EFFECT OF GENDER ON GALLBLADDER DISEASE AND GALLSTONES

Gallstone disease causes significant morbidity and mortality in the United States. Gallstones occur in more than 20 million persons in the United States and affects ten percent of the adult population (1). The etiology of gallstone formation is multi-factorial and specific predisposing factors have been identified. While environmental and genetic factors influence gallstone formation, women beyond puberty are at a two- to threefold higher risk for cholelithiasis compared to men. The peak incidence of gallstones in women is between the ages of 30 and 39 years (2). These differences fade beyond menopause.

Endogenous estrogen secretion may explain the observed gender differences in gallstone development (3,4). Women have smaller total bile acid pools and increased biliary cholesterol content that predisposes them to super-saturation of cholesterol in the bile pool, resulting in gallstone formation (5). Gallstones often
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form during pregnancy and the risk of gallstone formation proportionately increases with the increase in parity (6). Oral contraceptive use and postmenopausal hormone replacement therapy (HRT) have also been shown to increase the risk of cholesterol gallstone formation, however, the data is inconsistent. At higher estrogen doses, contraceptive steroids have been shown to double or triple the risk of developing gallstones by increasing biliary cholesterol saturation. However, newer formulations with very low estrogen content carry a substantially reduced risk of gallstones. Contraceptive steroids decrease bile acid secretion and alter gallbladder emptying (4). The gallbladders of female patients with gallstone disease have a higher concentration of progesterone receptors (7). Progesterone impairs gallbladder contraction by inhibiting cholecystokinin-mediated smooth muscle contraction. Gallbladder stasis is conducive to sequestration and precipitation of cholesterol or calcium salts of bilirubin. Hormonal replacement therapy is also associated with an increase in gallstone disease. The Heart and Estrogen/Progestin Replacement Study (HERS) showed a 38% increase in the relative risk of gallbladder disease in postmenopausal women randomized to estrogen/progesterone treatment (8). Increased biliary cholesterol secretion has been observed with the administration of conjugated estrogens (9,10). Estrogen treatment appears to influence gallbladder disease in both males and females. Males treated with estrogen have an increased risk of symptomatic gallstones and cholecystectomy (11). A two-fold increase in the incidence of gallstones in men treated with estrogen was noted in the Coronary Drug Project (12). In a separate study, men with prostate cancer treated with estrogen had 40% higher biliary excretion of cholesterol than age-matched controls (13).

The Rome Group for the Epidemiology and Prevention of Cholelithiasis (GREPCO) found that in men, gallstones were significantly associated with increasing age and serum triglycerides. On the other hand, parity, body mass index, increased total and LDL cholesterol, as well as increasing age and elevated serum triglycerides, were found to be independent risk factors in women. Gallstones may be either symptomatic or asymptomatic. Symptomatic gallstones follow a distinctly more aggressive course. The risk of development of biliary complications in patients with symptomatic gallstone disease is 1% to 2% per year, therefore, cholecystectomy is recommended early in this setting (14,15). If untreated, acute cholecystitis, acute pancreatitis, ascending cholangitis and gangrenous gallbladder may occur. Less common complications include Mirizzi syndrome (a stone lodged in the cystic duct or neck of the gallbladder causing compression of the common bile duct), gallstone ileus (a stone lodged in the ileum causing intestinal obstruction), cholecystocholedochal fistula, and Bouveret’s syndrome (gastric outlet obstruction by a gallstone lodged in the duodenum).

Male patients greater than 65 years have a greater incidence of complications including acute cholecystitis and acute pancreatitis. Moreover, the initial clinical presentation may underestimate the severity of gallbladder disease in men as compared to women. Morrow, et al found that in men over 60 years, presenting with acute cholecystitis, one third were afebrile; one third had a leukocyte count <10,000, and one fourth presented without abdominal symptoms (16). The role of male gender with regard to these differences is unclear. Males have a greater diameter duct system than females which potentially allows passage of stones into the CBD, thereby increasing the likelihood of complications (17). These discrepancies may also be due to women using health services more frequently and a greater willingness to seek medical attention for mild biliary symptoms as compared to men. Other unexplored theories include possible gender-based differences in pain thresholds. Male gender has also been correlated with increased postoperative mortality and gender differences in patient co-morbidities such as cardiac and pulmonary disease may contribute to worse outcomes. Male sex has been identified as a significant preoperative predictor of conversion from laparoscopic cholecystectomy to open technique (18).

