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Outcomes of gallstone disease during pregnancy: a population based data linkage study

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Abstract

Background

Gallstone disease is a leading indication for non-obstetric abdominal surgery during pregnancy. There are limited whole population data on maternal and neonatal outcomes. This population-based study aims to describe the outcomes of gallstone disease during pregnancy in an Australian setting.

Methods

Linked hospital, birth and mortality data for all women with singleton pregnancies in New South Wales, Australia, 2001-2012 were analysed. Exposure of interest was gallstone disease (acute biliary pancreatitis, gallstones with/without cholecystitis). Outcomes including preterm birth (spontaneous and planned), readmission, morbidity and mortality (maternal and neonatal) were compared between pregnancies with and without gallstone disease and within disease subtypes. Adjusted risk ratios (aRRs) and 99% confidence intervals were estimated using modified Poisson regression and adjusted for maternal and pregnancy factors.

Results

Among 1,064,089 pregnancies, 1882 (0.18%) had gallstone disease. Of these, 239 (12.7%) had an antepartum cholecystectomy and 1643 (87.3%) were managed conservatively. Of those managed conservatively, 319 (19.0%) had a postpartum cholecystectomy. Gallstone disease was associated with increased risk of preterm birth (aRR 1.3, 99% CI 1.1, 1.6) particularly planned preterm birth (aRR 1.6, 99% CI 1.2, 2.1), maternal

morbidity (aRR 1.6, 99% CI 1.1, 2.3), maternal readmission (aRR 4.7, 99% CI 4.2, 5.3), and neonatal morbidity (aRR 1.4, 99% CI 1.1, 1.7). Surgery was associated with decreased risk of maternal readmission (aRR 0.4, 99% CI 0.2, 0.7).

Conclusions

Gallstone disease during pregnancy was associated with adverse maternal and neonatal outcomes. Most women with gallstone disease during pregnancy are managed conservatively. Surgical management was associated with decreased risk of readmission.

Keywords

pregnancy; hospitalisation; cholecystectomy; cholecystitis; morbidity

Introduction

Symptomatic gallstone disease is a leading indication for emergency abdominal surgery during pregnancy along with suspected appendicitis and bowel obstruction.[1, 2] Pregnancy is associated with the formation of biliary sludge and gallstones as a result of the actions of oestrogen and progesterone promoting increased cholesterol secretion and biliary stasis.[3] It is estimated that 0.05-0.8% of pregnant women have symptomatic gallstones.[2]

Diagnosis and treatment of gallstone disease during pregnancy is challenging; balancing the risks and benefits to the mother and baby. Non-surgical management is reportedly associated with high rates of symptom recurrence and the risk of disease progression;[2] while surgery carries potential risks to the mother and baby from anaesthesia and radiation exposure from medical imaging.[4]

Population-based data on maternal and neonatal outcomes is important for counselling pregnant women with gallstone disease. However, given the rarity of this pregnancy complication, much of the evidence on maternal and neonatal outcomes come from reviews and meta-analyses of single centre retrospective case series and reports.[2, 5, 6] There are few population-based studies that have compared outcomes between pregnant and non-pregnant women; and there are no population data from an Australian context.[4]

Longitudinally linked population health data provide a unique opportunity to examine gallstone disease identified during pregnancy and subsequent birth outcomes for mothers and babies. Using linked birth, hospital and mortality data, the primary aim of this study was to describe the maternal and neonatal outcomes associated with gallstone disease during pregnancy in an Australian setting. The secondary aim was to compare maternal and neonatal outcomes by gallstone disease management during pregnancy.

Methods

Data sources and linkage

The study population included all women with a singleton pregnancy in New South Wales (NSW) giving birth to a live or stillborn baby between 2001 and 2012. Data from a number of sources were utilised. Birth information was obtained from the NSW Perinatal Data Collection and was linked to hospital admissions information from the NSW Admitted Patient Data Collection; along with mortality information from the NSW Register of Births Deaths and Marriages and the NSW Perinatal Death Review database. The NSW Perinatal Data Collection captures maternal demographic, pregnancy and infant information on all live and stillbirths of at least 20 weeks gestation or 400 grams birthweight occurring at home and in public and private hospitals. The NSW Admitted Patient Data Collection contains information on all hospital discharges from public, private and day procedure centres in NSW. The Register of Births Deaths and Marriages holds vital statistics on all registered deaths in NSW; while the NSW Perinatal Death Review database contains information from confidential reviews of perinatal mortality cases. Hospital admissions information was coded from medical records using the International Statistical Classification of Diseases and Related Health Problems, Australian modification (ICD10AM) for diagnoses and the Australian Classification of Health Interventions (ACHI) for procedures. Individual-level data linkage was conducted by the Centre for Health Record Linkage using probabilistic data matching methods;[7] with false positive and negative rates of 0.5%.[8] Ethics approval was obtained from the NSW Population and Health Services Research Ethics Committee (2012/12/430).

