%) were CGD (Table 1). Among the patients with CGD, 977 (56.5%) were acute cholecystitis only, 545 (31.5%) had gallstone pancreatitis only, 47 (2.7%) had cholangitis only, 146 (8.4%) had acute cholecystitis and gallstone pancreatitis, 7 (0.4%) had acute cholecystitis and cholangitis, 6 (0.4%) had gallstone pancreatitis and cholangitis, and 1 (0.1%) had acute cholecystitis, gallstone pancreatitis, and cholangitis. There was a total of 260 adverse birth events including 77 (29.6%) spontaneous abortions, 73 (28.1%) missed abortions, 68 (26.2%) stillbirths, and 42 (16.1%) other interruptions of pregnancy. Compared with patients with uncomplicated gallstone disease, those with CGD were significantly younger and were more likely to be white, undergo a biliary system procedure on their gallbladder and have a longer hospital stay. Regarding perinatal complications, CGD patients were more likely than those with uncomplicated gallstone disease to have hyperemesis, anemia, and tobacco use. Rates of adverse birth outcomes and preterm delivery were significantly higher among CGD patients.

Table 2 displays results from the multivariable logistic regression for adverse birth outcomes after adjusting for relevant covariates. In this model, although not statistically significant, delivery year and hypertension were retained as covariates due to improved model fitness. Compared with uncomplicated gallstone disease, CGD was associated with significantly increased odds for an adverse birth outcome (odds ratio [OR] 2.02, 95% confidence interval [CI], 1.48–2.76). Similarly, biliary system procedures were associated with significantly increased odds of an adverse birth outcome compared with nonprocedural management (OR 3.46, 95% CI, 2.48–4.82). Compared with white women, African American women were more likely to experience an adverse birth outcome (OR 2.64, 95% CI, 1.75–3.97). Among perinatal complications, hyperemesis demonstrated the greatest association with

**Table 1**  
Patient characteristics by gallbladder disease status.

Patient Characteristics	Uncomplicated Gallbladder Disease	Complicated Gallbladder Disease	<i>p</i>
Sample size, n	5868	1729	
Delivery year, %			0.269
2007	10.3	10.5	
2008	11.5	12.2	
2009	12.7	13.4	
2010	13.0	14.3	
2011	13.9	12.3	
2012	12.5	11.8	
2013	12.4	13.2	
2014	13.7	12.3	
Age, mean (SD), years	28.1 (6.1)	27.5 (6.4)	0.002
Length of stay in days, mean (SD)	3.2 (3.7)	4.0 (5.1)	<0.001
Race, %			0.017
White	57.0	61.7	
African American	6.7	6.0	
Native American	0.9	1.0	
Asian/Pacific Islander	5.4	4.7	
Other	29.4	26.1	
Unknown	0.7	0.5	
Ethnicity, %			0.756
Hispanic origin	59.1	58.1	
Non-Hispanic	40.2	41.0	
Unknown	0.8	0.9	
Intervention on gallbladder, %	2.5	36.6	<0.001
Perinatal complications, %			
Hypertension/Pre-eclampsia	14.7	14.0	0.765
Hyperemesis	0.9	1.7	0.010
Diabetes	2.1	2.8	0.103
Thyroid	3.3	3.0	0.584
Anemia	21.3	24.4	0.006
Drug use	0.7	1.0	0.265
Tobacco use	3.0	4.3	0.008
Past traumatic injury	0.3	0.2	0.685
Epilepsy	0.6	0.4	0.277
Outcomes, %			
Adverse pregnancy outcome	2.3	7.4	<0.001
Preterm delivery <sup>a</sup>	12.7	16.7	<0.001

SD, standard deviation.

<sup>a</sup> Among normal births.

adverse birth outcomes, while anemia and hypertension displayed statistically significant protective associations.

After stratification by gallbladder disease status, the association between biliary system procedures and adverse birth outcomes remained significantly elevated in six of the eight models evaluated (Table 3). Biliary system intervention consistently conferred higher

odds for adverse birth outcomes among CGD patients compared with uncomplicated gallstone disease patients. Among CGD patients, the odds of an adverse birth outcome were approximately four times higher for patients who underwent a biliary system intervention compared with patients managed without a procedure. Among uncomplicated gallstone disease patients, models 1 and 2 showed the strongest association between biliary system interventions and adverse birth outcomes, but this association gradually decreased with the inclusion of additional covariates (models 3 and 4) to the point of non-statistical significance.

Multivariable modeling of the secondary outcome of interest revealed that biliary system intervention was statistically significantly associated with preterm delivery (Table 4). Gallstone disease status was not statistically associated with preterm delivery during the model building procedure and was removed. African American race and Hispanic ethnicity were each independently associated with greater odds for preterm delivery compared with white race and non-Hispanic ethnicity, respectively. Among perinatal complications, hyperemesis, diabetes, tobacco use, and hypertension were each positively associated with preterm delivery.