The diagnostic algorithms for cholecystitis and choledocholithiasis are identical in men and women. Biochemical and hematologic parameters may be normal in uncomplicated biliary colic. Transient or complete obstruction of the bile duct typically results in varying abnormalities in alkaline phosphatase, bilirubin, and serum transaminases. Serum bilirubin greater than 4 mg/dL, or persistently elevated LFTs suggest choledocholithiasis. Ultrasonography is the procedure of choice to evaluate for gallstones. Depending on body
habitus, the bile duct can be visualized to varying extents. Bile duct dilation in a patient with gallstone disease should raise concern for choledocholithiasis. Computed tomography is also very sensitive to detect bile duct dilation and on occasion reveals the presence of bile duct stones. Magnetic resonance cholangiopancreatography (MRCP) is not typically required in the evaluation of gallstone disease, but is highly sensitive in detecting bile duct stones and can be used to comprehensively evaluate the bile duct. Endoscopic retrograde cholangiopancreatography (ERCP) is the gold standard for the diagnosis of choledocholithiasis (gallstones in the bile duct) (19), and has the added advantage of therapy, but it carries a risk of pancreatitis, bleeding, perforation, cholangitis and bacteremia. ERCP should be performed in patients with a significant likelihood of CBD stones. If clinical suspicion is confirmed, stone extraction can be accomplished after biliary sphincterotomy. In patients who are reasonable surgical candidates, a cholecystectomy will prevent further recurrence. Clinical follow-up is a reasonable option in patients with significant comorbidities who are an unacceptable risk for surgery and in older patients, if there is no concern for acute cholecystitis. In these individuals, cholecystectomy can be performed if symptoms recur despite biliary sphincterotomy. In the presence of acute cholecystitis, the gallbladder will have to be addressed more urgently. If cholecystectomy is not immediately feasible, a percutaneous cholecystostomy tube placement and subsequent cholecystectomy after medical stabilization is a reasonable approach.

**GALLBLADDER AND PANCREATIC DISEASE DURING PREGNANCY**

Cholecystitis occurs in approximately 1 in 1,600 to 1 in 10,000 pregnancies and cholecystectomy is required during one to eight of every 10,000 pregnancies (20,21). It is the second most common indication for surgery in pregnancy. During pregnancy, the residual volume and fasting gallbladder volume are increased as the contractility and rate of emptying are markedly reduced. Biliary sludge develops in one third of pregnant women and 10%–12% of women exhibit gallstones on ultrasonography before delivery. Approximately one third of pregnant women with stones experience biliary colic. Sludge is less often symptomatic (22). Acute pancreatitis in pregnancy is of biliary (gallstone) etiology in over 90% of cases. Pregnant women with cholecystitis have the same symptoms as nonpregnant patients, except the Murphy’s sign (tenderness under the right costal margin on deep inspiration) is less common in pregnant women with cholecystitis. Variable elevations in bilirubin and transaminases are seen in this setting. Serum alkaline phosphatase is less helpful because it is usually elevated in pregnancy. Other conditions specific to pregnancy such as acute fatty liver and HELLP syndrome should be explored in pregnant patients presenting with elevated liver enzymes (Table 1).

Ultrasonography safely and accurately diagnoses gallbladder disease and is the diagnostic choice in pregnancy (23). A conservative approach to treatment, particularly in the first and third trimesters is recommended. Choledocholithiasis requiring intervention during pregnancy is uncommon. However, if intervention is required, ERCP with the specific therapeutic goal of removing bile duct stones or treating cholangitis can be safely performed during pregnancy (24). Involvement of an obstetrician, anesthesiologist and a detailed informed consent that includes risks to the fetus are indispensable. Depending on the clinical scenario, biliary sphincterotomy with stone extraction or stent placement can be performed during ERCP. Sedation for such high risk patients is best provided by an anesthesiologist. Fluoroscopy is kept to a minimum required for a successful procedure. Radiation exposure is minimized by avoiding the additional radiation exposure required.

