Management of Gallstone Disease in Pregnancy. Aspects on Intervention, Outcome and Patient Experience

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Aspects on Intervention, Outcome and Patient Experience

Jonas Hedström

LUND
UNIVERSITY

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Title and subtitle: Management of Gallstone Disease in Pregnancy: Aspects of Intervention, Outcome and Patient Experience

Abstract:

Symptomatic or complicated gallstone diseases are among the most common and costly worldwide. Routine management is laparoscopic cholecystectomy and, when gallstones are present in the bile ducts, ERCP. Pregnancy is an independent risk factor for the formation of gallstones. Other risk factors increasing in the pregnant population are age, obesity, and rapid weight loss after bariatric surgery. This makes cholecystectomy the second most common surgical procedure performed during pregnancy. Even though gallstone surgery has advantages to conservative management, deciding to perform surgery on a pregnant patient is difficult. Several technical, obstetric, anesthesiologic, and radiologic considerations must be made. This thesis aims to further contribute to the knowledge of managing gallstone disease during pregnancy.

Paper I: A retrospective journal study of management of gallstone disease at Skane University Hospital 2001-2015. Differences in outcome between conservatively and surgically managed patients were analyzed. Most patients were treated conservatively. Complication rates were similar. A majority of conservatively treated patients had surgery performed within two years of delivery.

Paper II: An analysis of differences in surgical outcome and patient characteristics between pregnant and non-pregnant women aged 18-45 using the GallRiks database. Both cholecystectomy, ERCP, and combinations of these procedures were examined, and there were no differences in complications when adjusting for confounders. No differences in outcome were seen when comparing surgery in different trimesters.

Paper III: A study of differences in outcome if patients had undergone previous bariatric surgery or not. Pregnant patients with previous bariatric surgery, identified by crossmatching GallRiks and SOReg, were compared to pregnant patients without previous bariatric surgery and non-pregnant patients with and without previous bariatric surgery. Contrary to non-pregnant patients, pregnant patients did not have more complications.

Paper IV: An examination and comparison of maternal-fetal outcome parameters between patients that had gallstone intervention performed during pregnancy and pregnant patients without intervention. Data were obtained by crossmatching GallRiks and MBR. A 1:5-matched control group was identified in MBR. Patients with intervention weighed more, were more often smokers, and had more cases of premature birth. There were no differences in birth weight or APGAR score, and no differences in prematurity when comparing patients with acute care and the control group.

Paper V: An evaluation of the patient experience of gallstone intervention during surgery by sending a 35-item questionnaire and the Becks Depression Index II to patients identified in GallRiks and MBR. The patients were worried about their children and wanted more information about both gallstone disease and surgery during pregnancy. The prevalence of depression was similar to the general population.

In summary, our results support the safety and feasibility of gallstone intervention during pregnancy described in previous studies and guidelines. More pregnant patients should be considered for surgery, and general care has room for improvement.

Key words: Gallstones, Pregnancy, Cholecystectomy, ERCP, Cholelithiasis, Choledocholithiasis, Bile stones, Cholecystitis, Cholangitis, Pancreatitis,

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"My opinion is that a cholecystectomy is suitable for those cases in which both the patient and physician have reached the end of their patience."

Carl Langenbuch, 1882

Table of Contents

Abstract

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List of Papers

The thesis is based on the following original papers and will be referred to in the text by their Roman numerals I-V.

I. Hedström J, Nilsson J, Andersson R, Andersson B. Changing management of gallstone-related disease in pregnancy – a retrospective cohort analysis. Scandinavian J Gastroenterol. 2017;52:1016-1021.

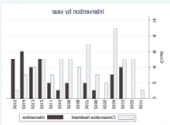
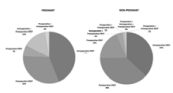
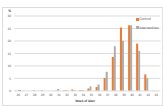
II. Hedström J, Nilsson J, Andersson B. Cholecystectomy and ERCP in pregnancy: A nationwide register-based study. *Submitted*.

III. Hedström J, Nilsson J, Ekelund M, Andersson R, Andersson B. Cholecystectomy After Previous Bariatric Surgery with Special Focus on Pregnant Patients-Results from Two Large Nationwide Registries. *Obes Surg*. 2020;30:1874-1880.

IV. Andersson B, Hedström J, Wide-Swensson D, Nilsson J. The impact of gallstone intervention during pregnancy on maternal and perinatal outcomes: A nationwide population-based cohort study. *Submitted.*

V. Hedström J, Andersson B. A survey of patients' perceptions and experiences of intervention for gallstone disease during pregnancy. *Heliyon.* 2022;8:e11184.

Thesis at a glance

Paper	Aim	Method	Results	Conclusion
Paper I 	To evaluate current management strategies, outcome, and changes over time.	A retrospective analysis of patients admitted for gallstone-related disease 2001-2015 in SUS Malmö and Lund.	64% were treated non-operatively. More patients had intervention 2008-2015. Complications were similar. Most non-operatively managed patients had surgery within two years.	More patients were treated with intervention in the latter period without increasing adverse events. Adverse events were rare. It seems safe to perform intervention during surgery.
Paper II 	To evaluate and compare outcome in pregnant and non-pregnant patients subjected to intervention.	A register-based (GallRiks) retrospective analysis.	Intraoperative complications were rare. No difference between pregnant and non-pregnant patients was seen when adjusting for confounders.	Cholecystectomy and ERCP are safe in the pregnant population regarding surgical outcome parameters.
Paper III 	To evaluate the surgical outcome of cholecystectomy during surgery in patients with previous bariatric surgery.	A register-based (GallRiks and SOReg) retrospective analysis.	In contrast to non-pregnant patients, the risk for adverse events was not increased for pregnant patients with previous bariatric surgery.	Cholecystectomy is safe in pregnant patients with previous bariatric surgery.
Paper IV 	To evaluate maternal-fetal outcome in patients subjected to gallstone intervention in pregnancy.	A register-based retrospective analysis. Patients with gallstone intervention during pregnancy were compared to a 1:5 matched control group.	The only adverse factor was more premature births in the whole intervention group. There were differences in patient characteristics.	Gallstone intervention is safe for pregnancy outcomes and the newborn child.
Paper V 	To evaluate the patient's experience of gallstone surgery during pregnancy.	A survey using a questionnaire and Beck´s Depression Inventory-II.	Most patients were worried about their child and experienced insufficient information.	Patients should be educated about their disease and upcoming procedure.

Abbreviations

AI	Artificial Intelligence
AOR	Adjusted Odds Ratio
APGAR	Appearance Pulse Grimace Activity Respiration
ASA	American Society of Anesthesiologist
BDI-II	Becks Depression Inventory II
BMI	Body Mass Index
CBD	Common Bile Duct
CI	Confidence Interval
EPDS	Edinburgh Postnatal Depression Scale
ERCP	Endoscopic Retrograde Cholangiopancreatography
GallRiks	The Swedish Registry for Gallstone Surgery and Endoscopic Retrograde Cholangiopancreatography
GIQLI	Gastrointestinal Quality of Life Index
HIS	Hyperemesis Impact of Symptoms
ICD-10	International Classification of Diseases 10th Revision
LC	Laparoscopic Cholecystectomy
LOS	Length of stay
MBR	Medical Birth Registry
MGI	Mother Generated Index
mGy	Milligray
OC	Open Cholecystectomy
OR	Odd Ration
PQUE	Pregnancy Unique Quantification of Emesis
PROMIS-10	Patient Reported Outcome Measurement Information System 10
PTC	Percutaneous Transhepatic Cholangiography
QR	Quality Register
RRCT	Registry-based Randomized Controlled Trials
SAGES	Society of American Gastrointestinal and Endoscopic Surgeons

SALAR	Swedish Association of Local Authorities and Regions
SF-12	12-item Short Form Survey
SF-36	36-item Short Form Survey
SOReg	Scandinavian Obesity Surgery Registry

Introduction

Gallstones have been a part of human physiology for at least 3500 years, according to radiological autopsies of Egyptian, Chinese, and South American Mummies[1, 2]. Unfortunately, no reliable peer-reviewed studies from this era exist, but it is safe to assume that managing symptomatic or complicated gallstone disease has been a clinical dilemma for physicians for a long time. Medicinal and technological progress has accelerated in the last century making surgical procedures such as cholecystectomy and ERCP mainstay and routine[3]. There are, however, still certain circumstances where decisions on treatment are difficult to make. One of those circumstances is when the patient is pregnant.

Historically, gallstone surgery during pregnancy was associated with a significant risk of severe adverse events. Fetal loss was reported in 15% of cases of uncomplicated gallstone disease. When performed because of complicated gallstone diseases such as acute pancreatitis, maternal mortality was reported as high as 15% and fetal loss at 60%.[4, 5] Even considering these numbers, intervention for gallstone-related disease had some early advocates.[6] The evolution of laparoscopic surgery did not initially change the view of surgery in pregnancy as a dangerous procedure. In fact, pregnancy was considered an absolute contraindication for laparoscopic surgery.[5]

However, non-operative management was not without risks. Relapse rates were 38-70%, and up to 6 relapses requiring admission were reported in the same patient. The severity of the disease increased with every admission.[7, 8] Acute pancreatitis is not treated by cholecystectomy, but surgery is preventive for recurrent episodes or development of acute pancreatitis from milder forms of gallstone disease. Although maternal mortality rates of acute pancreatitis have dropped from historically 37% to 3.3% and fetal death rates from 60% to 11.6-18.7%, prevention of acute pancreatitis is still essential. Non-operative management of cholecystitis in pregnancy is associated with significantly worse maternal-fetal outcome and more readmissions.[9]

The main concerns of laparoscopy were injury to the fetus or uterus by trocars, impaired blood flow to the fetus because of pneumoperitoneum, and adverse effects of anesthetic drugs. The risk of radiation-induced damage to the fetus was also considered in ERCP. Although the negative effect of pneumoperitoneum has since been refuted and new anesthetic drugs and methods to minimize radiation have been developed and studied, the risk of damage to the uterus remains, as does the general risk to the fetus concerning general adverse events.[10]

Gallstone disease during pregnancy is common enough that every abdominal surgeon will encounter these patients during a career. Even though the evidence suggests that gallstone intervention during pregnancy is safe and that indications for surgery should mainly be the same as for non-pregnant patients, recent research suggests that pregnant patients do not receive optimal care, as recommended in guidelines, probably because of apprehension of the treating surgeon.[9, 11]

The aim of this thesis is to add further information to the growing body of knowledge about gallstone intervention during pregnancy with the hope of improving the care of this particular patient group.

Figure 1.
Changed dietary patterns during pregnancy might contribute to the risk of forming gallstones. (© Bodil Johansson Photography)

Anatomy and physiology

Bile is produced in the liver cells and transported through bile ducts, eventually emptying into the duodenum through the Ampulla of Vater and sphincter of Oddi. Connected to the common bile duct (CBD) is the gallbladder. The function of the gallbladder is to act as a reservoir for bile – when fasting, no bile is emptied to the bowel but instead collects in the gallbladder. When eating, the gallbladder contracts and the sphincter of Oddi opens, thus allowing the bile to meet the food in the duodenum.

Although anatomical variants may occur, the pancreas is usually connected to the CBD through the pancreatic duct, emptying its exocrine secret through the sphincter of Oddi (Figure 2).