Study variables

The exposure of interest was gallstone disease including acute biliary pancreatitis (K85.1), gallstones without cholecystitis (K80.2, K80.5), gallstones with cholangitis (K80.3) and gallstones with cholecystitis (K80.0, K80.4) identified among pregnancies using hospital admissions data. Pregnancies with cholecystitis without gallstones (K81.0) were excluded. The comparison group consisted of pregnancies without gallstone disease who also did not have any abdominal surgery such as cholecystectomy, appendicectomy, laparoscopy or laparotomy performed during pregnancy. Management of gallstone disease was determined by the presence of procedure codes for cholecystectomy (cholecystectomy group) or its absence (conservative management group) during pregnancy. The ascertainment of cholelithiasis (gallstones) and cholecystectomy from hospital data is high. Sensitivity and positive predictive values of 85% and 81% have been reported for cholelithiasis; [9] likewise sensitivity and positive predictive values of 80.5% and 98.5% have been reported for cholecystectomy.[10]

Pregnancy outcomes assessed included antepartum and postpartum haemorrhage, onset of labour, mode of delivery, maternal readmission within 90 days of birth, maternal morbidity and mortality. Maternal morbidity was a composite measure derived from birth and hospital data and occurring during the birth admission and included severe adverse outcomes such as cerebrovascular accident, shock, blood transfusion and cardiomyopathy.[11]

Neonatal outcomes included preterm birth (<37 weeks gestation), small-for-gestational age (<10^{th} population percentile for gestational age),[12] low Apgar scores, neonatal morbidity and mortality. Preterm births were further classified as spontaneous or planned according to onset of labour. Planned births included labour induction and caesarean delivery

without labour. Neonatal morbidity was a composite measure of serious adverse outcomes including intraventricular haemorrhage, respiratory failure, sepsis, blood transfusion and body cavity surgical procedures occurring before the first discharge home and determined from birth and hospital admissions data.[13] Perinatal mortality included stillbirth (fetal death of at least 20 weeks gestation or 400 grams birthweight) and neonatal death (death of liveborn infant within 28 days of birth); and was identified from birth, hospital admissions and mortality data.

Other variables assessed included maternal age, parity, baby's year of birth, maternal country of birth, smoking, diabetes, hypertension, socioeconomic status, gallstone disease subtype, whether multiple types of gallstone disease were present and the number, length and gestational age at gallstone disease-related admissions. Socioeconomic status was determined from maternal residential postcodes and the Australian Bureau of Statistics Index of Relative Socio Economic Disadvantage scores[14] grouped into quintiles based on the distribution of the NSW obstetric population.

Statistical analysis

Characteristics of the study population were summarised using mean and standard deviation or median and interquartile range for continuous data, and frequency and proportions for categorical data. Lifetables were used to assess the proportion of undelivered pregnancies according to gestational age at the time of cholecystectomy compared with the proportion of undelivered pregnancies among women without gallstone disease.

Outcomes were compared according to: presence or absence of gallstone disease and mode of management (surgical versus conservative management) using unadjusted and

adjusted risk ratios. Adjusted risk ratios with 99% confidence intervals were estimated using modified Poisson regression with robust variances and adjusted for potential confounding. In multivariable analyses comparing outcomes by gallstone disease status, potential confounders were selected *a priori* based on the literature and included maternal (age, socioeconomic status, country of birth) and pregnancy (parity, hypertension, diabetes and baby's year of birth) factors. For comparisons by mode of management, potential confounders were included in multivariable analyses where $p<0.05$ in univariate analysis. Due to the number of comparisons made, statistical significance level was set at $p<0.01$ for multivariable models to reduce the probability of obtaining false positive results.Analyses were performed using SAS 9.4 (SAS Institute, Cary, NC).