**Table 1**

**Differential Diagnosis of Cholecystitis in Pregnancy**

- Acute Fatty Liver of Pregnancy
- HELLP syndrome
- Severe preeclampsia
- Acute hepatitis
- Myocardial infarction
- Pancreatitis
- Peptic ulcer disease
- Pyelonephritis
- Pneumonia
- Herpes zoster

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for hard copy films and shielding of the fetus. Recent reports favor an early operative intervention with laparoscopic cholecystectomy. The benefits include avoiding the morbidity of relapses and recurrent hospital admissions, as well as reducing the frequency of premature labor (25). It is widely accepted that the second trimester is a safe time to undergo a cholecystectomy to mitigate concerns regarding fetal injury. Operations during the third trimester have a much higher incidence of precipitating premature labor and present unique challenges because of the size of the gravid uterus.

Pancreatitis in pregnancy is rare and occurs in approximately 1 in 1,000 to 10,000 births, usually late in the third trimester or early postpartum period with cholelithiasis as the most common etiological factor (26). Pancreatitis during pregnancy could also result from hyperlipidemia (27). Hyperlipidemic gestational pancreatitis usually occurs only in women with pre-existing abnormalities in lipid metabolism. Pancreatitis occurs typically in the third trimester of pregnancy, due to increased levels of lipids, lipoproteins, and triglyceride levels as a consequence of high concentrations of circulating estrogen in those with a genetic predisposition to hypertriglyceridemia. Other causes are alcohol ingestion, abdominal surgery, blunt abdominal trauma, infections, medications (diuretics, antihypertensives, and antibiotics), perforated duodenal ulcer, connective tissue diseases and hyperparathyroidism. Pancreatitis has been associated with a fetal mortality rate as high as 37.9%, mostly due to preterm labor (28).

Pregnant patients with pancreatitis have a clinical presentation that is no different from those not pregnant. Symptoms include sudden and severe epigastric pain radiating to the back, postprandial nausea and vomiting, and fever. Bowel sounds are usually hypoactive secondary to ileus and the abdomen is diffusely tender. Serum amylase and lipase levels will confirm the diagnosis. However, serum and urinary amylase levels are low to normal in more than 50% of patients with hypertriglyceridemic pancreatitis. This has been attributed to an interference of plasma lipids with the assay (29) or to the presence of an inhibitor in the plasma and urine that inhibits the assay (30,31). Amylase and lipase levels increase spontaneously as gestation progresses and the upper limits of normal in the first and second trimesters are 100U/deciliter for amylase and 200U/deciliter for lipase. Calculation of an amylase to creatinine clearance ratio may be helpful in pregnancy because several conditions may also result in elevation of amylase and lipase such as cholecystitis, bowel obstruction, hepatic trauma, and perforated duodenal ulcer. This ratio has been found to be elevated in pregnant women with pancreatitis. Hypocalcemia from fat saponification may be severe. Severe pancreatitis can occasionally result in peripancreatic fluid collections, pseudocyst formation and abscesses.

Medical management of pancreatitis during pregnancy consists of bowel rest, fluid/electrolyte management, and pain relief. Abdominal ultrasonography and magnetic resonance imaging can potentially identify gallstone disease, bile duct stones and complications such as peripancreatic fluid collections. Intravascular fluid loss is usually underestimated and intravenous fluids should be aggressively administered. With close monitoring, pain control and correction of blood sugar and electrolytes, including calcium, most patients will respond to medical management and are ready for a clear liquid diet on day 4 or 5. However, care must be taken to monitor for poor prognostic indicators including respiratory and renal insufficiency, hypotension and hypocalcemia. Close monitoring in the intensive care unit is often required in severe pancreatitis. If cholangitis or biliary obstruction is suspected endoscopic retrograde cholangiopancreatography (ERCP) should be performed. Jamidar, et al described 23 pregnant women with pancreaticobiliary disease who underwent therapeutic ERCP from six different medical centers. Prophylactic antibiotics were given, the abdomen was shielded with a lead apron and fluoroscopy time was kept under one minute. The authors concluded that cautious and selective use of this procedure appears safe and effective in pregnancy (32).