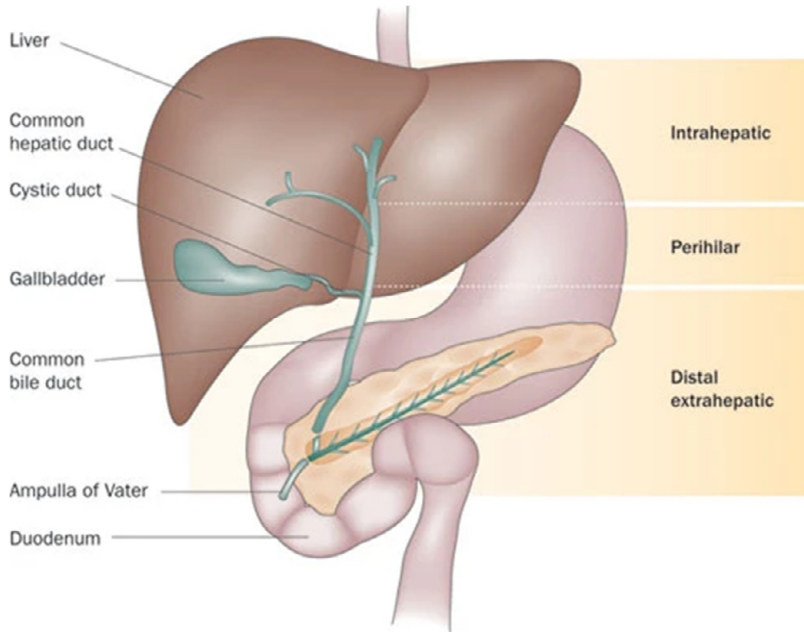


Figure 2.
Anatomy of the biliary tract. (From Blehacz et al. [12] Reprinted with permission from Springer Nature)

Bile has two main physiological functions. One is secreting insoluble waste products mainly from heme catabolism, and the other is to aid in food digestion and nutrient uptake. The main components of bile are bile acids, phospholipids, cholesterol, bilirubin, and smaller amounts of ions and trace metals[13]. The composition and regulation of bile and bile synthesis are complex and delicate. Genetic as well as environmental factors and individual differences significantly affect these processes[14].

Pathophysiology

Gallstone formation

Gallstone formation occurs due to three different circumstances. One is an imbalance in bile composition and supersaturating of bile which occurs when there is either an abundance of specific molecules (such as cholesterol) or when the solubility properties are changed. The other circumstance is impaired gallbladder motility, where bile is stored longer in the gallbladder. The third reason is the accelerated nucleation process, where certain biochemical processes make the molecules form conglomerates and eventually solidify.[14] Gallstone formation usually occurs in the gallbladder, from which the stones might eventually migrate into the bile ducts or, more seldom, primarily be formed in the bile ducts.[15] Classically, gallstones are divided into three subgroups depending on composition, cholesterol stones (with >70% cholesterol), pigment stones (<30% cholesterol), and mixed stones (30-70% cholesterol).[16] Later research has suggested further division into more detailed groups.[17] Although there are differences in the chemical composition and formation mechanisms that might be interesting to study further, the traditional classification suffices for clinical and practical purposes. Cholesterol stones are by far the most common type of stone in the western world at 80%.[18, 19]

Gallstone disease

Most gallstones are asymptomatic. Approximately 20% of patients with gallstones will develop symptoms or have a complication of gallstones during their lifetime[20]. Symptoms or complications occur depending on the location of the gallstone and patient-specific conditions (Figure 3).

Stones in the gallbladder can cause biliary colic, an episode of intensive pain in the upper part of the abdomen thought to be caused by outflow obstruction when a gallstone lodges in the cystic duct. When the gallbladder contracts, high pressure and gallbladder wall stress cause pain. When the gallstone dislodges, either spontaneously or with the help of medication, the symptoms subside.

Cholecystitis is clinically characterized by persistent pain in the upper right quadrant and is usually accompanied by fever. Cholecystitis is also thought to be caused by outflow obstruction and high pressure but is complicated by triggering an acute inflammatory response mediated by prostaglandins. Damage to the mucosa makes the gallbladder susceptible to secondary bacterial infections, which occur in about 20% of cases.[21]

Acute pancreatitis is a possibly life-threatening disease and is most often caused by gallstones that have either migrated from the gallbladder or formed in the bile ducts, which causes outflow obstruction of the pancreatic duct. The resulting high pressure in the pancreatic duct triggers unregulated activation of digestive enzymes, in turn causing an inflammatory response.[22] Acute pancreatitis ranges in severity from mild

pain and discomfort for a few days to severe pain and fulminant systemic inflammation with multiorgan failure and death.

Gallstones in the bile ducts can cause jaundice by partially or entirely blocking bile excretion to the small bowel, leading to the accumulation of bile in the body that gives the skin a yellow tone. These stones can also be asymptomatic and detected by coincidence.

Bile duct stones can also predispose to bacterial infection leading to cholangitis, characterized by high fever, jaundice, and pain.[23]

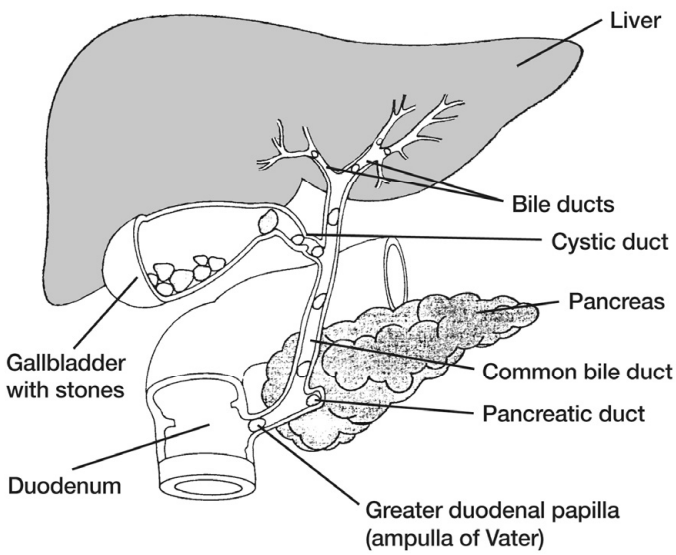


Figure 3.
Symptoms and complications of gallstones depend on location. (Reprinted with permission from National Institute of Diabetes and Digestive and Kidney Diseases, National Institutes of Health)

Risk factors

Several risk factors affect the risk of forming bile stones, both hereditary and exogenous. Traditionally, age, obesity, and female gender have been considered the main culprits, but later research has widened this list.[24] Age is a risk factor because of other accumulated risks over the years. The other risk factors have different mechanisms but are all related to the three circumstances described above – bile supersaturation, impaired gallbladder motility, and accelerated nucleation process. Risk factors that mainly affect bile supersaturation are associated with metabolic syndrome (obesity, insulin resistance, and diabetes but also physical inactivity) and diet (high-calorie diet, high carbohydrate diet, and low fiber intake, for example). Risk factors associated with impaired gallbladder motility are prolonged fasting

(dieting or weight cycling, rapid weight loss after bariatric surgery, total parenteral nutrition, and gastrectomy, for example). Through complex mechanisms, all these risk factors also affect the accelerated nucleation process. Several additional conditions, such as Crohn's disease, liver cirrhosis, and other diseases, as well as several types of medication, including hormone-replacement therapy, octreotide, and fibrates, enhance the risk for gallstone formation.[20] Some of the risk factors mentioned above are independent, some are more or less depending on other risk factors, and some are not yet completely understood.[18]

Pregnancy is an independent risk factor for the formation of gallstones, later discussed in detail.

Epidemiology

The prevalence of gallstones differs in different populations worldwide (Figure 4). In Europe, an estimated 5.9-21.9% of the general population harbors gallstones, with a yearly incidence of 0.60-1.39%. Incidence is higher for women and increases with age. [25] In Sweden, a prevalence of gallstones of 15% and an annual incidence of 1.39% in the general population have been reported. Prevalence rates among women in Sweden are 11-25%.[26] An estimated 20% of patients with gallstones will develop symptoms or complications during their lifetime, making gallstone-associated disease one of the most common reasons for emergency care visits, admissions, and surgery worldwide.[20, 27-29] Several risk factors have increased in the general population and gallstone disease is expected to increase.[24]

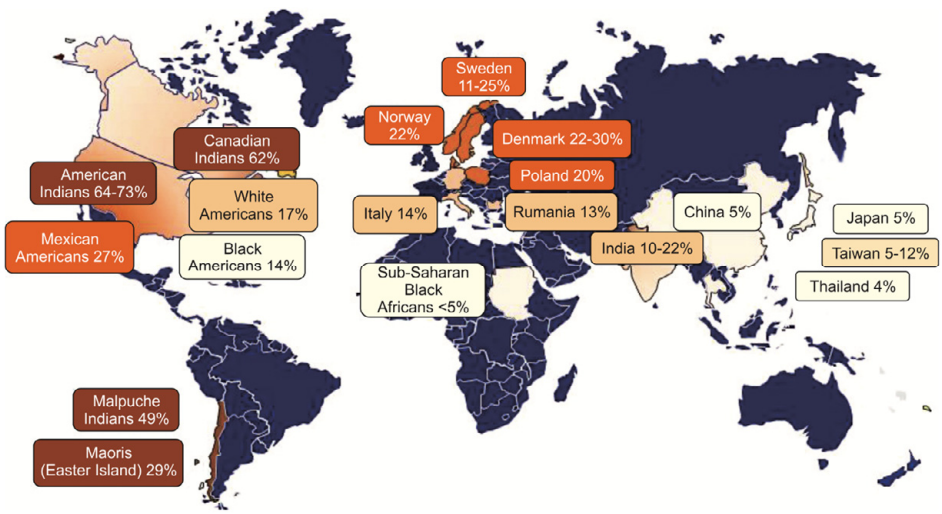


Figure 4.
Worldwide prevalence of gallstones in females based on ultrasonographic surveys. (Reproduced from Shaffer et al.[26] Open Acess, CC BY-NC 3.0)

Management

The management of symptomatic and complicated gallstones is two-fold. One part is the general acute treatment of symptoms and complications, such as analgesics, fluid resuscitation, and antibiotics. The other part is interventional and can be performed acutely or delayed for treatment or relapse prevention. Indications differ with different manifestations of gallstone disease. All patients subjected to intervention must be carefully selected since no intervention is without risk.[30]

Gallbladder surgery

The purpose of cholecystectomy is to remove the gallbladder, including all stones, and is most often used to prevent future episodes of biliary colic or complications. In certain circumstances, such as severe cholecystitis, the procedure is performed as an emergency procedure as a means to achieve source control.

The first cholecystectomy was performed by Carl Langenbuch in Berlin in 1882 through a large abdominal incision. The patient survived and was released from the hospital two months later. [31] In the following century, open cholecystectomy developed into a mainstay procedure. Another German, Eric Muhe, performed the first laparoscopic cholecystectomy in Böblingen in 1985. Although initially met with some skepticism, the advantages of the laparoscopic technique soon made it the golden standard for gallbladder surgery.[32, 33] Even though the laparoscopic technique is advantageous in terms of morbidity, mortality, length of stay, and not inferior in certain complications (bile duct injury and bleeding), there is still a role for the open technique; In some patients, laparoscopy might be difficult or contraindicated, in some of the cases initially performed laparoscopically, difficulties or complications might prompt conversion to open surgery.[34, 35] In 2021, 97% of planned cholecystectomies and 92% of emergency cholecystectomies in Sweden were performed using laparoscopic technique.[36]

Open Cholecystectomy

Open cholecystectomy is performed through a right-sided subcostal incision. The gallbladder is usually mobilized from the top down, using an energy instrument such as bipolar scissors, unipolar knife, or in some cases, microwave instruments. The cystic artery and the cystic duct are identified and dissected. A cholangiography can be obtained by inserting a catheter through the cystic duct and administering contrast. The cystic duct and the cystic artery are then ligated, and the gallbladder is removed. The abdominal wall is closed in two layers, and the skin is usually stapled.

Laparoscopic Cholecystectomy

A standard laparoscopic cholecystectomy is usually performed using two 10-12mm trocars in the midline, one just above or below the umbilicus and one below the xiphoid process, and two 5mm trocars in the right flank. Pneumoperitoneum is achieved by insufflation of CO2 or air. The first step is usually to dissect the area below the gallbladder, freeing the cystic plate from fat and fibrous tissue, identifying the cystic duct and the cystic artery, and thus obtaining "critical view of safety".[37, 38] A cholangiography can then be performed via a catheter in the cystic duct. The cystic duct and the cystic artery are then divided using metallic clips, and the gallbladder is dissected from the liver bed.

