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Cholelithiasis – a particular threat to women. A review of risk factors

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Abstract

In Poland, cholelithiasis affects approximately 20% of the population and require approximately 45.000 cholecystectomies per year. Women, especially mature women, are more at risk of developing this condition. Hormonal and reproductive factors are the reason for higher incidence in women. In this publication, we review significant factors affecting this situation. The anatomical structure of the gallbladder may have a significant impact on the course of the cholecystectomy, and the occurrence of any intra- or post-operative complications. The pathomechanism of cholelithiasis is described, as well as the basic risk factors.

Running title: Cholelithiasis in females

Keywords: cholelithiasis, bile cyst, cholelithiasis risk factors

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Introduction

Cholelithiasis (gallstone disease) is one of the most common diseases of the gastrointestinal tract worldwide [1-3], and gallbladder surgeries for gallstones are the most common procedures performed in general surgery [4]. The incidence of gallstones varies from 0.1% to 50.5% worldwide [5]. In Poland, it affects about 20% of the population [6], and about 45.000 cholecystectomies (surgical removal of the gallbladder) are performed annually [7]. While in Germany the number of surgeries is at about 175.000 [2], and in the USA 750.000 (although it is suspected that some of the procedures are performed too early) [8], in Spain about 60.000, and in the UK about 70.000 [9] performed annually. The treatment of gallstones imposes a significant burden on health care worldwide [10,11], amounting to approximately $6.2 – 6.5 billion annually in the USA alone [5,12]. Women are at a higher risk of gallstone disease than men [13-16]. The male to female ratio for cholelithiasis is 0.52 [17]. Gender difference begins in adolescence and continues through the reproductive years [18]; between the ages of 50 and 65, approximately 20% of women and 5% of men have gallstones [16]. The reason for higher risk of developing cholelithiasis probably has to do with hormonal and reproductive factors, i.e. oral contraceptives or hormone therapy taken by women as well as pregnancy [19]. Naturally occurring menopause around the age of 49 is associated with the start of hormone replacement therapy [MHT]. This therapy is the most effective way of treating vasomotor and genitourinary symptoms, while observational studies show a relationship between MHT and an increased risk of gallstones [8]. It is estimated that 10% of all pregnant women suffer from cholelithiasis [13], in addition, a study conducted in Chile showed that the incidence of gallstones was 12.2% in multiparous women compared to 1.3% in nulliparas at the same age [18].

The gallbladder is a pear-shaped structure (**Fig. 1**). In adults, its size measures to approximately 7 to 10 centimeters in length and 4 centimeters in diameter, when fully distended, it has a capacity of approximately 50 milliliters in total.

It consists of the fundus, i.e. the widened part, the body, i.e. the main part, and the neck, which narrows and turns into the cystic duct. The



FIGURE 1 Image of a normal gallbladder. Endoscopic retrograde cholangiopancreatography (ERCP) – documentation of Vitalii Lazarchuk

fundus is a rounded base, usually protruding beyond the lower border of the liver, facing the anterior abdominal wall. The body lies in a depression – a fossa of the same name on the visceral surface of the liver, which is located under the junction of the IV B and V segments of the liver [14]. The neck narrows and becomes the cystic duct, which merges with the common hepatic duct to become the common bile duct.

The beginning of the course of the common bile duct is marked as the branching point of the cystic duct and the common bile duct. The common bile duct is approximately 6 millimeters in diameter.

The mucous folds in the neck of the gallbladder, otherwise known as Heister's spiral valves [20], and the bile duct are the most common sites of gallstone trapping, which can occlude the lumen and cause distention of the gallbladder (**Fig. 2, 3**).

The arterial blood that vascularizes the gallbladder comes from the cystic artery, which usually, in about 90% [14], is a branch of the right hepatic artery. Although there is significant variability in the course of this artery. Rarely, it arises from the left hepatic artery or the proper hepatic artery, running anteriorly or posteriorly to the common hepatic duct [20]. On the other hand, the outflow of venous blood, is carried out by veins that run along the bile ducts to drain to the liver through the portal system, and also via veins that drain directly from the gallbladder to the liver.