**SCHINCTER OF ODDI DYSFUNCTION**

Sphincter of Oddi dysfunction (SOD) refers to increased basal pressure in the complex muscular structure consisting of smooth muscle fibers that surround the distal common bile duct (CBD), pancreatic duct (PD), and ampulla of Vater (common channel of both ducts). SOD is believed to lead to functional obstruction of the biliary and pancreatic outflow leading to bil-[...](continued from page 51)
Sphincter of Oddi dysfunction should be suspected in patients with pain of presumed biliary or pancreatic origin in the absence of an organic cause. The question of SOD can arise in diverse clinical scenarios: persistent or recurrent biliary pain after cholecystectomy in the absence of structural abnormalities, idiopathic recurrent pancreatitis, and biliary pain in patients with intact gallbladders without gallstone disease. Twenty nine percent of patients with unexplained right upper quadrant abdominal pain have manometric evidence of sphincter of Oddi dysfunction (34). Hogan and Geenen have suggested a classification for suspected sphincter of Oddi dysfunction that could predict the outcome of therapy with endoscopic sphincterotomy (35) (Table 2).

A similar classification for pancreatic pain has been described (36) and is outlined in Table 3.

Noninvasive studies including secretin stimulated pancreatic duct measurement and hepatobiliary scintigraphic imaging previously has been used in an attempt to identify patients with sphincter dysfunction. Unfortunately, none of these studies can reliably predict response to a sphincterotomy. Sphincter of Oddi manometry (SOM), with its associated risks, is the only definitive means of diagnosis and should be considered only in patients with significant symptoms. Measurements are made in both the biliary and pancreatic sphincters. A basal sphincter pressure greater than 40 mmHg confirms the diagnosis of SOD and is treated with a sphincterotomy. Preliminary data suggests that placement of a narrow caliber pancreatic stent prophylactically after manometry, regardless of the manometric findings may decrease the risk and severity of post procedure pancreatitis. Patients with suspected SOD have the highest complication rates for endoscopic retrograde cholangiopancreatography (ERCP) and sphincterotomy. Post ERCP pancreatitis rates as high as 25% have been reported in this group of patients and females are 2.5 times more likely to develop post ERCP pancreatitis as compared with men (37). It is speculated that the higher incidence of post ERCP pancreatitis in females undergoing ERCP may be related to the higher incidence of SOD among women. Relief of abdominal pain following sphincterotomy occurs in 90%–95% of biliary type I patients, 85% of biliary type II patients, and 55% to 60% of biliary type III patients with abnormal manometry findings.

EFFECT OF GENDER ON PANCREATIC DISEASE: OVERVIEW

The differences in pancreatic disease with regard to gender appear to be related to the sex steroid hormones (SSH) including estrogens (estradiol, estrone, and...
estriol), progestagens (pregnenolone, progesterone) and androgens (testosterone, dihydrotestosterone [DHT], dehydroepiandrosterone, androstenedione). The SSH have been associated with healthy and neoplastic pancreatic biology. Receptors for the different types of SSH have been identified in normal and neoplastic pancreatic tissue with varying profiles related to cell origin (exocrine and endocrine) and the type of neoplasm.

SEX DIFFERENCES IN PANCREATITIS

Alcohol and gallstones account for about 70% of all cases of pancreatitis. Approximately 2%–5% of cases are drug related. Numerous drugs including azathioprine/6-mercaptopurine, valproic acid, pentamidine and dideoxyinosine (ddI) have been implicated. Rarer causes include hypertriglyceridemia, hypercalcemia, sphincter of Oddi dysfunction, malignancy, viral infections and ischemia. There are recognized sex differences in gallstone pancreatitis and in the relationship of estrogens to pancreatitis.