Other techniques

There are several variants of both open and laparoscopic techniques that have been proposed and tested and sometimes used for a while, such as a minimally invasive technique for open cholecystectomy, in Sweden referred to as "Minigalla", and variants of laparoscopic techniques such as single port or natural orifice surgery. However, none of these techniques has achieved any widespread use.

Bile duct procedures

Traditionally, before the era of laparoscopy and endoscopy, open bile duct surgery with choledochotomy was performed if stones were present in the bile ducts. In the laparoscopic era, several techniques have been developed to handle bile duct stones, such as laparoscopic choledochotomy and trans-cystic bile duct exploration. In the present day, the most common procedure utilized for bile duct stones is Endoscopic Retrograde Cholangiopancreatography, ERCP. Initially, ERCP was developed for diagnostic purposes, and the first procedure was performed by WS McCune and colleagues in 1968. Since then, several technological advancements, specifically in the therapeutic area, have been made.[39, 40]

ERCP

An endoscope is advanced to the duodenum, where the Papilla of Vater is located. Under fluoroscopy, a guidewire is advanced into the bile ducts. Using an electrocautery instrument, the sphincterotome, the Sphincter of Oddi is incised, a procedure called sphincterotomy. A cholangiogram is obtained by injecting contrast, and stones can be retrieved using balloons or baskets. Larger stones can be fragmented using laser or mechanical instruments. Several advanced techniques can be used for inspecting the bile ducts visually. When performed either during or directly after cholecystectomy, a guidewire can be placed through the cystic duct into the duodenum, thereby increasing success rates and diminishing the risk of post-ERCP pancreatitis.[41]

Other techniques

Besides open and laparoscopic choledochotomy and trans-cystic bile duct exploration, there is a radiological method, percutaneous transhepatic cholangiography (PTC), for transcutaneous drainage and stent placements in the bile ducts. There are modifications to traditional techniques if circumstances demand, for example, transgastric ERCP in patients that have performed bariatric surgery in the form of gastric bypass. In this procedure, a trocar is inserted into the stomach with laparoscopic technique, and ERCP is performed through this port.[42] Novel modifications, such as EUS-guided ERCP, are being evaluated for the same patient group.[43]

Current surgical management in non-pregnant patients

Biliary colic

As previously described, most patients with gallstones will never have any symptoms or complications and should not be subjected to interventional treatment.[44] Biliary colic attacks range from single episodes that might never return to debilitating frequent attacks requiring prompt treatment. Complicating the picture is that pain in the upper abdomen might be multifactorial, even with gallstones confirmed on ultrasound. A reported 10-40% of patients have persistent pain in the upper abdomen following cholecystectomy, highlighting the need for meticulous patient selection before surgery.[30]

There are several guidelines regarding the management of patients with symptomatic gallstones, although the definition of symptomatic gallstones varies. Cholecystectomy is generally recommended for recurrent attacks, frequent attacks, and after a thorough individual cost-benefit analysis of the procedure for each patient.[3]

Cholecystitis

Early laparoscopic cholecystectomy (within one week of onset of symptoms, or, preferably, within 72 hours) is recommended for cholecystitis in the absence of contraindications. If early cholecystectomy is not possible, conservative treatment with planned cholecystectomy after at least six weeks is recommended.[45, 46] In certain patients, where surgery under general anesthesia is not an option, drainage in the form of ultrasound-guided transcutaneous cholecystostomy might be considered.[47]

Acute pancreatitis

Due to the high risk of recurrent disease, same-admission laparoscopic cholecystectomy is recommended for gallstone-induced acute pancreatitis when

symptoms have subsided. Same-admission ERCP is recommended in the presence of bile duct stones.[48]

Cholangitis

Biliary drainage is recommended for all severity grades of cholangitis. The preferred method is drainage through ERCP, although PTC is acceptable if circumstances make ERCP impossible. Cholecystectomy is recommended if gallbladder stones are present, when the symptoms have subsided.[46, 49]

CBD stones

Laparoscopic cholecystectomy and clearance of bile ducts, either through intraoperative ERCP, laparoscopic common bile duct exploration, or trans-cystic bile-duct exploration, are recommended. If those methods are unavailable, preoperative ERCP is recommended. [50]

Gallstone disease and Pregnancy

Pathophysiology

Pregnancy is considered an independent risk factor for the formation of gallstones and sludge. The mechanisms are not yet completely understood, and several mechanisms probably interact. It is thought to be mainly facilitated by female sex hormones, where, for example, concentrations of estradiol and estrone increase 100-fold in late pregnancy. These elevated estrogen levels are associated with increased hepatic secretion of cholesterol, leading to supersaturation of bile which in turn leads to increased lithogenicity. Elevated estrogen and progesterone levels also affect gallbladder motility, leading to gallbladder stasis and promoting gallstone formation (Figure 5). The accumulated exposure of elevated hormones in multiparity increases the risk of gallstone formation.

Several other risk factors are proposed in gallstone formation in pregnancy, among them a changed dietary pattern with higher calorie intake and a switch to a high-cholesterol and high-fat diet. Related to this is lowered insulin resistance, also a risk factor. Immunological factors, as well as altered gut microbiota, are also thought to have an influence on gallstone formation in pregnancy.[51]

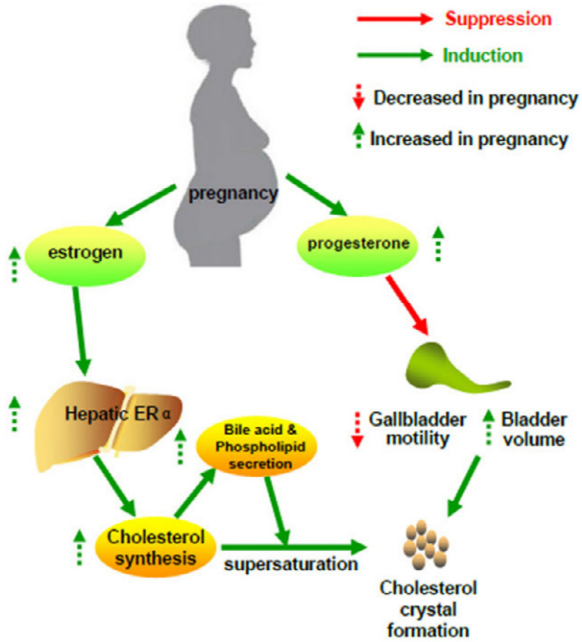


Figure 5.
Cholesterol stone formation during pregnancy. (Reproduced from Wu et al.[52] Reprinted with permission from John Wiley and Sons)

Other, general risk factors are also increasing in the pregnant population. Obesity among pregnant women is rising rapidly in Sweden, from 6% in 1992 to 14% in 2016.[53, 54] Along with the obesity pandemic, bariatric surgery has exploded in the last decade, and most of those patients are female of childbearing age.[55] With the increasing incidence of first-birth rates in women aged 35-39 and a generally higher maternal age in some populations, this risk factor is also to be considered in the pregnant population.[56]

Epidemiology

The incidence of gallstones detected on ultrasound in pregnancy is 3.5-12.1%.[57, 58] The incidence increases with increasing gestational age.[59] Newly formed sludge during pregnancy, in a previously normal gallbladder, has been reported to be 10.9-31%. Incidence rates of newly formed gallstones in the same studies were 2-5.2%.[60, 61] Interestingly, sludge in particular, but also stones, might disappear after delivery. The mechanism behind this regression is unknown.[59, 61]

Most pregnant patients with gallstones or sludge will remain asymptomatic throughout the pregnancy. An estimated 39-40% of patients with gallstones or

sludge detected on ultrasound will experience symptoms, most of which are mild and do not require admission or surgery.[57, 58, 60]

The most common specific disease is biliary colic, with an incidence of 0.2-2%.[62] Of the cases of pregnant patients with gallstone-related admissions during pregnancy or in the immediate postpartum period, biliary colic makes up 76-80%[63, 64] Total incidence of gallstone-related complications during pregnancy is estimated to be 0.05-0.8%.[65] Cholecystitis is reported to complicate pregnancy in 0.06-0.2%, and acute pancreatitis incidence is 0.03-0.1%, with an estimated 70% caused by gallstones in the western hemisphere and a range of 14-96% worldwide.[66] The incidence has increased in later years, probably because of better diagnostic tools.[67-69] CDB stones are found on cholangiography during cholecystectomy in 5-20% of all patients.[70] There are no data on the incidence of asymptomatic CBD stones in pregnancy. Biliary obstruction is rare during pregnancy, and incidence numbers are uncertain. CBD stones have been reported to be present in 14-15% of patients, either as the primary reason for admission or associated with another gallstone complication. [71, 72] Based on the number of ERCP procedures in a pregnant population, the incidence of CBD stones is 1/1415 pregnancies.[73] Even more rare is cholangitis; the proportion of cholangitis in pregnant patients with complicated gallstone disease is often referred to as 5%, based on a population study with one case of cholangitis.[74]

Current guidelines for management in pregnant patients

The SAGES guidelines for the use of laparoscopy during pregnancy, initially published in 2007 and updated in 2011 and 2017, recommends early laparoscopic cholecystectomy for pregnant patients in all trimesters.[11, 75, 76]. Several other guidelines have been published with consensus and moderate levels of evidence that pregnant patients should be managed in the same way as non-pregnant patients.[77] The American College of Obstetricians and Gynecologists Committee on Obstetric Practice and The American Society of Anesthesiologists states that *"A pregnant woman should never be denied medically necessary surgery or have that surgery delayed regardless of trimester because this can adversely affect the pregnant woman and her fetus"*.[78] At present, sixteen years after the initial publication of the SAGES guidelines, more pregnant women with symptomatic or complicated gallstone disease are still managed conservatively compared to non-pregnant patients, resulting in worse outcome and more readmissions.[9, 63, 79] Further, hesitation to perform surgery leads to delay, with increased risk of adverse fetal events every day.[69]

Biliary colic

In cases with symptomatic gallstone disease in pregnancy without complications, nuances in guidelines exist. Some guidelines recommend that laparoscopic

cholecystectomy should be considered for all patients at presentation, while others suggest that initial admission and observation are acceptable and subsequent laparoscopic cholecystectomy performed if therapy fails or if there are recurrent episodes.[3, 11, 80]

Complicated gallstone disease

When complications to gallstones occur, such as cholecystitis, acute pancreatitis, or cholangitis, recommendations are to treat pregnant patients in the same way as non-pregnant patients; for cholecystitis, early laparoscopic cholecystectomy is recommended. For acute pancreatitis, same admission laparoscopic cholecystectomy is recommended, as well as bile duct clearance through ERCP or laparoscopic bile duct exploration intraoperatively, or ERCP preoperatively if the other options do not exist. In cholangitis, bile duct drainage might be indicated before surgery is considered, preferably through ERCP, and laparoscopic cholecystectomy when symptoms have subsided.[3, 11, 77, 80, 81] Asymptomatic CBD stones should be managed with the least invasive method available, ERCP or laparoscopic bile duct exploration, depending on resources.[3, 11]

Non-operative management of gallstone disease in pregnancy

Most patients with biliary colic during pregnancy are managed non-operatively (82-92.5%). A significant number (38-70%) of patients hospitalized for biliary colic have one or more relapses during pregnancy requiring admission, with increasing severity grade or the development of gallstone complications.[7, 8, 71, 79] Relapse incidence has been reported to be as high as 92% in the first trimester, 64% in the second and 44% in the third, and subsequent complicated gallstone disease in 23-39%.[3, 64, 79]

Cholecystectomy is performed in 38-64% of pregnant patients with cholecystitis, with an increasing trend since 2007.[9, 69, 72, 82] In a non-pregnant population with cholecystitis, cholecystectomy rates are 82-90%.[82, 83] Non-operative management of cholecystitis are associated with twice the odds of maternal-fetal complications, including pre-term delivery and fetal loss in some recent studies but associated with small but significant differences in surgical complications in other.[9, 69, 82]

Acute pancreatitis during pregnancy is caused by gallstones in 66% of patients, significantly more than in an age-adjusted female control group. In the same study, 32% of the pregnant patients had a cholecystectomy performed, similar to the non-pregnant group.[84]