Patient characteristics, gallstone disease status, and study outcomes by specific biliary system intervention are shown in Table 5. Among the interventions, cholecystectomy was the dominant method. There was no observed difference in age by intervention category. CGD status was more prevalent across all three intervention types compared with nonprocedural patients. None of the 17 patients who underwent cholecystostomy had an adverse birth

**Table 2**  
Multivariable logistic regression model for adverse birth outcomes.

Patient Characteristics	Odds Ratio	95% Confidence Interval	<i>p</i>
Gallbladder disease status			
Uncomplicated	1.00	-	<0.001
Complicated	2.02	1.48–2.76	
Intervention on gallbladder			
No	1.00	-	<0.001
Yes	3.46	2.48–4.82	
Delivery year	0.95	0.90–1.00	0.059
Age, years	1.03	1.01–1.05	0.007
Race			
White	1.00	-	-
African American	2.64	1.75–3.97	<0.001
Native American	0.99	0.24–4.16	0.988
Asian/Pacific Islander	0.65	0.31–1.37	0.262
Other	1.29	0.96–1.73	0.089
Unknown	1.09	0.22–5.49	0.918
Hyperemesis	8.80	5.13–15.09	<0.001
Diabetes	2.14	1.15–3.96	0.016
Anemia	0.67	0.47–0.93	0.018
Hypertension	0.68	0.45–1.02	0.063

**Table 3**

Adjusted association between intervention versus nonprocedural management (reference) and adverse birth outcomes stratified by gallbladder disease status.

	Uncomplicated Gallbladder Disease		Complicated Gallbladder Disease	
	Odds Ratio	95% Confidence Interval	Odds Ratio	95% Confidence Interval
Model 1	2.59	1.24–5.44	4.28	2.89–6.33
Model 2	2.60	1.24–5.44	4.33	2.92–6.41
Model 3	1.58	0.69–3.58	4.21	2.83–6.27
Model 4	1.62	0.71–3.66	4.26	2.86–6.35

Model 1: adjusted for age, and race.

Model 2: model 1 covariates + delivery year.

Model 3: model 2 covariates + hyperemesis, diabetes, anemia, and hypertension.

Model 4: model 3 covariates + tobacco use, thyroid issues, drug use, and epilepsy.

**Table 4**

Multivariable logistic regression model for preterm delivery among normal births.

	Odds Ratio	95% Confidence Interval	p
Intervention on gallbladder			
No	1.00	-	0.018
Yes	1.31	1.05–1.63	
Delivery year	0.93	0.90–0.96	<0.001
Log-transformed length of stay	3.24	2.86–3.89	<0.001
Race			
White	1.00	-	-
African American	1.59	1.20–2.10	0.001
Native American	0.95	0.44–2.08	0.906
Asian/Pacific Islander	1.04	0.74–1.48	0.806
Other	1.04	0.87–1.25	0.636
Unknown	1.20	0.45–3.15	0.717
Ethnicity			
Non-Hispanic	1.00	-	-
Hispanic origin	1.24	1.04–1.49	0.016
Unknown	1.15	0.48–2.76	0.749
Hyperemesis	2.96	1.62–5.43	<0.001
Diabetes	1.60	1.09–2.34	0.016
Anemia	1.14	0.97–1.35	0.121
Tobacco use	1.50	1.05–2.14	0.026
Hypertension	2.18	1.84–2.58	<0.001

outcome and all were originally treated with ERC/ERCP. However, patients who underwent cholecystectomy or ERC/ERCP only had significantly higher rates of adverse birth outcomes compared with nonprocedural patients. Patients who underwent cholecystectomy or ERC/ERCP only also had significantly higher rates of preterm birth compared with nonprocedural patients. Evaluation of open versus laparoscopic cholecystectomy did not yield any statistically significant differences (data not shown). Cholecystostomy patients showed the lowest rate of preterm births among all strata analyzed.

## Discussion

In this population-based study, we identified over 7,500 hospitalized pregnant patients with gallstone disease. We found that CGD was associated with a significantly increased risk of adverse birth outcomes and preterm delivery when compared with uncomplicated gallstone disease. Risk for an adverse birth outcome was even greater among those who underwent biliary system surgical or endoscopic intervention compared with patients treated without a procedure. Preterm birth was also significantly associated with biliary system intervention. We were unable to identify a significant difference in outcomes between patients treated with open versus laparoscopic cholecystectomy.

Previous data on CGD during pregnancy has not adequately defined the risks of nonprocedural versus operative intervention for mother and fetus. The largest study thus far on the management of gallstone disease in pregnancy compared the outcomes of cholecystectomy in over 9,700 pregnant patients with those in a group

of age-matched non-pregnant controls.<sup>1</sup> Compared with their non-pregnant counterparts, pregnant patients who underwent cholecystectomy had a significantly increased number of complications. In addition, when compared with laparoscopic cholecystectomy, open cholecystectomy was associated with increased rates of maternal and fetal complications. Among all pregnant patients admitted for biliary tract disease, when compared with those who had a cholecystectomy, those who did not undergo surgery had a nearly four-fold increase in both maternal (16.5% versus 4.3%) and fetal (16.5% versus 5.8%) complications.<sup>1</sup> Unfortunately, the latter results were insufficiently addressed by the authors. We are therefore unable to explain why the patients managed without a procedure in our study instead had lower rates of adverse birth outcomes and preterm delivery.