Results

A total of 1,092,058 pregnancies were recorded in New South Wales between 2001 and 2012. Of these, 27969 (2.6%) pregnancies were excluded from analyses due to: multiple births (1.5%), missing hospital data (0.8%), gallstone disease diagnosis after pregnancy (0.2%) and abdominal surgery prior to pregnancy (0.1%). There were less than 5 pregnancies diagnosed with gallstones with cholangitis and these pregnancies were excluded from further analyses.

Characteristics and outcomes of women with gallstone disease

Among the 1,064,089 eligible singleton pregnancies, 1882 (1.8 per 1000) had a diagnosis of gallstone disease during pregnancy. Of the pregnancies with gallstone disease, 175 (9.3%) were diagnosed with multiple subtypes of gallstone disease. Women with

gallstone disease were more likely to be younger, multiparous and socioeconomically disadvantaged. There were also higher rates of maternal smoking, diabetes, hypertension and late preterm birth among pregnancies with gallstone disease compared to those without gallstone disease (Table 1).

Gallstone disease was associated with increased risk of preterm birth (aRR 1.3, 99% CI 1.1, 1.6); particularly planned preterm births (aRR 1.6, 99% CI 1.2, 2.1) (Table 2). Of the 155 preterm births among women with gallstone disease, 114 (73.5%) delivered at 34-36 weeks gestation. Compared to pregnancies without gallstone disease where 96.4% of pregnancies were undelivered at 36 weeks, the proportions of undelivered pregnancies by gestational age at the time of cholecystectomy were: 96.1%, 97.9% and 73.7% for cholecystectomies performed at less than 20 weeks, 20-28 weeks and 29-36 weeks, respectively.

The risk of maternal morbidity and readmission for any reason was significantly higher among pregnancies with gallstone disease; as was the risk of neonatal morbidity and neonatal readmission to hospital within 28 days of birth (Table 2). Morbidity among infants born to mothers with gallstone disease included higher rates of respiratory distress/failure, ventilation support, blood vessel catheterisation, parenteral nutrition, and sepsis. Jaundice was the main reason for neonatal readmission. Among the gallstone disease group, there were no maternal deaths up to 90 days postpartum and the rate of maternal morbidity was 2.9%. There was no difference in the rate of stillbirths (0.4% vs 0.6%, aRR 0.7, 99% CI 0.3, 1.8) or perinatal deaths (0.6% vs 0.8%, aRR 0.7, 99% CI 0.3, 1.5) among pregnancies with or without gallstone disease.

Hospitalisation and subtypes of gallstone disease

Among pregnant women with gallstone disease, 1462 (77.7%) had one gallstone-related hospital admission and 420 (22.3%) had two or more such admissions. Antepartum cholecystectomy was most frequently performed among pregnancies with acute biliary pancreatitis while the highest proportion of conservative management during pregnancy occurred among pregnancies with gallstones but no cholecystitis (Table 3). Of those managed conservatively, the rate of postpartum cholecystectomy was marginally higher among pregnancies with acute biliary pancreatitis (Table 3). Among 90 pregnancies with a diagnosis of acute biliary pancreatitis, 15 (16.7%) initially presented with other subtypes of gallstone disease.

Management of gallstone disease

Of the 1882 pregnancies with gallstone disease, 239 (12.7%) had an antepartum cholecystectomy while 1643 (87.3%) were managed conservatively. A total of 28 pregnancies (1.5%) had their cholecystectomy performed during the birth admission. Three hundred and twelve (19.0%) of those managed conservatively had a postpartum cholecystectomy. Sixty eight (28.5%) of antepartum cholecystectomies and 51 (16.3%) of postpartum cholecystectomies were performed in tertiary perinatal centres. Of the 551 cholecystectomies performed, 523 (94.9%) were laparoscopic, 22 (4.0%) were open and 6 (1.1%) were conversions from laparoscopic to open cholecystectomies.

Maternal and neonatal outcomes by management

Pregnancies with gallstone disease managed surgically had decreased risk of maternal readmission (Table 4). Similarly lower rates of maternal readmission with surgical management were observed among gallstone disease subgroups. There were no differences in mode of delivery or preterm birth rates between surgical and conservative management.

While there was some evidence of low Apgar scores among pregnancies managed surgically, the results were not statistically significant after adjustment (Table 4).