Other studies have shown that cholecystectomy is performed in 27-53% of pregnant patients and ERCP in 21-24%, somewhat less than in comparable non-pregnant patients. In these studies, patients managed operatively had fewer readmissions and adverse events.[68, 85] Earlier studies has also shown unfavorable outcome when acute

pancreatitis is managed non-operatively, with higher rates of pre-term births and fetal loss as high as 10-60%.[65, 86]

Literature on cholangitis during pregnancy is scarce. Case reports and small case series have shown that both ERCP and cholecystectomy can be performed safely in pregnancy.[87, 88] Cholangitis in pregnancy is associated with a risk of premature birth and spontaneous abortion in 10% of cases.[11]

Asymptomatic CBD stones can progress to complicated bile stone disease. In a small study, 11/12 patients initially presenting with biliary obstruction were subjected to ERCP.[71]

Surgery during pregnancy

The incidence of acute abdomen in pregnancy is 1/500-635, and the incidence of non-obstetric surgery during pregnancy is 1-2%.[65, 89] After appendectomy, cholecystectomy is the second most common procedure, with an incidence of 1/1,600-10,000 pregnancies.[90]

Surgery in the pregnant patient requires certain measurements to be taken to ensure not only the well-being of the mother but of the fetus as well. A thorough preoperative evaluation and preparation is mandatory, including coordination and consulting of obstetrical, neonatological, and anaesthesiological expertise.[91]

Since the stakes are higher for surgery during pregnancy, it is recommended that the highest possible surgical or endoscopic competence is used, as this significantly affects the outcome (Figure 6).[92]

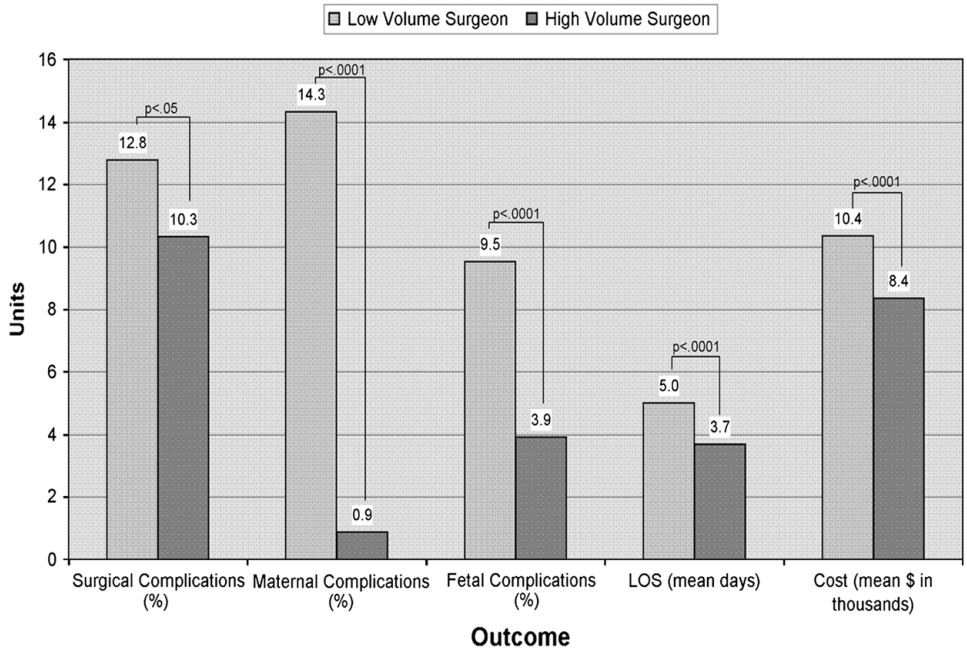


Figure 6.
Outcomes after cholecystectomy in pregnant women based on surgeon volume. (From Kuy et al.[92] Reprinted with permission from Elsevier)

Specific considerations

Surgical considerations

The laparoscopic technique has the same advantages in pregnancy as in non-pregnant patients, and no additional risks have been seen using this technique. However, the gravid uterus might interfere with the operational field after the first trimester, and damage needs to be carefully avoided.

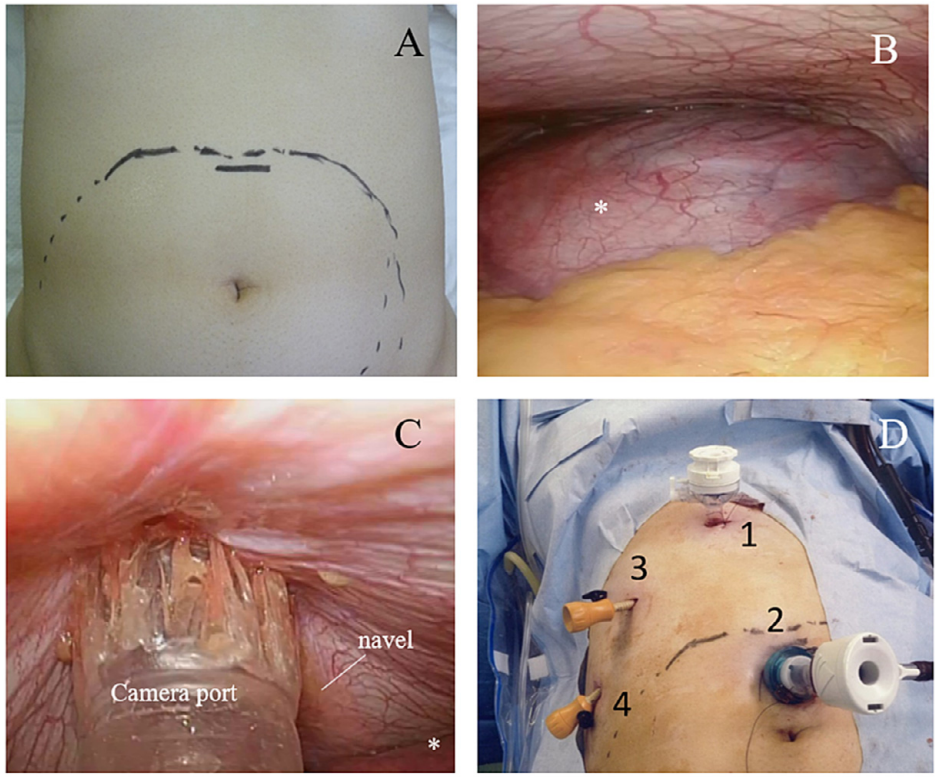


Figure 7.
Laparoscopic cholecystectomy in week 21. Procedure for port insertion: A) Marked the uterine fundus after the induction of anesthesia. B) The point of view from the first port (epigastric region). The large uterine was observed (*)C) To avoid uterine damage, the camera port was placed under laparoscopic observation. D) LC with four ports. (From Iwai Et. al.[93] Open Acess, CC-BY 4.0).

Port placement might need to be adjusted, but both open (Hasson) and closed (Verres needle) techniques for initial port placements are considered safe, if executed properly (Figure 7).[94]

Pressure from the uterus on the inferior vena cava can lead to decreased blood flow to the placenta, and a left lateral decubitus position is recommended.[95]

Carbon dioxide insufflation has not been shown to affect human fetuses negatively, but uncertainties remain, and intraoperative monitoring of CO2 with capnography is recommended.[96] In fact, Fetoscopic procedures with CO2 insufflation directly into the uterus are performed with no apparent adverse effect on the fetus.[97] Pressure of pneumoperitoneum has been proven safe in the range of 10-15 mmHg[11]

Individual assessment of the need for medical antithrombotic prophylaxis is recommended but not routine administration in uncomplicated cases. However, it

should be given if the surgery implies bed rest, until full mobilization. Other measures to prevent thrombosis, such as early mobilization and compression devices, are recommended.[69, 98]

Obstetrical considerations

Surgery should be performed in an institution where obstetric and neonatal services are available, and expertise consulted preoperatively.[91]

Fetal heart rate monitoring should be performed, preferably continuously but at least before and after surgery in all viable fetuses after week 23.[99]

Tocolytics should not be used routinely, but individual assessments should be made by proper experts.[11]

Prophylactic cortisone should be considered to help speed up lung maturation and improve outcome in pre-term births.[91]

Anesthetic considerations

There is no evidence of detrimental fetal effects of anesthetic agents administered in standard doses.[91]

Beyond 16-20 weeks, the pregnant patient's stomach should be considered full, regardless of food intake, and necessary precautions against aspiration should be taken.[91]

Cardiovascular, pulmonary, renal, gastrointestinal, endocrine, and hematological changes caused by pregnancy should be recognized and proper adjustments made.[91]

Ionizing radiation

When intraoperative cholangiography or ERCP is performed, there is fetal exposure to ionizing radiation. High doses might cause teratogenic effects or increase the risk of childhood blood malignancies or other diseases.[100] The effect on the fetus depends on the cumulative dose of ionizing radiation and the age of exposure. Radiation doses below 50-100 mGy are generally considered acceptable if the procedure is relevant. The current recommendation is that no radiological procedure should exceed 50 mGy.[11, 101] Radiation doses for ERCP are estimated to be 1.02-12 mGy but vary depending on the difficulty of the procedure and operator experience[80, 102, 103] Intraoperative cholangiography produces even lower doses of radiation.[104] Although theoretically safe, there is still controversy regarding ionizing radiation during pregnancy. Even if the increased risk to the fetus is minimal, the recommendation is that measures to decrease radiation should be taken, including lead shielding. An experienced endoscopist might shorten procedure time and thereby minimize exposure time.[102]

Timing of surgery

Traditionally, surgery during the second trimester has been advocated. The rationale for this is the theoretically higher risk of teratogenic effects on the fetus in the first trimester, the size of the uterus and the risk of preterm labor in the third trimester.[96, 105] This recommendation is primarily based on older and small studies, mainly on open surgery. The dogma prevails, however, which might contribute to hesitation to perform surgery with a negative effect on the outcome.[106] Several studies have since confirmed the safety of surgery in all trimesters.[86, 107] There are some controversies in this subject, where some researchers suggest postponing surgery in the third trimester until after birth.[108] This might be the correct management in some cases, but a thorough evaluation of every individual patient needs to be made since a delay in surgery might prove to be associated with a worse outcome.[109]

Aims of the thesis

The overall aim of this thesis was to investigate outcome of intervention in pregnant patients with gallstone disease, with the hope of identifying modifiable parameters to improve management. Specific aims were:

I. To examine the incidence of gallstone disease in pregnancy, outcome, management strategies, and changes in management strategies over time.

II. To investigate the outcome of patients subjected to either cholecystectomy, ERCP, or both and compare outcome between pregnant patients and non-pregnant females of similar age.

III. To investigate outcome of pregnant patients with previous bariatric surgery to non-pregnant patients with or without previous bariatric surgery.

IV. To investigate maternal-fetal outcome of patients subjected to surgery during pregnancy and compare this to maternal-fetal outcome in a matched pregnant control group without surgery during pregnancy.

V. To investigate patient perception and experience before, during, and after surgery and identify modifiable factors that might improve the general care of these patients.

Materials and Methods

There is no ethically reasonable way to perform a randomized, double-blind, placebo-controlled study of this patient group. Hence, all evidence is derived from observational studies. Current recommendations and guidelines are mainly based on case series, large and small, and administrative database population studies. In Sweden, the use of the personal identification number, unique for every citizen and repeated throughout every administrative and clinical database and registry as well as in journal documentation, makes it possible to crosslink data and obtain detailed information about patients and events. This feature has been used in all papers. Although mainly the same patients are evaluated in the different papers, every specific study has been performed separately, including inclusion and exclusion, grouping, and statistical calculations (Figure 8).