In the submucosal layer of the gallbladder there are lymphatic vessels that pass into the so-called Calot's node or Lund's node, and lymph nodes that run along the porta hepatis. Also, lymphatic drainage can go directly to the liver along segments IV B and V before reaching the lymph nodes in the hepatoduodenal ligament. Such structure of the lymphatic system influences the necessity of routine excision of these liver segments in case of radical resection of gallbladder carcinoma. Of particular importance in surgery is the cystohepatic triangle (hepatobiliary triangle), otherwise known as Calot's triangle. It is an anatomical landmark formed by the cystic duct inferiorly with a slight shift laterally, the common hepatic duct medially, and the inferior hepatic edge superiorly. This triangle is important during laparoscopic cholecystectomies as this is whe-

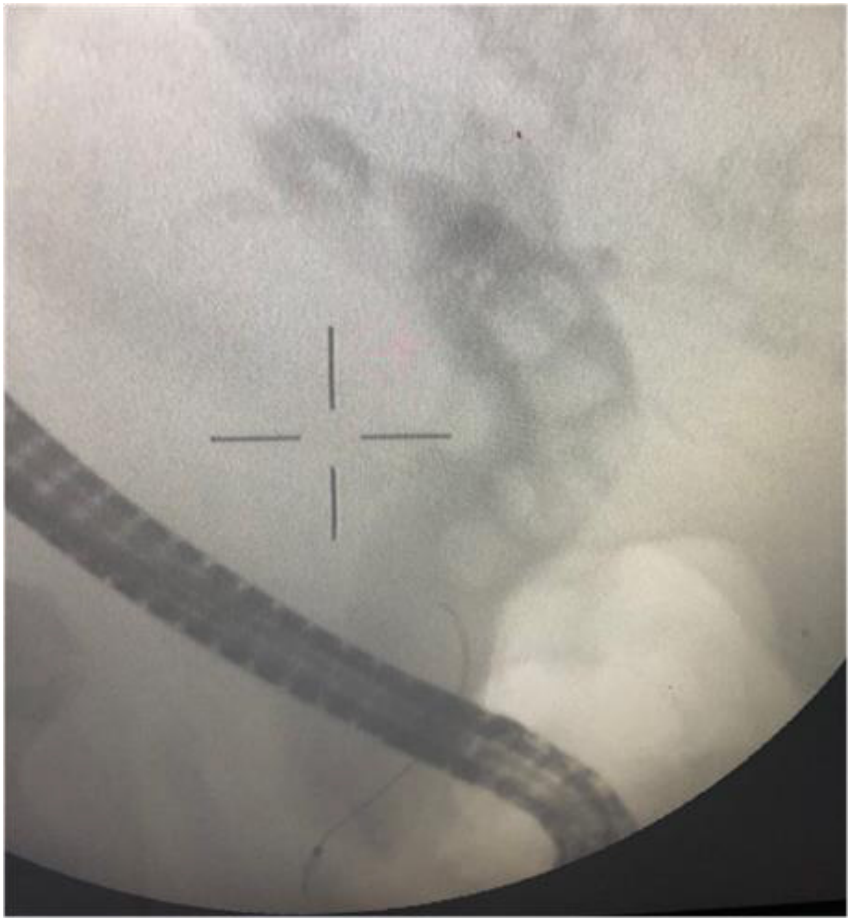

FIGURE 2 Gallstones seen in the common bile duct. ERCP – documentation of Vitalii Lazarchuk