Comment

Main findings

The prevalence of gallstone disease during pregnancy among our study population was 1.8 per 1000 singleton pregnancies. Gallstone disease during pregnancy was associated with increased risk of preterm birth, maternal and neonatal morbidity and hospital readmissions. The majority of pregnant women with gallstone disease were treated conservatively, although 19% of these women subsequently had a cholecystectomy in the postpartum period. Antepartum surgical management of gallstone disease was associated with decreased risk of maternal readmission; however, there was no difference in the risk of preterm birth or maternal morbidity between surgical or conservative management.

Interpretation

The prevalence of gallstone disease among pregnant women in New South Wales between 2001 and 2012 was 0.18%, within the range of 0.05-0.8% previously reported.[2, 15] Likewise, the antepartum cholecystectomy rate within our population (12.7%) was similar to rates ranging from 13.2% to 17.9% reported for complicated symptomatic gallstone disease during pregnancy.[16, 17] Our rate of conversion from laparoscopic to open cholecystectomy (1.1%) was slightly lower than the 2.2% rate reported by Nasioudis and colleagues in their meta-analysis of 51 studies involving laparoscopic cholecystectomies in 590 pregnancies over 1992-2015.[5] Interestingly, around 70% of the laparoscopic cholecystectomies in the

meta-analysis were performed in the second trimester, compared with 44.8% and 38.1% of cholecystectomies performed in the second and first trimesters in our study.

A number of risk factors for gallstone disease have been identified including high parity,[18] obesity [18, 19] as well as diabetes.[18, 20] Similar to these reports, we also found an overrepresentation of gallstone disease among pregnant women who were multiparous and those who had diabetes. Although ascertainment of obesity in our data was low (0.4%) compared with other Australian reports of 12-20% prevalence among pregnant women [21, 22], we did find higher rates of obesity among women with gallstone disease (2.3% vs 0.4%). Furthermore, we also found higher rates of gallstone disease among pregnant women with diabetes and hypertension; both markers of obesity. While an association between older maternal age and gallstone disease has been reported,[18] our study found higher prevalence of gallstone disease among younger women (less than 35 years), a finding supported by at least one other study.[19]

We found gallstone disease was associated with increased risk of preterm birth, maternal and neonatal morbidity (including neonatal intraventricular haemorrhage and respiratory distress) and hospital readmission. Similarly, a US population cohort study reported increased odds of preterm birth, jaundice, small-for-gestational age, respiratory distress syndrome and intrauterine fetal death associated with pancreatitis.[23] However, the aetiology of pancreatitis within the cohort was not specified and it has been reported that biliary pancreatitis has a milder course during pregnancy than other forms such as alcohol induced pancreatitis.[24] In our study, the absolute rate of maternal morbidity was low (2.9%) and there were no cases of maternal mortality among the gallstone disease group. These findings are encouraging, suggesting that there are no substantially increased risks of maternal morbidity or mortality for pregnancies complicated with gallstone disease.

Furthermore, the increased risk of preterm birth appears to be related to decisions to intervene rather than spontaneous preterm delivery.

Guidelines recommend early surgical management of gallbladder disease during pregnancy; with laparoscopic cholecystectomy being the treatment of choice irrespective of pregnancy trimester.[25] Early surgical management is recommended as delay is associated with increased rates of hospital admission, preterm labour and preterm delivery; as well as development of cholecystitis and pancreatitis.[25] In our study, we found that the mean number of gallstone hospital admissions was low (1.2-1.3 admissions) and the median time from first presentation to antepartum cholecystectomy was short (ranging from two to six days); these would suggest early intervention is occurring. Encouragingly, fewer than 10% of women with gallstones and no pancreatitis had 3 or more gallstone-related admissions during their pregnancy.

Most pregnant women in this study were managed conservatively; particularly for women who had biliary colic without cholecystitis or pancreatitis. This may reflect the use of conservative management as the first line of treatment, with surgery reserved for failure of conservative management or recurrent gallstone disease. Clinicians are reluctant to perform operative cholangiograms to visualise the gallbladder due to potential radiation exposure to the unborn baby. This may additionally contribute to low antepartum cholecystectomy rates.