Gallstone pancreatitis: Three to seven percent of patients with gallstones develop pancreatitis (38). Differences exist between the sexes in their predisposition toward gallstone pancreatitis (39). The relative risk of developing acute pancreatitis due to gallstones is greater in men, however, there is a higher prevalence of gallstones in women and gallstone pancreatitis is more common in women. The predisposition to pancreatitis has been attributed to stone and pancreatic duct size. It has been found that acute pancreatitis occurs more frequently when stones are less than 5 mm in diameter. Small stones are more likely than large stones to pass through the cystic duct and cause ampullary obstruction (40). There is no evidence implicating differences in stone size between the sexes. However, men have been found to have a larger diameter duct system and possibly a different anatomic disposition of the sphincter of Oddi, which predisposes them to a higher incidence of pancreatitis than women (41).

Estrogen-induced pancreatitis: Bank and Marks first reported estrogen induced pancreatitis in 1970 (42). Estrogen–induced pancreatitis develops most commonly in moderately obese women with hyperlipoproteinemia who may have impaired glucose intolerance. Persons over the age of 40 are at particularly high risk if they have a family history of hyperlipidemia. Pancreatitis develops during administration of estrogens for birth control, postmenopausal symptoms, menstrual irregularity, and after prostatectomy for adenocarcinoma. In most cases, pancreatitis developed within 3 months of the initial estrogen administration. Serum triglyceride levels during the acute attack have generally exceeded 3500 mg/100 mL (43). Women with baseline elevated TG levels >700 mg/dL should be considered at a higher risk for development of estrogen-induced hypertriglyceridemia with subsequent pancreatitis and are poor candidates for contraception or hormonal replacement therapy.

Clinical characteristics of acute pancreatitis do not differ between the sexes. Classic symptoms are severe

Table 3
Pancreatic Type Pain Classification

<table>
<thead>
<tr>
<th>Recurrent pan/pancreatic pain</th>
<th>Abnormal enzymes*</th>
<th>Dilated pancreatic duct**</th>
<th>Delayed drainage***</th>
</tr>
</thead>
<tbody>
<tr>
<td>Type I</td>
<td>+</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>Type II</td>
<td>+</td>
<td>1 or 2 of above</td>
<td>+</td>
</tr>
<tr>
<td>Type III</td>
<td>+</td>
<td>None</td>
<td></td>
</tr>
</tbody>
</table>

*More than 1.5–2× upper limit
**Greater than 6 mm in head / >5 mm body on ERCP
***More than 9 minutes
pain in the upper abdomen with radiation to the back and at least a threefold elevation of pancreatic enzymes in the blood. Radiologic abnormalities are common. Abdominal ultrasonography is the single best noninvasive test for detecting the presence of stones within the gallbladder. A CAT scan should be considered when the diagnosis of acute pancreatitis is in question, to stage the severity of acute pancreatitis, and to determine the complications of acute pancreatitis. Complications of pancreatitis may be local or systemic. Local complications include necrosis, pseudocyst formation, pancreatic abscess, ileus, fistulization, GI hemorrhage, pancreatic fluid collections, and pseudoaneurysm. Systemic complications may include shock, respiratory failure, metabolic derangement such as hypocalcemia, hyperglycemia, coagulopathy, and intravascular coagulation. There is no known sex predilection to the course, complications or outcome of acute pancreatitis.

Treatment for pancreatitis includes supportive care, reduction of inflammation, and early identification of complications. IV fluids, nutritional support, and pain relief are mainstay. ERCP is indicated in patients with a high likelihood for residual bile duct stones or cholangitis. Prospective randomized trials have examined the role of ERCP versus conservative management in acute biliary pancreatitis and concluded that ERCP should be performed within 24–72 hours of evaluating the patient and sphincterotomy benefits patients with severe disease. Hypertriglyceridemia resulting in acute pancreatitis often requires the expertise of an endocrinologist after resolution of acute pancreatitis.