Several retrospective studies have shown that operative management of CGD is safe during pregnancy and associated with decreased recurrence of symptoms, decreased frequency of hospitalization, and decreased number of hospital days with no significant increase in adverse birth outcomes.<sup>2,3,9,15–19</sup> Each of these studies is limited by small sample size, with the largest examining a total of 112 patients.<sup>19</sup> Based on the results of these studies, guidelines published by multiple professional societies including the Society of American Gastrointestinal and Endoscopic Surgeons, the American College of Gastroenterology, and the American Academy of Family Physicians recommend the safe use of laparoscopy for the treatment of CGD during pregnancy.<sup>20–22</sup> Our data suggest that, even when adjusting for relevant covariates, biliary system intervention is associated with a four-fold increased risk of

**Table 5**  
Patient characteristics by intervention.

	Nonprocedural Management	Cholecystectomy	Cholecystostomy	ERC/ERCP	<i>p</i>
Sample size, n	6,816	746	17	18	
<b>Characteristics</b>					
Age, mean (SD)	28.0 (6.1)	27.6 (6.4)	28.7 (7.2)	26.9 (6.6)	0.277
Length of stay, median (IQR)	3 (2–4)	3 (2–5)	2 (2–4)	3.5 (3–9)	<0.001
Complicated gallstone disease, %	16.1	81.6	82.4	55.6	<0.001
<b>Outcomes</b>					
Adverse birth outcome, %	2.4	12.5	0.0	11.1	<0.001
Preterm birth, %	12.7	19.9	11.8	18.8	<0.001

ERC, endoscopic retrograde cholangiography; ERCP, endoscopic retrograde cholangiopancreatography; SD, standard deviation; IQR, interquartile range.

adverse birth outcomes when compared with nonprocedural management of CGD.

In a more recent population-based study utilizing the OSHPD dataset, Fong et al.<sup>14</sup> examined women undergoing cholecystectomy during the third trimester of pregnancy and compared them with those having this procedure during the three months postpartum. They found that surgical management of gallstone disease prior to delivery was associated with greater abnormal maternal delivery outcomes as measured by a composite end-point which included eclampsia, antepartum hemorrhage, and preterm delivery. Our analysis goes beyond their assessment of maternal delivery outcomes after cholecystectomy by including adverse fetal outcomes besides preterm birth, such as stillbirths and miscarriages.

There are no previous studies of significant sample size that longitudinally compare operative with nonprocedural management of gallstone disease in the pregnant population. Examining a large population-based dataset, we found that intervention for gallstone disease during pregnancy is not as safe as previously described.<sup>1–3,9,13–20</sup>

Our study has some limitations many of which are inherent to use of the OSHPD dataset. Given the administrative nature of the dataset, which relied on the ICD-9-CM coding system, we were unable to describe the circumstances of each admission or specific patient details such as vital signs, laboratory data, gestational age of the fetus and fetal monitoring metrics. We were also unable to independently verify the accuracy of the OSHPD diagnostic coding. While it is possible that the poor outcomes observed among those patients who received a biliary system intervention were due to the severity of their biliary disease, as opposed to the intervention itself, the difference is expected to be non-differential by category of gallbladder disease status. In addition, lacking the ability to identify gestational age, we were unable to evaluate any relationship between the stage of pregnancy and each outcome. Given the absence of trimester data in the OSHPD dataset, we used an interval of four months prior to a birth outcome to classify our primary and secondary exposures (i.e., gallstone disease status and biliary system intervention). We selected this classifier on the basis that four months represented a logical temporal interval wherein these exposures may affect the birth outcome. Moreover, we did not analyze the setting (e.g., outpatient versus inpatient) in which patient interventions were performed, a factor which may have had an impact on outcomes. Finally, while our dataset included all licensed, non-federal hospitals in the state of California, we were unable to evaluate patients who received treatment and subsequently left the state, or those who received care at federal or unlicensed facilities.

## Conclusions

The results of this study suggest that biliary system intervention

for gallstone disease during pregnancy is associated with significantly increased risk of adverse birth outcomes when compared with nonprocedural management, and this association is most pronounced among patients with CGD. We recommend that all pregnant patients be educated on the changes in biliary physiology that put them at increased risk for gallstone disease as well as the signs and symptoms of gallstone disease. Patients with known cholelithiasis should be carefully counseled regarding the risk of complications related to developing CGD and intervention for gallstone disease.

## Funding

This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

## Previous presentation

This work was presented as a poster presentation at The American College of Obstetricians and Gynecologists Annual Clinical and Scientific Meeting held in Austin, Texas, April 2018.

## Declaration of competing interest

The authors report no proprietary or commercial interest in any product mentioned or concept discussed in this article.

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