Sweden has a long history of using quality registers. The first was the Swedish Knee Arthroplasty Register, established in 1975.[110] Since then, a multitude of additional registries has been founded. The Swedish Government finances the Swedish registries through the Board of Health and Welfare (Socialstyrelsen) and the Swedish Association of Local Authorities and Regions (SALAR) with a 70/30% split. The purpose of the registries is to make it possible to compare and evaluate national data for quality assurance as well as being utilized for research. In the Swedish Patient Data Act, the definition of a quality registry is: "A QR is an automated and structured collection of personal data that were initiated with the purpose to systematically and continuously develop and safeguard the quality of care. A national or regional QR refers to a QR in which personal data have been collected from several caregivers and which allows for comparisons within healthcare at a national or regional level".[111] In addition to the specific registries, Sweden has a national, government-funded, mandatory register of all patients in Sweden, including the National Inpatient Register, which can be used for research in itself but also as a tool to evaluate and validate other registries.

The quality of a quality register is evaluated by the completeness and correctness of data, usually performed by randomized sampling and comparison with other registries or journals. A high coverage rate and continuous and structured validation of data is also an important factor in assessing the quality.[111]

The Swedish Registry for Gallstone Surgery and Endoscopic Retrograde Cholangiopancreatography (GallRiks) is a nationwide register that offers a unique

opportunity to study patients subjected to intervention. It has a coverage rate of 90%, and annually, about 14,000 cholecystectomies and 9000 ERCPs are added.[36, 112] The register has demonstrated high correctness at 97.1-98.1% and is continuously validated.[113] Since 2009, the parameter "Pregnant" was added, making it possible to identify patients that were pregnant at the time of their procedure.

MBR, the Swedish Medical Birth Registry, founded in 1973 and managed by The National Board of Health and Welfare, has recorded 97-98% of all births in Sweden since 2000 and records 99% since 2015. The register includes antenatal, obstetric, and neonatal parameters and has shown high correctness of data.[114]

SOReg, the Scandinavian Obesity Surgery Registry, was initiated in 2004 and includes all units that perform bariatric surgery, both publicly funded and private, since 2013. Multiple preoperative and intraoperative data are entered, as well as follow-up data at six weeks. QoL questionnaires are sent to the patients at baseline and one, two, and five years.[115] The register has been validated repeatedly and shows high accuracy of data.[116]

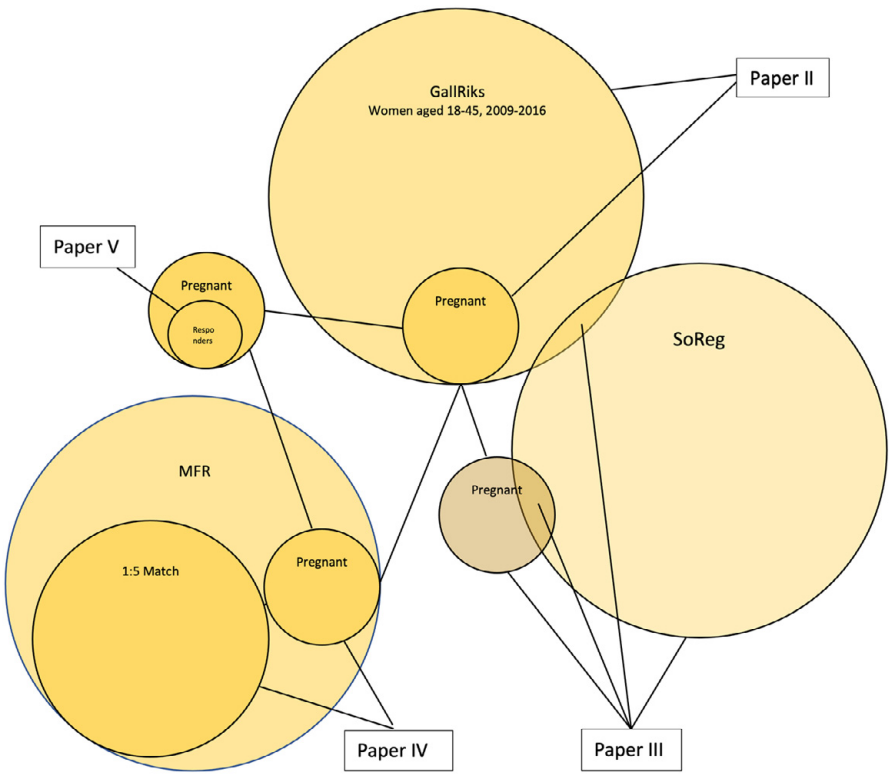


Figure 8.
Chart of extraction and crossmatching of data from the GallRiks, SOReg, and MBR. Sizes do not represent actual proportions.

Several well-established and validated generic questionnaires are used to assess the subjective outcome of surgery, for example, SF-36, GIQLI, SF-12, and PROMIS-10. These questionnaires measure different aspects of physical, mental, and social health, quality of life, pain, and more.[117] None of these are designed to measure obstetric outcomes. Further, generic questionnaires that measure obstetric outcomes, such as HIS, PQUE, MGI, EPDS, et cetera, do not cover all areas of interest in our study.[118] A combination of several generic questionnaires was not deemed suitable for our patient group. Hence, a unique questionnaire was constructed, including filter questions, closed questions answered on a Likert scale or with an undecided or "do not know" alternative, and open, free-text alternatives as recommended in guidelines.[119, 120] To evaluate psychological impact in a structured way, we included Becks Depression Index-II, a well-validated tool that was used to complement the targeted questionnaire.[121]

Paper I

A database search of all patients with ICD-10 diagnose codes for pregnancy and gallstone-related disease in Skane University Hospital between January 1, 2001, and December 31, 2015, was performed. Skane University Hospital consists of two large regional hospitals, formerly known as Lunds Universitetssjukhus and Malmö Allmänna Sjukhus. The official date for the fusion was January 1, 2010, but the fusion process was started before that and was not finalized administratively until several years later. Hence, medical records were located in both locations and different departments, both surgical departments, obstetrical departments, and outpatient maternal care departments. Digitalization was also ongoing during the study period, so some medical records were digital, and some were on paper files. After arduous work compiling a database with a set of predetermined parameters, including preoperative data, data on intervention, and surgical and maternal-fetal outcome, the patients were divided into two groups – one that had intervention performed and one that was treated conservatively and compared. We also analyzed differences in presentation and management in index admission and following admissions for relapse. The patients were further divided into two time periods to analyze the change in management strategies.

Paper II

GallRiks data for all female patients aged 18-45 between January 1, 2009, and March 12, 2016, were obtained. Pregnant patients were identified and grouped after which procedure or procedures was performed; Cholecystectomy, ERCP, or

combinations of cholecystectomy and ERCP. A comparison was made between all cholecystectomies as well as all cholecystectomies in combination with ERCP between pregnant and non-pregnant patients. All ERCPs in pregnancy were compared to all ERCPs in non-pregnant patients, including multiple ERCPs in the same patients. All index ERCPs performed as only procedure during pregnancy were compared to index ERCPs in non-pregnant patients. Lastly, pregnant patients that had cholecystectomy performed were further divided into trimesters and compared to the other trimesters.

Paper III

The same cohort as in paper II was examined. Using the personal identification number, the patients from GallRiks were crossmatched with SOReg to identify patients that had previous bariatric surgery performed. The patients were divided into four groups depending on pregnancy status and previous bariatric surgery and compared for differences in patient characteristics, indications, intraoperative parameters, and postoperative parameters, including 30-day follow-up. An additional analysis was performed for patients with emergency indication since we hypothesized that pregnant patients were more often treated acutely.

Paper IV

Again, the same cohort from GallRiks was examined. A crossmatch was made using their personal identification number with MBR, and antenatal, obstetric, and neonatal parameters were collected. A 1:5 matched non-pregnant control group was extracted from MBR. Matching criteria were age, place of birth, and season of the year. The pregnant patients were compared to the matched group. The pregnant group was further divided and compared depending on emergency or elective surgery performed. Finally, pregnant patients aged <30 years were compared to pregnant patients >30 years.

Paper V

A questionnaire comprised of 35 questions regarding subjective patient experience of the general care in association with their cholecystectomy was constructed and mailed to patients identified in GallRiks crossmatched with MBR. In addition, the Becks Depression Index-II questionnaire was included in the mail. An analysis of differences between responders and non-responders was performed using GallRiks

data. Text answers were scrutinized and interpreted by the authors, and Likert-scale data were statistically analyzed. Observations were reported, as well as a comparison of the patients who were generally dissatisfied and those who were generally satisfied with their care.

Statistical Methods

All statistic calculations have been made using Stata MP, version 14.1-17, 2015-2020, (StataCorp LP, College Station, TX).

Continuous data in all papers are presented as median and interquartile range (IQR) if not otherwise specified. Categorical data are presented as absolute numbers (n) and proportions as percentages. All statistical analysis was made two-sided, and a p-value <0.05 was considered significant.

Comparisons between groups were made using several different statistical methods. For continuous data, Mann-Whitney U-test was used. For categorical data, chi-square, student´s t-test, or Fisher´s exact test was used, if expected frequencies were less than 5. Comparison of more than two groups was performed with Kruskal-Wallis, and multiple logistic regression was used for calculating OR and adjusting for confounders.

Specific tests

Mann-Whitney U-test

The Mann-Whitney U-test, also known as the Wilcoxon rank-sum test, is a non-parametric (no assumption of normal distribution required) test of the null hypothesis, with the null hypothesis being that both groups have an equal distribution of values. All sample values are ranked, the ranks are summed, and the score is used to calculate differences. The parameters tested need to be either continuous or ordinal, and independent.

Chi-square test

The chi-square test is a non-parametric test of categorical variables. Both ordinal and nominal data can be tested. The test compares samplings of observed and expected frequencies in a contingency table and identifies if there is a difference. The chi-square test uses sampling, and for robustness, the number of observations should be >5.

Fisher´s exact test

Fisher´s exact test is similar to chi-square in that it uses a contingency table (usually 2x2, but larger tables can be used). Instead of using sampling and calculating differences in expected and observed samples, it calculates all possible contingency tables with the same row and column totals and finds all tables that are more extreme than the observed table. Fisher´s exact test can theoretically be used for all sample sizes in the same way as the chi-square test, but for practical reasons, it is used for smaller sample sizes.

Student´s t-test

Student´s t-test is a parametric test used for normal distributed data. It calculates the differences in mean between two groups. Data can be continuous, in ratio or interval scale, and appropriately large sample sizes are needed.

Kruskal-Wallis

The Kruskal-Wallis one-way analysis of variance is a non-parametric test for comparing more than two samples. It uses the same rank-sum method as Mann-Whitney U-test, but for three or more samples. A significant result means that there is a difference between the groups, not caused by chance, but there is no analysis of which group or groups that differ.

Multiple logistic regression

Logistic regression is an extension of linear regression, where continuous variables, one independent and one dependent, are plotted, and a linear equation between the variables is fitted with the best possible correlation. Several independent continuous variables can be used to adjust the correlation. In logistic regression, a dichotomous outcome (dependent) variable is used. By using the natural log odds of the dichotomous outcome, the relationships can be linearized and used as in linear regression. Multiple dichotomous independent variables can be used for adjustment. Results are often reported as an odds ratio. In simple logistic regression, an odds ratio for the dependent variable >1 is interpreted as a correlation with the independent variable, i.e., the odds of the outcome are higher if the independent variable is present. For multiple logistic regression, odds ratio for the outcome is adjusted for the other parameters, and only >1 if there is still a significant association between the independent and the dependent variable.

Ethics

The ethics of all papers included in this thesis was approved by the Regional Ethical Committee in Lund (Dnr:2014/177).

There are three main ethical considerations in our patients. The first is the risk of causing discomfort by reminding the patients of a potentially traumatic event. The second is the risk of reidentification. Studying small patient groups with rare adverse events means there is a risk for unique combinations of parameters such as patient characteristics, disease, intervention, and adverse events that might make individual patients identifiable even though no personal information is provided. The third is the issue of informed consent.

For Paper V, we used crossmatching to identify any deceased mother or child. One patient with a deceased child was found and excluded. Personal identification numbers have been used for identifying and cross-matching patients, but all further analysis and databases have been anonymized. Identification keys have been kept secure and analog. For Papers II-IV, informed consent is required to be registered initially, and this consent includes the use of the data for anonymous participation in scientific research.[122] For paper I, measures were taken to ensure consent by informing about ways to opt out in the local newspaper.