In our study, we showed that pregnant women with acute biliary pancreatitis were more likely to be managed surgically compared to other types of gallbladder disease (32.5% vs 11.9%). Furthermore, they were more likely to have a cholecystectomy in the postpartum period.. Acute biliary pancreatitis has been reported to be associated with high maternal and fetal mortality[15] in the past, as well as high rates of recurrence with conservative management.[26]

Our study showed that surgical management of gallstone disease was associated with decreased risk of maternal hospital readmission, a finding that has been reported elsewhere.[17, 27] Also consistent with other reports,[2, 6] we found no difference in rates of preterm birth or fetal mortality between surgically and conservatively managed pregnancies.

Strengths of the study

This study is to our knowledge the largest population-based study comparing maternal and neonatal outcomes between pregnant women with and without gallstone disease. Using routinely collected longitudinally-linked population data, we were able to: assess maternal and neonatal outcomes taking into account pregnancy and maternal factors, obtain representative population estimates of symptomatic gallstone disease prevalence, track progression of gallstone disease during pregnancy and determine gestational age at the time of diagnosis, surgery and delivery. Use of routinely collected population data minimised bias as a result of loss to follow up found in traditional cohort studies. Furthermore, use of whole population data minimises selection bias.

Limitations of the data

Limitations associated with using routinely collected data included missing information and possible misclassification. As the purpose of data collection was not specifically for this study, information on important and relevant risk factors and potential confounders may not be available. Restricting our cohort to gallstone disease during pregnancy meant we could not determine whether admissions for gallstone disease were due to newly-onset disease or recurrent attacks. In addition, further analyses of gallstone disease management were limited by lack of clinical detail on important factors such as indication for

cholecystectomy and acuity of gallstone disease. While case heterogeneity may be a factor in the use of routinely collected data, it has been shown that ascertainment of gallstones and cholecystectomy within administrative hospital data is high.[9, 10] Given the non-specific nature of symptoms of gallstone disease it is possible some cases were misclassified to the no gallstone disease group; this would have the effect of biasing results towards the null.

Conclusions

In summary, gallstone disease during pregnancy is associated with increased risk of preterm birth, neonatal morbidity and maternal and neonatal readmission. However, the prevalence is low and most women were managed conservatively. Surgical management of gallstone disease is associated with decreased risk of maternal readmission and no difference was found in the rate of preterm birth or maternal morbidity between surgical or conservative management. In the majority of pregnant women with symptomatic gallstone disease, conservative management is a feasible option and appears to be standard practice.

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Table 1: Characteristics of 1,064,089 singleton pregnancies with and without gallstone disease in New South Wales, Australia, 2001-2012

Characteristics	Gallstone disease (N=1882) n (%)	No gallstone disease (N=1062207) n (%)
Maternal age, mean (sd)	28.3 (5.8)	30.0 (5.6)
Less than 20	109 (5.8)	37876 (3.6)
20-34	1479 (78.6)	793741 (74.7)
35+	294 (15.6)	230373 (21.7)
Parity		
Primiparous	707 (37.7)	447128 (42.2)
1	611 (32.5)	355873 (33.6)
2+	560 (29.8)	257698 (24.3)
Maternal country of birth		
Australia	1512 (80.3)	727918 (68.5)
South East Asia	43 (2.3)	57537 (5.4)
Other	327 (17.4)	276752 (26.1)
Smoker	430 (22.9)	141659 (13.4)
Diabetes	152 (8.1)	70074 (6.6)
Hypertension	254 (13.5)	94135 (8.9)
SEIFA (quintiles)		
1 (most disadvantaged)	468 (24.9)	207647 (19.6)
2	443 (23.6)	212646 (20.1)
3	424 (22.6)	212266 (20.0)
4	331 (17.6)	213407 (20.2)
5 (least disadvantaged)	211 (11.2)	213117 (20.1)
Gestational age at birth		

Characteristics	Gallstone disease (N=1882) n (%)	No gallstone disease (N=1062207) n (%)
<28 weeks	11 (0.6)	6414 (0.6)
28-31 weeks	17 (0.9)	5706 (0.5)
32-33 weeks	13 (0.7)	6986 (0.7)
34-36 weeks	114 (6.1)	43500 (4.1)
37-38 weeks	559 (29.7)	235232 (22.2)
39-40 weeks	900 (47.8)	585023 (55.1)
41 weeks	240 (12.8)	163813 (15.4)
42+ weeks	28 (1.5)	15380 (1.5)
Year of birth		
2001-2003	409 (21.7)	245941 (23.2)
2004-2006	458 (24.3)	258158 (24.3)
2007-2009	519 (27.6)	277924 (26.2)
2010-2012	496 (26.4)	280184 (26.4)