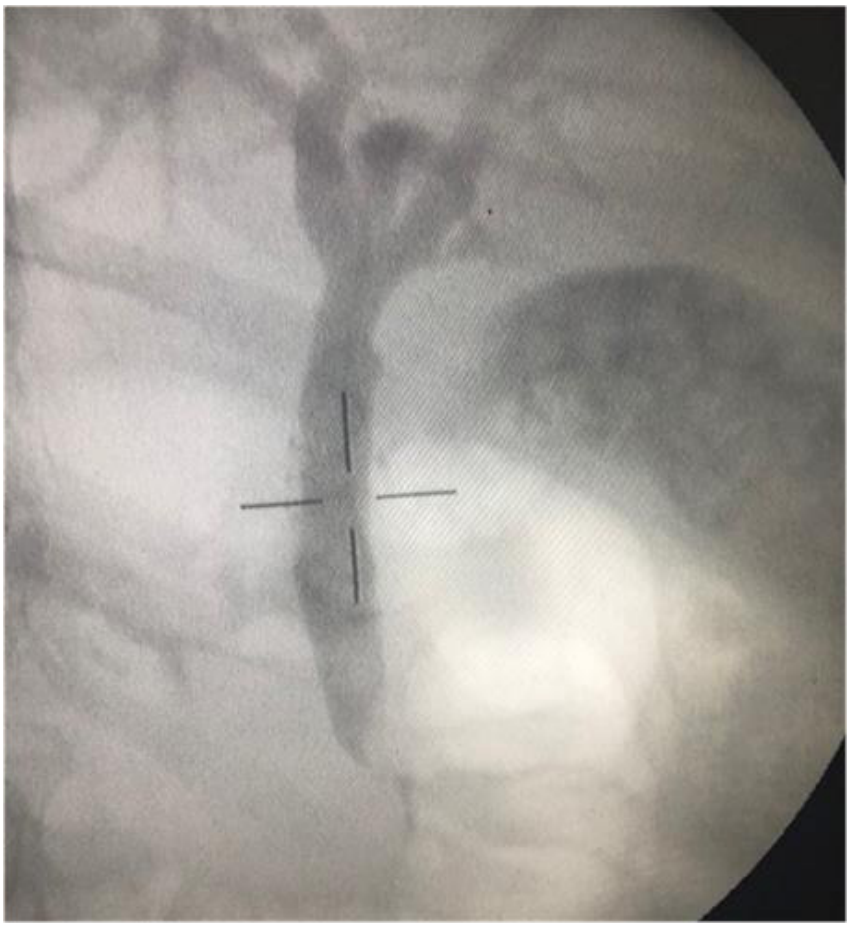

FIGURE 3 The entire gallbladder is filled with gallstones. ERCP – documentation of Vitalii Lazarchuk

re the alveolar artery should be located. The contractions of the gallbladder are under the regulatory control of many systems, mediators or other factors. Cholecystokinin (CCK) and parasympathetic innervation are the main mediators initiating contraction of the gallbladder. CCK is a hormone that is secreted by the duodenal epithelium in response to nutrients within its lumen. Secretion of CCK causes postprandial contraction of the gallbladder to deliver bile to the duodenum for digestion. The hepatic branch of the vagus nerve provides the parasympathetic innervation, which also stimulates contraction. Like the rest of the digestive tract, the gallbladder is innervated by a highly complex enteric nervous system.

As the gallbladder empties, the gallstones move towards the bile duct. Small stones entering the duct can irritate the mucosa (which is made up of columnar epithelium) leading to contraction of the smooth muscles in the wall of the duct and dilation of the proximal bile ducts, resulting in the pain known as biliary colic.

Cholelithiasis

Cholelithiasis is a condition in which the gallbladder and/or bile ducts have hardened deposits of bile, which is released into the small intestine. Bile consists of water, bile acids, cholesterol, fatty acids, bilirubin, phospholipids, proteins and inorganic compounds [21]. Most people with gallstones do not report pain, but 10% of patients will develop symptoms within five years, and 20% of patients will develop symptoms within 20 years of being diagnosed with gallstones [22]. The clinical course of gallstone disease is variable and ranges from asymptomatic to uncomplicated symptomatic disease with pain attacks and complicated symptomatic disease including acute cholecystitis, cholelithiasis, pancreatitis, cholangitis and rarely intestinal obstruction [23]. Gallstones are divided into cholesterol, which account for about 80-90% of cases [13,21] and pigmented [10]. The origin of cholesterol gallstones has common links with widely characterized metabolic abnormalities by altered cholesterol homeostasis, e.g. obesity, dyslipidemia, type II diabetes and metabolic syndrome [24].