In summary, ethical considerations were made, and proper steps to minimize impact were taken. Further, a thorough cost-benefit discussion was held between the authors internally and with the Ethical Committee to ensure that the benefits of the study would outweigh any ethical dilemmas.

Results

Paper I

After exclusion, 96 patients were included. A majority, 62 (64%), were treated conservatively, and 35 (36%) had some intervention performed, of which only one patient had an ERCP. The conservatively managed patients were further progressed in their pregnancies at admissions and had more readmissions but shorter length of stay. (Table 1). There were no differences in maternal-fetal outcomes, such as number of miscarriages, premature birth, and low birth weight.

Table 1. Conservative vs. Interventional management
All patients treated with surgical intervention during any admission compared with conservatively treated patients.

Variable	Conservative treatment, N=62	Intervention (LC, OC or ERCP) N=35	P-value
Baseline data*	N (%) or Median (IQR)		
Age	32 (26-35)	29 (27-33)	0.264
BMI	28 (24-32)	28 (23-30)	0.616
Comorbidity	20 (32%)	12 (34%)	1.000
Known biliary stones	8 (13%)	12 (34%)	0.019
Length of pregnancy (weeks)	26 (20-33)	17 (10-22)	<0.001
Complications to pregnancy	26 (43%)	9 (26%)	0.125
Diagnose at admission*			
Biliary colic	43 (70%)	21 (60%)	0.379
Cholecystitis	14 (23%)	7 (20%)	1.000
Pancreatitis	8 (13%)	8 (23%)	0.257
Cholangitis	0 (0%)	1 (3%)	0.361
Jaundice	3 (5%)	12 (34%)	<0.001
Number of admissions**	1 (1-2)	1 (1-2)	0.784
Emergency care visits	2 (0-2)	0 (0-1)	0.071
Outcome			
Total length of stay**	4 (2-6)	6 (5-9)	0.001
Apgar 5	10 (10-10)	10 (10-10)	0.875
Birth week	39 (38-40)	39 (38-40)	0.051
Fetal birth weight (grams)	3358 (3132-3940)	3512 (3235-3795)	0.683

*Data representing the first admission during pregnancy **Data for all admissions combined

A significant difference was seen in management strategies in the different time periods, with more patients managed with intervention in 2008-2015, without any significant differences in outcome (Figure 9).

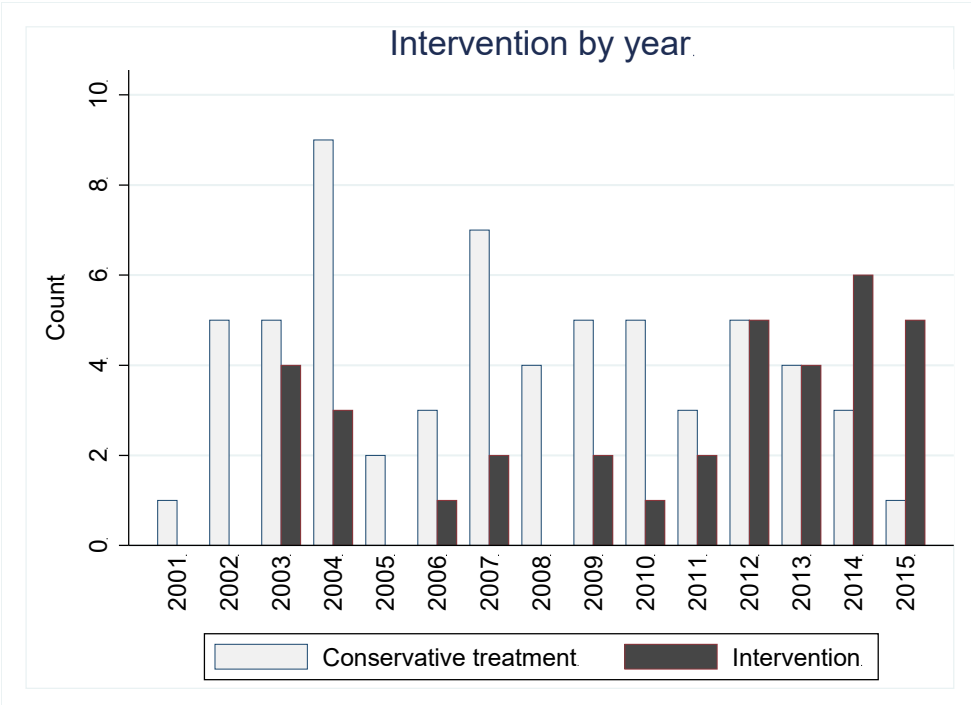


Figure 9.
Graph illustrating the trend over time for conservative treatment versus surgical intervention of gallstone-related disease during pregnancy. (From Hedström et al.[72] Reprinted with permission from Taylor&Francis)

An additional finding was that of the 62 patients treated conservatively, 32 (56%) had cholecystectomy performed within two years of their pregnancy.

Paper II

Two hundred ninety-one cholecystectomies and 63 ERCPs were included and compared to 20,594 cholecystectomies and 2,602 ERCPs in non-pregnant patients. Differences were observed regarding cholecystectomies in baseline characteristics and indications as well as surgical technique and management of CBD stones. There was a low incidence of intraoperative complications in both groups and no significant differences. The pregnant patients had longer LOS and a higher number of postoperative complications at 30-day follow-up. When adjusting for emergency surgery, ASA classification, previous complicated gallstone disease, intraoperative complication, and CBD stones found on cholangiography, there was no difference. (Table 2)

Table 2.
Univariable and Multivariable Analysis of Risk Factors for any Postoperative Complication at 30-day Follow-up.

	N	Unadjusted			Adjusted		
		OR	95% CI	p	AOR	95% CI	p
Pregnancy	20885	1.56	1.03-2.36	0.037	1.21	0.79-1.84	0.379
Previous complicated gallstone disease*	20885	1.32	1.09-1.59	0.003	1.36	1.13-1.65	0.001
Intraoperative complication	20794	4.04	2.95-5.54	<0.001	3.91	2.83-5.39	<0.001
ASA>1	20884	1.29	1.39-1.46	<0.001	1.29	1.14-1.64	<0.001
Emergency surgery	20885	1.94	1.72-2.18	<0.001	1.61	1.42-1.83	<0.001
CBD stones on cholangiography	20797	2.90	2.52-3-35	<0.001	2.49	2.14-2.89	<0.001

*Combined variable of complicated bile stone disease preoperative: previous cholecystitis, previous pancreatitis, or previous jaundice.

Most patients had surgery performed in the second trimester. There were no significant differences in outcome for surgery in the different trimesters.

Although ERCP procedures were more often performed as emergency procedures, there was no difference in outcome, either for all ERCPs or ERCPs performed as only treatment.

Cholecystectomies combined with ERCP numbered 41(14%) in pregnancy and 1576 (8%) in non-pregnant patients. The higher incidence of ERCP in pregnant patients was statistically significant. No differences in outcome were observed.

Type of ERCP was also analyzed: intraoperative ERCP was the most common procedure performed during pregnancy, and preoperative ERCP in non-pregnant patients (Figure 2).

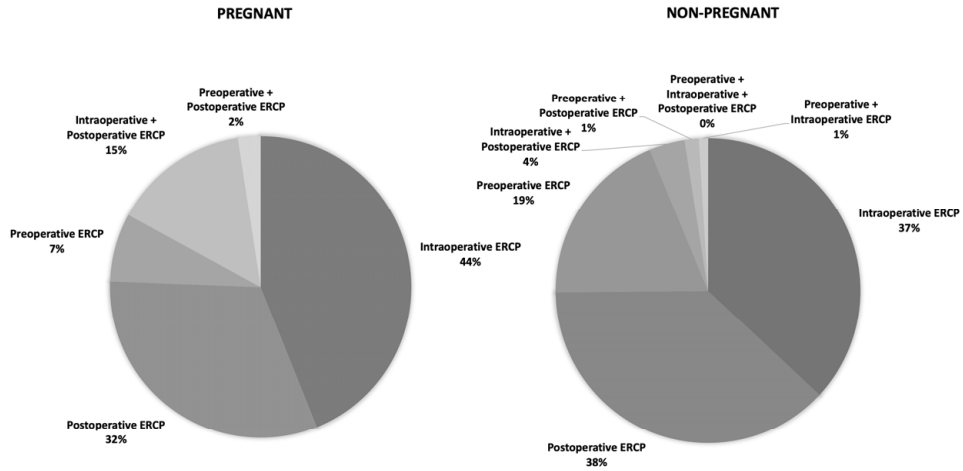


Figure 10.
Frequency of type of ERCP in pregnant and non-pregnant patients.

Paper III

After crossmatching, 1282 patients with bariatric surgery performed before cholecystectomy were identified. Of these, 16 patients were pregnant at the time of cholecystectomy. Pregnant and non-pregnant patients without previous bariatric surgery numbered 276 and 19756, respectively.

The pregnant patients had longer LOS and a higher frequency of emergency surgery, but there was no difference in complications, either intraoperative or at 30-day follow-up (Table 3).

This differed from the non-pregnant groups, where patients with previous bariatric surgery had more conversions from laparoscopic to open surgery and more complications at 30-day follow-up.

Table 3.
A comparison between pregnant and non-pregnant patients with previous bariatric surgery. Both elective and acute cholecystectomy cases are included. n (%) or median (IQR).

	N=1282	Not pregnant Previous bariatric surgery n=1266	Pregnant Previous bariatric surgery n=16	P-value
Age	1282	35 (29-40)	27 (26-36)	0.040
BMI	928	28 (25-32)	30 (25-32)	0.581
Acute cholecystectomy	1282	414 (33%)	11 (69%)	0.005
Pancreatitis	1282	42 (3%)	1 (6%)	0.423
Cholecystitis	1282	141 (11%)	3 (19%)	0.411
Jaundice	1282	97 (8%)	1 (6%)	1.000
Outcome				
Postoperative LOS (Days)	1230	1 (1-2)	2 (2-3)	<0.001
Operative time (minutes)	1282	90 (65-120)	108 (82-140)	0.091
Intraoperative complications	1282	19 (1%)	0 (0%)	1.000
Conversion laparoscopic to open	1282	45 (3%)	1 (6%)	0.444
Complications 30-d	1229	132 (11%)	1 (7%)	1.000

Paper IV

After crossmatching and randomized selection of a control group, we identified and compared 274 patients that had either cholecystectomy, ERCP, or both performed during pregnancy and compared these to 1346 pregnant patients without gallstone intervention during pregnancy. Differences were seen in patient characteristics with more smokers and higher body weight in the intervention group.

More patients in the intervention group had a cesarean section as induction of surgery, but there was no difference in the final mode of birth. There were more cases of premature births but no birth before week 28 in the intervention group (Figure 11). There were no differences in premature births when only comparing elective surgery and the control group. Further, the median length of pregnancy was somewhat shorter in the intervention group, but there were no differences in other fetal outcome parameters such as APGAR or birth weight.