SEIFA=Socio economic indexes for areas

^ 5 or less

Table 2: Maternal and neonatal outcomes by gallstone disease status among 1,064,089 pregnancies, New South Wales, 2001-2012

Characteristics	Gallstone disease (N=1882) n (%)	No gallstone disease (N=1062207) n (%)	Unadjusted Risk Ratio (95% CI)*	Adjusted Risk Ratio (99% CI)*
Antepartum haemorrhage	69 (3.7)	35364 (3.3)	1.1 (0.9, 1.4)	1.1 (0.8, 1.5)
Preterm birth	155 (8.2)	62606 (5.9)	1.4 (1.2, 1.6)	1.3 (1.1, 1.6)
Spontaneous	69 (3.7)	36105 (3.4)	1.1 (0.9, 1.4)	1.1 (0.8, 1.4)
Planned	86 (4.6)	26488 (2.5)	1.8 (1.5, 2.3)	1.6 (1.2, 2.1)
Mode of birth				
Vaginal, non-Instrumental	1161 (61.7)	645292 (60.8)	Reference	Reference
Instrumental	160 (8.5)	118768 (11.2)	1.0 (1.0, 1.0)	1.0 (1.0, 1.0)
Caesarean – labour	245 (13.0)	126758 (11.9)	1.0 (1.0, 1.0)	1.0 (1.0, 1.1)
Caesarean – no labour	315 (16.8)	170922 (16.1)	1.0 (1.0, 1.0)	1.0 (1.0, 1.1)
Maternal morbidity	55 (2.9)	18305 (1.7)	1.7 (1.3, 2.2)	1.6 (1.1, 2.3)
Maternal readmission for any reason	388 (20.6)	43253 (4.1)	5.1 (4.6, 5.5)	4.7 (4.2, 5.3)

reasons other than cholecystectomy	234 (12.4)	42805 (4.0)	3.1 (2.7, 3.5)	2.9 (2.4, 3.3)
Postpartum haemorrhage	163 (8.7)	81789 (7.7)	1.1 (1.0, 1.3)	1.1 (0.9, 1.4)
Apgar score				
5 minutes less than 7	39 (2.1)	20934 (2.0)	1.1 (0.8, 1.4)	1.0 (0.7, 1.5)
Small for gestational age	192 (10.3)	104325 (9.9)	1.0 (0.9, 1.2)	1.0 (0.9, 1.2)
Large for gestational age	221 (11.8)	106877 (10.1)	1.2 (1.0, 1.3)	1.1 (0.9, 1.3)
Neonatal morbidity	119 (6.3)	44988 (4.2)	1.5 (1.3, 1.8)	1.4 (1.1, 1.7)
Neonatal length of stay, *median (IQR)*	3 (2, 4)	3 (2, 4)		
Neonatal readmission	118 (6.3)	40830 (3.8)	1.6 (1.4, 1.9)	1.5 (1.2, 1.9)

*Adjusted RR for gallstone disease relative to no gallstone disease

Planned preterm birth includes births less than 37 weeks with labour induction or pre-labour caesarean section

Multivariate model adjusted for maternal age, parity, hypertension, diabetes, socioeconomic status, maternal country of birth and baby's year of birth

Table 3: Hospitalisation and gallstone disease subtype among 1882 pregnancies, New South Wales, 2001-2012

Characteristics	Gallstones without cholecystitis (N=1497)	Gallstones with cholecystitis (N=308)	Acute biliary pancreatitis (N=77)
Gestational age at first presentation (weeks), *median (IQR)*	27.3 (16.9, 34.9)	20.9 (10.6, 30.7)	24.9 (12.6, 31.1)
Number of gallstone disease hospital admissions during pregnancy, *mean(sd)*	1.3 (0.8)	1.2 (0.6)	1.3 (0.8)
Maternal length of stay – gallstone disease admissions (days), *mean(sd)*	3.8 (5.2)	4.3 (4.0)	6.1 (5.5)
Pregnancies with 3 or more gallstone disease-related hospital admissions, *n(%)*	112 (7.5)	31 (10.1)	14 (18.2)
Management of gallstone disease during pregnancy			
Antepartum cholecystectomy	123 (8.2)	91 (29.6)	25 (32.5)
Conservative management	1374 (91.8)	217 (70.5)	52 (67.5)
Cholecystectomy during pregnancy			
First presentation	95 (77.2)	77 (84.6)	20 (80.0)
Subsequent admissions	28 (22.8)	14 (15.4)	^ (20.0)
Gestational age at time of cholecystectomy during pregnancy (weeks), *median (IQR)*	15.4 (7.9, 21.9)	14.0 (7.0, 22.7)	18.9 (14.1, 24.7)
Time from first presentation to	10.0	2.0	6.0