The basic defects that play a key role in the pathogenesis of cholesterol gallstones include: genes and genetic factors, hepatic hypersecretion of cholesterol causing bile saturation of the gallbladder, rapid phase transformation of cholesterol into bile with precipitation of a solid cholesterol crystal, impaired mobility

of the gallbladder with hypersecretion and the accumulation of mucin gel in the lumen of the gallbladder, immune-mediated cholecystitis and intestinal factors consisting of cholesterol absorption, as well as slowing of intestinal peristalsis and altered intestinal microbiota [24]. Normally, under normal physiological conditions, bile can dissolve a certain amount of cholesterol excreted by the liver. However, if the liver produces more cholesterol than the bile can dissolve, then the excess cholesterol may precipitate out as crystals. These crystals may become trapped in the gallbladder mucus, producing gallbladder sludge. Over time, the crystals enlarge, merging into larger clusters, forming stones and thus closing the ducts, and ultimately intensify the development of gallstone disease [21].

Bilirubin is formed by the breakdown of red blood cells and is secreted into the bile by the liver cells. In some haematological conditions, the liver may produce too much bilirubin by breaking down haemoglobin. This excess bilirubin can also cause the formation of gallstones [21].

Risk factors

A number of factors can contribute to the development of gallstones. These are e.g. cholesterol production by the liver, gallbladder function (stasis or inflammation), production of bile acids or intestinal absorption of cholesterol and bile acids [13] described above. The risk factors for gallstones can be divided into modifiable and non-modifiable.

The first group includes factors that we are able to change. These include conditions such as obesity, rapid weight loss, high-calorie diet, certain medications, type II diabetes, metabolic syndrome, dyslipidemia, smoking, and a sedentary lifestyle.The second group takes into account ethnicity, female gender, family history, pregnancy and age over 40. Unfortunately, people over the age of 40 have a 4 to 10 [25] times higher risk of developing gallbladder disease [26]. If there was a family history of urolithiasis, these people are 5 times more likely [25] to develop gallbladder disease. An interesting fact is that women of reproductive age are about 2 times more likely to develop gallstones than men [25]. However, postmenopausal women have a similar incidence of gallstones to men [13].

Modifying factors

Obesity

Obesity is consistently recognized as a major risk factor for the development of gallstones, but this disease has also been reported in non-obese patients [27]. *Aune et al.* reported that an increase of more than 5 points in the BMI value may increases the risk of gallstone formation by 1.63 times [28], while *Stender et al.* showed that the risk of symptomatic gallstones increases by 7% for every 1 kg/m2 increase in BMI [29]. It has been established that one of the pathophysiological mechanisms by which obesity increases the risk of gallstone development is an increase in plasma insulin levels. High plasma insulin levels stimulate the activity of 3-hydroxy-3-methylglutaryl-coenzyme A (HMGCoA) reductase, causing cholesterol hypersecretion [27]. In addition, overweight and obese individuals often exhibit greater fasting gallbladder volumes and decreased postprandial gallbladder emptying, two conditions indicative of gallbladder stasis, which has been implicated as a factor in promoting gallstones. Altered mobility of the gallbladder is already present in obese children and adolescents, and in obese adults it is further deteriorating [24]. It has been estimated that for each extra kilogram of body fat, approximately 20 mg of additional cholesterol is produced. This excess of cholesterol contributes to the supersaturation of bile with cholesterol [30].

In Europe, Asia and the United States, the food consumed is usually hypercaloric and low in fiber. With this type of diet, the development of cholesterol stones increases [27]. There are many studies from Western countries showing the association of gallstones with edible oils, refined sugars, meat and margarine [31], which affects the course of the disease.

Rapid weight loss

Rapid weight loss (i.e. >1.5 kg per week) [31] is a risk for developing gallstones, and such significant weight loss is an expected outcome of bariatric surgery [32]. Bariatric surgery is used to promote weight loss by limiting the amount of food that can fit in the stomach [33]. Among patients who undergo bariatric surgery, up to 40% develop gallstones, and approximately 8-15% develop symptoms requiring surgical intervention – cholecystectomy [30].

Diabetes Type II

Cholelithiasis and type II diabetes have several risk factors in common, such as general obesity, central obesity, dyslipidemia, hyperinsulinemia, cardiovascular disease, metabolic syndrome, and dysbiosis of the intestinal microflora. *Wang et al.* reported that people with gallstones had a 22% increased risk of type II diabetes [34].