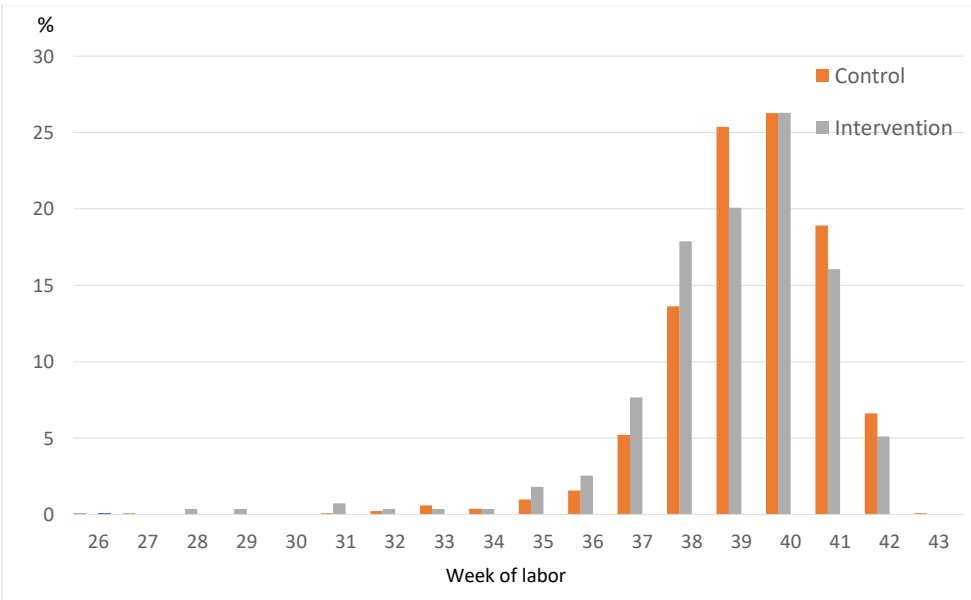


Figure 11.
Week of labor for patients with (orange bar) and without (grey bar) gallstone intervention during pregnancy.

Paper V

Questionnaires were sent to 275 patients, and 146 (53) answered. Responders were older than non-responders, but no other significant differences were seen. A majority of the responders were worried or very worried about their child (Figure 12).

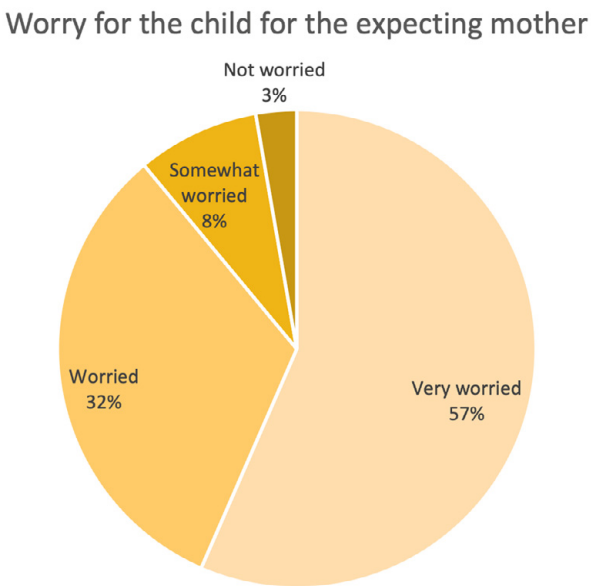


Figure 12.
Frequency of grades of worry for the child.

A quarter of the patients thought that information on both their condition and the upcoming surgery was insufficient, and a majority felt that no measures were taken to help them relieve their worries. There was a significant difference in the opinion on lacking information among the pregnant patients unsatisfied and satisfied with the care in general.

Symptoms of gallstone disease had been present in 62 (42%) before pregnancy, and 17 patients were in queue for surgery at conception.

Median BDI-II scores were 8, similar to other surveys in general populations. A third had BDI-II scores of >14, indicating some level of depression.

Reoccuring in the text answers, regarding what the patients would have wanted to improve their experience, was the wish for more information as well as routine ultrasound postoperatively to ensure the wellbeing of the fetus.

Discussion

Gallbladder surgery and ERCP during pregnancy seem to be safe in terms of intra- and postoperative complications as well as safe for the expected child, regardless of trimester, previous bariatric surgery, indication, or if one or more ERCPs are needed in adjunct. Nevertheless, pregnant patients worry about their children and wish for more information.

The incidence numbers of admission for gallstone-related disease during pregnancy was estimated to be 1/1000 pregnancies in Paper I, in line with reported data of an incidence of 0.05-0.8%[64, 105, 123, 124] Although rare; these incidence numbers make it almost a certainty that every general surgeon will encounter pregnant patients with gallstone disease during their career.

Aspects of Clinical Management and Outcome

As previously mentioned, several guidelines recommend early intervention regardless of trimester, as this has proven to be safe and associated with a better outcome. The recommendations are mainly based on retrospective studies, often with relatively small sample sizes. In a review by Date et al. (2008), which included six studies with a total of 310 patients, conservative versus surgical treatment was compared. Readmission rates for conservatively managed patients were 38-70% and an average of 1-6 readmissions, in line with the results from Paper I, where we observed a 34% readmission rate. 27% of the patients initially managed nonoperatively had therapy failure and needed subsequent surgery. There was no difference in premature births or fetal demise in either the review or Paper I.[65] Nasioudis et al. (2016) reviewed 51 studies with a total number of 590 patients subjected to laparoscopic cholecystectomy during pregnancy and found intraoperative maternal complications in 3.86% and postoperative maternal complications in 4%, most of which were minor, and a generally lower rate of complications compared to the general population.[125] There is considerable heterogenicity in outcome variables in both of these reviews and the studies they are based on. For example, in the study by Nasioudis et al., the most common adverse event classified as an intraoperative complication was bile spillage. A meta-study by Athwal et al. (2016), including 470 patients, compared the specific maternal outcome parameters premature birth and fetal mortality rates and found no

significant differences between conservative or surgical treatment, concluding that operative treatment probably is preferable.[126] In paper IV, measured maternal-fetal outcome parameters were length of pregnancy and premature births, with slightly shorter length and more cases of premature births in the intervention group. The incidence of premature births in Paper IV was 6.93% and 3.94%. For reference, preterm birth in Sweden in the general population is 5.7%.[127] Birth weight and APGAR score were also compared, and no differences were observed. Interestingly, no difference was seen in the final birth mode (for cesarean section, no intervention 17.1% vs. intervention 21.6%), but a higher proportion of the intervention group had a cesarean section as the start of labor. In Paper V, the frequency of cesarean section of patients with gallstone intervention was 20% as compared to the general frequency of cesarean sections in Sweden, which was 18%.[53]

There are a few population-based observational studies performed. One study by Kuy et al. (2009) compared outcome of 9,714 patients subjected to cholecystectomy versus 27,215 patients managed non-operatively and found that surgical management was associated with significantly lower maternal and fetal complication rates but longer LOS and higher cost. When compared to non-pregnant patients, more surgical complications were observed. This difference vanished when adjusted for patient (such as disease severity, urgency, etc.) and provider characteristics, similar to our findings in Paper II. A recent population-based study by Rios-Diaz et al. (2020) analyzed 6,390 patients with cholecystitis. It showed that despite recommendations for surgery, only 38.3% were managed operatively and that non-operative management was associated with significantly worse maternal-fetal outcomes and significantly higher readmission rates.[9]

ERCP in pregnancy is less studied than cholecystectomy but has repeatedly been proven safe.[128] The results in Paper II confirm that complication rates do not differ from non-pregnant patients. No maternal-fetal complications were examined, however. There are several options for managing CBD stones, with their own advantages and disadvantages. The most studied are preoperative ERCP followed by laparoscopic cholecystectomy. The obvious downside of this is the two-step approach, leading to additional risk of anesthesia. More feasible is the intraoperative ERCP, performed with rendezvous technique, the most common in pregnancy in Paper II.[41, 129] No differences in outcome were seen in our study, but the numbers were small, so no conclusions of which strategy is best for managing CBD stones in pregnancy could be drawn from our material. As CBD stones in pregnancy are rare, and no differences were seen in outcome, it is probably preferable to use the method in which local expertise is most experienced. This includes laparoscopic bile duct exploration and trans-cystic techniques, in addition to ERCP.

The psychological impact of gallstone surgery has not been studied previously, and comparisons to the existing research are, therefore, impossible. The effects of prenatal stress, however, have been shown to have a negative effect on pregnancy outcomes, as has depression for surgical outcomes.[130-132] As shown in Paper V, there

is a considerable incidence of worry among the patients. Gallstone disease during pregnancy probably leads to higher anxiety in itself, but the added trauma of surgery probably makes anxiety levels even higher. The mitigating factor proposed by the participants in the study – more information, is a reasonable measure that can be taken at a low cost and low risk.

Methodological considerations

As previously mentioned, randomized, double-blind, placebo-controlled studies of this subject are unrealistic for many reasons. Therefore, other types of studies are necessary to achieve the best possible knowledge and draw conclusions to be able to offer these patients optimal care. There are several issues that need to be taken into consideration. First, gallstone-related disease during pregnancy is relatively rare, as are, fortunately, adverse events to both mother and fetus. These circumstances require large materials for robust statistical results. The population reports are based on administrative databases that have a large number of patients and instead lack detail. Gallstone disease during pregnancy has a wide span in seriousness, from asymptomatic gallbladder stones to life-threatening biliary acute pancreatitis. To evaluate outcome, detailed information about individual patients and the decision-making process would be preferable. Strengths and weaknesses of the included Papers are outlined in Table 4.

There are a wide variety of outcome parameters used in the different studies. Structured classification such as Clavien-Dindo is rarely used.[133] Causality for some maternal outcomes can be questioned, such as pre-eclampsia and frequency of cesarean section. Also, causality between the intervention or the gallstone disease itself and outcome is sometimes not adequately investigated.

Comparative analyses are made with different control groups, such as non-pregnant patients or pregnant patients without surgery during pregnancy, thereby biased because they either have no pregnancy outcomes or no underlying disease that would indicate surgery. Both pregnancy and gallstone disease are dynamic conditions. Different patient conditions during pregnancy require different interventional considerations as the pregnancy progresses. For example, asymptomatic gallstone disease might become symptomatic or progress to severe, complicated disease. Biliary acute pancreatitis might be mild and self-limiting in a few days, but there is always a high risk for a recurrent disease that might turn out to be severe acute pancreatitis in the same patient later in the pregnancy. Further, as pregnancy progresses, surgical circumstances change. Cholecystectomy in the first trimesters differs little technically from cholecystectomy in non-pregnant patients, while surgery late in the third trimester requires advanced expertise.

Observational studies are dependent on the quality of the data that are analyzed. The level of detail limits administrative databases, quality registries often suffer from different kinds of bias, and medical journal reviews are time-consuming. GallRiks is continuously validated and has a high coverage grade and high correctness.[112, 113] Nevertheless, underreporting of complications might cause bias, and missing data or loss to follow-up are undoubtedly present. The register uses online registration where the treating surgeon should preferably enter pre- and intraoperative parameters directly after the procedure, but this is not always the case. The 30-day follow-up is usually performed by a local coordinator who is not necessarily familiar with the details of complications. This was evident in Paper II, where the 30-day follow-up did not discriminate between complications caused by cholecystectomy or ERCP when patients had both procedures performed. On the other hand, follow-up by someone other than the operating surgeon or endoscopist might reduce some bias.[134] These limitations aside, quality registers such as GallRiks, SOReg, and MBR offer a unique possibility to study rare diagnoses and patient groups.

Two recent population-based studies have sparked controversy in the field. The first regards the timing of surgery, where Fong et al. (2019) examined differences in outcome of patients that had surgery performed during the third trimester and compared them to patients that had surgery sometime in the three months post-partum. The main finding was a higher rate of premature births and a recommendation to postpone surgery until after birth. [108] Criticism has been expressed concerning study design, patient selection, selection of outcome parameters (for example, eclampsia), and no stratification of different types of gallstone-related disease. [135-137] The second study by Bowie et al. (2020) examined 7,597 pregnant patients admitted for gallstone disease, of which 1,729 had complicated gallstone disease. Complicated gallstone disease and intervention were associated with worse maternal-fetal outcomes.[138] Only 36.6% of the patients with complicated gallstone disease in that study had intervention performed. Although the authors state that since the difference remains when comparing complicated gallstone disease with intervention versus complicated gallstone disease without intervention, it should be non-differential, no data on individual disease severity or decision-making is available. There is reason to believe that only the patients with the most severe disease and patients were conservative treatment failed were subjected to intervention. In all studies of surgical outcome in pregnancy, it is difficult to discern whether the outcome is dependent on the surgical procedure or the underlying disease. One example of this is the prematurity rate in Paper IV. A higher incidence was seen when comparing the whole intervention group with the control group, but there were no differences when only comparing elective surgery. This difference is probably a reflection of disease rather than intervention. Poorly designed or interpreted studies might contribute to a delay in diagnosis or decision to perform surgery, further enhancing the risk.[106]

LOS and cost are often used as outcome parameters.[9, 10, 92, 125, 138-140] In many studies, but not all, surgery during pregnancy is associated with a longer LOS, as we have confirmed in Papers I, II, and III. Although these are interesting parameters in an administrative sense, and that there in some cases might be a causal relationship to adverse events, longer LOS might be caused by increased vigilance and wishes of the pregnant patients and thus not an adverse event per se.