**PANCREATIC NEOPLASMS**

Pancreatic neoplasms most commonly originate from pancreatic exocrine cells. Ductal adenocarcinoma accounts for 90% of pancreatic tumors. Autopsy studies have shown that 60% to 70% are localized to the head of the pancreas, 5% to 10% to the body, and 10% to 15% in the tail. It is the fourth leading cause of cancer death in both men and women. The male-to-female ratio is 1.3:1. Cystic neoplasms account for 1% of pancreatic neoplasms and have a strong female preponderance. Mucinous cystic neoplasms (mucinous cystadenomas, mucinous cystadenocarcinomas) and papillary cystic neoplasm (PCN) occur primarily in fertile women and an increase in growth can be seen during pregnancy, indicating estrogen and/or progesterone influence (44). These are considered to be tumors with malignant potential. Serous cystadenomas typically affect postmenopausal women and mostly represent benign tumors. Intraductal papillary mucinous tumors (IPMT) occur primarily in males (>50%) and represent premalignant papillary neoplasms within the main pancreatic duct. While the reasons for these gender differences are not clear, a SSH process has been implicated. A summary of characteristics of the most common cystic neoplasms is outlined in Table 4.
While exocrine pancreatic cancer is more common in women, there is no gender difference beyond age 70. The reduced risk of pancreatic cancer that levels off after menopause suggests a protective effect of estrogen and progesterone in premenopausal women. The etiology of pancreatic cancer remains unknown, but genetic and environmental factors, including smoking and high fat/meat diet, have been found to be associated with its development. The male predominance is partly attributable to cigarette smoking. Ductal pancreatic adenocarcinomas have significant levels of estrogen, progesterone, and androgen receptors (45,46) and there is a substantial body of data that supports the promoting action of androgens and protective action of estrogens on pancreatic carcinogenesis. Signs and symptoms typically develop late in the course of disease and are not gender specific. Less than 20% of patients present with resectable disease. Micheli, et al evaluated the prognostic role of gender in cancer patients and found female patients typically survive longer once diagnosed with pancreatic cancer (47). It has been suggested that this enhanced survival may be a reflection of their overall greater biological durability as females have lower infant mortality and lower overall death rates (48).

Jaundice, fatigue, anorexia, and weight loss are characteristic of tumors of the head of the pancreas, while tumors of the body and tail typically present after metastatic disease has developed. Pain in pancreatic cancer is due to invasion of the celiac and superior mesenteric plexus and is typically localized to upper abdomen and back. New-onset diabetes mellitus and acute pancreatitis may herald pancreatic cancer and must be kept in mind especially with the elderly. Computed tomography or MRI and endoscopic ultrasound (EUS) are complementary modalities to assess pancreatic cancer. EUS is accurate for staging local invasion (EUS) are complementary modalities to assess pancreatic cancer. EUS is accurate for staging local invasion compared with laparotomy and radiotherapy have been advocated in an attempt to improve the outcome in this setting.

CPN) can relieve pain in many patients, however, conventional pain management with oral narcotics is preferred since the response to CPN is not consistent or durable. Pancreatic ductal adenocarcinoma carries a poor prognosis even after resection with negative histologic margins. Adjuvant and neoadjuvant chemotherapy and radiotherapy have been advocated in an attempt to improve the outcome in this setting.

Predictors of better outcome are tumor size less than 3 cm, absence of lymph node metastases, negative margins, well-differentiated tumors, and intraoperative blood loss less than 750 mL (52). In patients who are inoperable, biliary obstruction can be effectively palliated with a nitinol or polyethylene endoscopic stent placement. Duodenal obstruction can be effectively palliated with an enteral stent or by surgical enteric bypass. Surgical, endoscopic, and percutaneous chemical neurolysis of the celiac ganglion (celiac plexus neurolysis, CPN) can relieve pain in many patients, however, conventional pain management with oral narcotics is preferred since the response to CPN is not consistent or durable. Pancreatic ductal adenocarcinoma carries a poor prognosis even after resection with negative histologic margins. Adjuvant and neoadjuvant chemotherapy and radiotherapy have been advocated in an attempt to improve the outcome in this setting.

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