antepartum cholecystectomy (days), *median (IQR)*	(0.0, 42.0)	(0.0, 11.0)	(1.0, 11.5)
Postpartum cholecystectomy*	251 (18.3)	47 (21.7)	14 (26.9)

Where multiple gallstone disease conditions were coded for the same presentation, categorisation was based on the most severe condition coded. Scale of severity (most to least severe): 1) Acute biliary pancreatitis, 2) Gallstones with cholecystitis, 3) Gallstones without cholecystitis

^ 5 or less

* denominator = pregnancies with gallstone disease managed conservatively

Table 4: Maternal and neonatal outcomes by management of gallstone disease during pregnancy

Characteristics	Cholecystectomy (n=239)	Conservative management (n=1643)	Unadjusted risk ratio (95% CI)*	Adjusted risk ratio (99% CI)*
Antepartum haemorrhage	7 (2.9)	62 (3.8)	0.8 (0.4, 1.7)	0.8 (0.3, 2.4)
Preterm birth	18 (7.5)	137 (8.3)	0.9 (0.6, 1.4)	0.9 (0.4, 1.7)
Spontaneous	12 (5.0)	57 (3.5)	1.4 (0.8, 2.6)	1.2 (0.5, 3.1)
Planned	6 (2.5)	80 (4.9)	0.5 (0.2, 1.2)	0.5 (0.2, 1.8)
Mode of delivery				
Vaginal, non-instrumental	147 (61.5)	1014 (61.8)	Reference	Reference
Instrumental	13 (5.4)	147 (9.0)	1.0 (0.9, 1.0)	1.0 (0.9, 1.1)
Caesarean – labour	28 (11.7)	217 (13.2)	1.0 (0.9, 1.1)	1.0 (0.9, 1.1)
Caesarean – no labour	51 (21.3)	264 (16.1)	1.1 (1.0, 1.2)	1.1 (0.9, 1.3)
Maternal morbidity	8 (3.4)	47 (2.9)	1.2 (0.6, 2.4)	1.4 (0.4, 4.3)
Maternal readmission				
for any reason	18 (7.5)	370 (22.5)	0.3 (0.2, 0.5)	0.4 (0.2, 0.7)
reasons other than cholecystectomy	18 (7.5)	216 (13.2)	0.6 (0.4, 0.9)	0.6 (0.3, 1.2)
Postpartum haemorrhage	19 (8.0)	144 (8.8)	0.9 (0.6, 1.4)	0.9 (0.5, 1.7)
Apgar score at 5 minutes	10 (4.2)	29 (1.8)	2.4 (1.2, 4.8)	2.6 (0.8, 8.7)
Less than 7				

Characteristics	Cholecystectomy (n=239)	Conservative management (n=1643)	Unadjusted risk ratio (95% CI)*	Adjusted risk ratio (99% CI)*
Small for gestational age	24 (10.1)	168 (10.3)	1.0 (0.7, 1.5)	1.0 (0.5, 1.8)
Large for gestational age	30 (12.7)	191 (11.7)	1.1 (0.8, 1.6)	0.9 (0.5, 1.6)
Neonatal morbidity	14 (5.9)	105 (6.4)	0.9 (0.5, 1.6)	0.9 (0.4, 1.9)
Neonatal length of stay (days), *median (IQR)*	3 (2, 4)	3 (2, 4)		
Neonatal readmission	15 (6.3)	103 (6.3)	1.0 (0.6, 1.7)	1.2 (0.5, 2.5)

*Adjusted RR for cholecystectomy relative to conservative management

Multivariate models adjusted for parity, gestational age at first gallstone admission, gallstone disease subtype, and presence of multiple types of gallstone disease.

Planned preterm birth includes births less than 37 weeks with labour induction or pre-labour caesarean section