The complexity of causality can be illustrated by the findings of higher rates of smoking mothers with gallstone surgery compared to non-intervention mothers in Paper IV and the higher rate of smokers in Paper I compared to the general pregnant population in Sweden.[141] These high smoking rates in the study groups are also seen in several of the population studies mentioned above.[63, 138] Despite being the largest preventable factor in adverse pregnancy and birth outcomes, smoking is seldom adjusted for in calculations.[142]

In summary, our results are mainly in line with previous findings and conclusions in the literature of this heterogenous and challenging group of patients. Current guidelines give room for considerable flexibility and discretion of the treating surgeon and stress the importance of consultation with other relevant specialties to make an individual assessment of the best possible course of action in every case. Educational efforts to increase knowledge of the parameters that need to be considered and further research into the topic are warranted to ensure that every decision is timely and correct.

Table 4.
Strengths and weaknesses of included Papers.

	Strengths	Limitations
Paper I	Comparatively large patient cohort. Detailed parameters from multiple sources. Several different aspects of outcome. Long time period.	Retrospective design. No randomization. Missing data. No evaluation of the decision-making process.
Paper II	Large patient cohort. Detailed parameters from a well-validated registry (GallRiks). Detailed 30-day follow-up. Both Cholecystectomy, ERCP, and combinations.	Retrospective design. No randomization. Missing data. Risk of underreporting of adverse events. 30-day follow-up by non-surgical expertise. No follow-up >30 days. No maternal-fetal outcome parameters.
Paper III	Rare patient group eligible for the study. Detailed parameters from well-validated registries (GallRiks and SOReg).	Retrospective design. No randomization. Small study group. No information on surgeon skill set. No stratified registration of complications.
Paper IV	Large patient cohort. Detailed parameters from well-validated registries (GallRiks and MBR). Maternal-fetal outcome parameters.	Retrospective design. No randomization. Missing data. Loss of patients when crossmatching.
Paper V	Unique study of patient perceptions. Detailed data on many aspects of subjective care experience.	Low response frequency. Long time between surgery and survey in some cases. Missing data. Risk of observer bias.

Conclusions

Pregnant women with gallstone disease do not have more complications if intervention is performed. More and more pregnant patients are subjected to intervention. Most pregnant patients treated non-operatively have cholecystectomy performed within two years of childbirth.

There are no differences in cholecystectomy outcome between pregnant and non-pregnant patients when adjusted for patient characteristics and disease severity. Surgery in all trimesters has similar outcome. There are no differences in the outcome of ERCP, even if more pregnant patients had emergency procedures performed. Intraoperative ERCP was the most common method of managing CBD stones. Cholecystectomy, ERCP, and combinations of these procedures are safe in pregnancy.

Pregnant patients with previous bariatric surgery have longer LOS, but there are no differences in outcome, even though pregnant patients have more emergency procedures. Cholecystectomy is safe in pregnant patients with previous bariatric surgery.

There are differences in patient characteristics between pregnant patients that have cholecystectomy performed during surgery and pregnant patients without surgery. Pregnant patients with surgery performed had slightly shorter gestation length and more premature births but no other differences in maternal-fetal outcome parameters. There were no differences in prematurity between patients with elective surgery and the control group. Surgery during pregnancy is safe for the fetus.

Pregnant women that had intervention performed during surgery worried about their children. They wish for more information on the disease and the upcoming surgical procedure.

Future perspectives

The technological advances during the last decades, especially with the development and refinement of laparoscopic cholecystectomy and endoscopic procedures, have drastically improved the possibilities of managing pregnant patients with gallstone disease. Several further developments, such as single-port laparoscopy, have yet to prove beneficial but should not be immediately dismissed since there might be some benefits during pregnancy.[143] Other, more imaginative variants such as natural orifice surgery or gallbladder preserving cholecystolithotomy (or these in combination) are probably not feasible alternatives in the near future.[144-146] Advances in endoscopic procedures such as the use of EUS, non-radiation ERCP or direct vision endoscopy (i.e., SpyGlass) might diminish the perceived risk of radiation in the case of CBD:s[52, 147, 148] Advancements in diagnostic tools, or increased use of existing modalities such as MRI might give a better basis for decision-making in the pregnant patient.[149] In summary, technological advances in several areas should be monitored closely. There is reason to believe that new or modified procedures that benefit non-pregnant patients are also beneficial to pregnant patients.

As for further research, efforts should be made to continue to evaluate outcome in a stringent and comprehensive way. As time passes, more pregnant patients are eligible for inclusion. An interesting new way to use quality registries is the concept of registry-based randomized trials, RRCT:s, where rare diagnoses and patient groups can be studied rationally and inexpensively. Some aspects of gallbladder intervention during pregnancy would be possible to study using this method.[150-152]

The complex nature and the relative rarity of these patients make it difficult for individual surgeons to be sufficiently updated and informed. The use of AI and machine learning to construct tools to aid in decision-making might be one way to improve the proper and timely selection of management.[153]

Patient experience is an understudied parameter with the potential to improve outcome.[154] Several generic patient-reported outcome measure instruments have been used to assess outcome after gallstone surgery, but all have different shortcomings.[117] There is an increased interest in Patient Reported Outcome Measures (PROMs) that needs to be further explored.[155] The ongoing project to develop a disease-specific questionnaire (GGQ24) for patients undergoing gallstone surgery is very interesting and might improve research in this field.[156]

Populärvetenskaplig sammanfattning

Var femte person kommer bilda gallstenar under sitt liv och ungefär 20% av de som får gallstenar kommer att få besvär av dem. Besvären kan variera i svårighetsgrad från enstaka gallstensanfall som går över inom några timmar till livshotande akut bukspottskörtelinflammation. Gallstenarna kan också fastna i gallgångarna och hindra gallan från att komma ut i tarmen. Om en patient har mycket besvär av sina gallstenar eller har drabbats av en komplikation av sina gallstenar kan det bli aktuellt med ett ingrepp. För att bli av med stenar i gallblåsan görs en operation där hela gallblåsan inklusive gallstenarna tas bort, en kolecystektomi. För att åtgärda stenar i gallgångarna görs en endoskopisk undersökning som kallas ERCP. Eftersom gallstenar är så vanligt i befolkningen är dessa två ingrepp några av de vanligaste operationerna som utförs världen över. I Sverige görs ca 14 000 kolecystektomier och 8000 ERCP:er årligen. Även om det rör sig om rutiningrepp, med låg risk för komplikationer, finns det speciella omständigheter som kan göra beslutet att operera svårt. En av dessa omständigheter är när patienten är gravid.

Gravida kvinnor har på grund av graviditetshormonerna en ökad risk att drabbas av gallstenar. Två andra riskfaktorer för att bilda gallstenar är ålder och övervikt, och snabb viktnedgång, tex den man ser efter överviktskirurgi. Dessa riskfaktorer ökar stadigt bland gravida.

Flera tidigare studier har visat att det är säkert att operera gravida kvinnor och det finns internationella riktlinjer som säger att gravida bör behandlas precis som alla andra. Det finns också flera studier som visar att det kan vara farligt, både för mamman och barnet, att inte bli opererad. Trots detta opereras gravida i mycket mindre utsträckning än icke-gravida.

Målet med denna avhandling är att bidra till kunskapen om gallstenskirurgi hos gravida, med förhoppningen om att förbättra vården för dem. I Sverige har vi många bra register med detaljerade data om patienter som gör det möjligt att studera även lite ovanligare patientgrupper på ett bra sätt. Dessutom gör det svenska personnumret att det går att spåra patienter mellan olika register och journalsystem. Vi har använt oss av det svenska registret för gallstenskirurgi, GallRiks där över 90% av alla kolecystektomier och ERCP:er som utförs i Sverige registreras. Med hjälp av detta har vi kunnat identifiera i stort sett alla gravida som opererats i Sverige. Vidare har vi använt det svenska registret för överviktskirurgi, SOReg, och

Socialstyrelsens Medicinska Födelseregister för att få information om tidigare överviktskirurgi och uppgifter om graviditet, förlossning och det nyfödda barnet.

I den första artikeln gick vi igenom journalerna för alla gravida som vårdats på grund av gallstenssjukdom i Malmö och Lund åren 2001-2015. Vi såg att en större andel gravida opererades under den senare halvan av studieperioden, de som opererades hade inte större risk för komplikationer och av de som inte opererades behövde majoriteten opereras inom två år efter förlossningen.

I den andra artikeln gick vi igenom alla gravida patienter som opererats och registrerats i GallRiks mellan 1 Januari 2009 till 12 Mars 2016. Vi identifierade 250 gravida som gjort enbart genomgått kolecystektomi, 41 gravida som genomgått både kolecystektomi och ERCP och 12 som endast genomgått ERCP. Vi jämförde sedan dessa med icke-gravida kvinnor i samma ålder och det visade sig att graviditeten i sig inte gjorde att de patienterna hade större risk för att drabbas av komplikationer. Däremot såg vi att de gravida opererades på andra indikationer och genomgick fler ERCP :er, vilket vi tolkade som att de gravida var sjukare när de väl opererades.

I den tredje artikeln undersökte vi om gravida som tidigare gjort en överviktsoperation hade större risk för att drabbas av komplikationer. Vi identifierade 16 patienter som tidigare gjort överviktskirurgi som kolecystektomerats under graviditet. Bland de icke-gravida var risken större för de som tidigare gjort överviktskirurgi jämfört med de som inte gjort överviktskirurgi, men det var ingen skillnad i komplikationer för de gravida som gjort överviktskirurgi jämfört med någon av de andra grupperna. De gravida hade längre operationstid och längre vårdtid, men också större andel akuta operationer. När vi bara jämförde de som gjort akuta operationer fanns det ingen skillnad.

Den fjärde artikeln handlar om utfallet vad gäller graviditet, förlossning och det nyfödda barnet. Här undersökte vi de patienter vi tidigare identifierat i GallRiks men samkörde också med Medicinska Födelseregistret för att få dessa data. Vi tog också ut data på en kontrollgrupp gravida som inte opererats under sin graviditet, för att kunna jämföra utfallet. De gravida vägde mer och var oftare rökare men den enda andra skillnaden I utfall vi såg var att de i genomsnitt hade en något kortare graviditetslängd och större antal för tidigt födda. När vi bara jämförde de med planerad kirurgi och kontrollgruppen var det ingen skillnad i andelen för tidigt födda.

I den femte artikeln undersökte vi en annan aspekt av gallstenssjukdomen och operationen, nämligen patienternas egna upplevelser av att drabbas av gallstenssjukdom som innebar intervention under graviditeten. Vi skickade en enkät till de som opererats där de fick svara på 35 frågor om tiden innan operationen, operationen och tiden efter operationen. Det visade sig, föga förvånande, att de flesta var oroliga för sina barn. Många upplevde att informationen, både om själva sjukdomen och om ingreppet de skulle gå igenom var bristfällig. Av de 53 som svarade på enkäten stod 17 i kö för galloperation när de blev gravida.

Sammanfattningsvis har vi undersökt ett i sammanhanget stort patientmaterial ur olika aspekter och funnit ett klart stöd för att det är säkert att operera gravida patienter. Gravida patienter bör erbjudas operation, efter en noggrann individuell riskanalys, precis så som görs hos icke-gravida. Det är viktigt att sprida denna information både till kirurger och vårdpersonal för att inte fördröja operationsbeslut och också viktigt att ge information till de gravida kvinnorna för att göra upplevelsen av vården bättre.

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