Metabolic syndrome

Metabolic syndrome (MetS) occurs in association with a group of major cardiovascular risk factors and metabolic disorders, including, but not limited to, impaired fasting glucose, glucose intolerance or diabetes mellitus, insulin re-

sistance, pro-atherosclerotic dyslipidemia (i.e., elevated triglycerides and decreased HDL cholesterol), arterial hypertension, as well as central and general obesity (35,36). MetS is a serious public health problem with an incidence of approximately 25% of adults worldwide [37].

Metabolic syndrome and gallstones share common risk factors, the most significant of which are abdominal obesity and insulin resistance, which are associated with increased cholesterol synthesis in the body, hypersecretion of cholesterol with bile, and increased bile lithogenicity [35] discussed above.

Smoking

Smoking may increase the risk of gallbladder disease by reducing plasma high-density lipoprotein cholesterol levels [38]. *Papadopoulos et al*. report that as a result of smoking, currently or in the past, the odds ratio of developing the disease increases by 25%, and each additional cigarette per day increases the risk of gallstones by 0.01139] 0.002±]. *Aune et al*., based on their study, reported a 10% increase in risk for past smokers and emphasizes that smoking is a risk factor for type II diabetes, which also has a positive effect on the occurrence of gallstones [38], as discussed above.

Sedentary lifestyle

A sedentary lifestyle – spending many hours watching TV and sitting while working or driving, for example, is positively associated with the risk of developing cholelithiasis. A study by *Zhang et al.* showed an 11%-15% reduction in the risk of gallstones in response to an increase in physical activity of 20 MET-hours (amount of activity in metabolic equivalents) per week. The systemic anti-lithogenic effects of physical activity include lipid metabolism, intestinal motility, insulin resistance, enterohepatic circulation and their hormones, as well as the energy needed to maintain body weight or reduce excess body weight, and thus, the reduced impact of dysmetabolic prolithogenic factors [40].

Non-modifying factors

Female sex

Most, but not all, studies confirm that the risk of developing cholelithiasis is significantly increased by the use of oral hormonal contraceptives and coupled with estrogen metabolism in premenopausal women [18]. Cholesterol stones may be precipitated by the sex hormones estrogen and progesterone. Estrogen is responsible for increasing cholesterol secretion and decreasing bile salt secretion. Progesterone, on the other hand, reduces gallbladder motility, thereby increasing the risk of developing gallstones in people using oral contraceptives or hormone therapy (HT). This increase in cholesterol production and stagnation due to delayed gallbladder emptying can result in the formation of gallstones [13]. In hormone therapies, the formulations, doses and routes of administration vary considerably, therefore estimating the risk of exposure to gallstones is somewhat complicated. A meta-analysis of 19 studies involving approximately 556.620 participants showed that HT was associated with an increased risk of gallstones (Risk ratio (RR), 1.79; 95% CI, 1.61-2.0), but oral contraceptives were not associated with an increased risk of cholelithiasis (RR 1.19; 95% CI, 0.97-1.45) [13].

A prospective cohort study using data collected from the *Million Women Study* evaluated 19.889 postmenopausal women to determine the risk of hospital admission for gallbladder disease. The authors assessed the risk ratio of gallbladder disease in women who were currently using oral or transdermal HT, had used HT in the past, or had never used HT. The study found that current and former HT users were at higher risk of developing cholelithiasis than women who had never used HT. The risk ratio of admission for cholelithiasis in current HT was 1.64 (95% CI, 1.58-1.69) compared with never-users. The risk of admission for cholelithiasis was also varied depending on the route of administration of HT. Women using transdermal HT preparations had a significantly lower risk than women using oral preparations (RR 1.17; 95% CI, 1.10-1.24 vs RR, 1.74; 95% CI, 1.68-1,80, respectively) [13].

Pregnancy

The risk of gallstones in women begins to increase as puberty begins, and decreases as menopause begins. The use of oral contraceptives has been correlated with the risk of cholelithiasis. Estrogen and progesterone levels are therefore believed to be involved in the development of gallstones. Cholecystitis is the second most common cause of acute abdomen, after appendicitis, in pregnant women and occurs in 1600/10.000 pregnant individuals. Cholelithiasis is the most common cause of cholecystitis in pregnancy and accounts for 90% or more of all causes of cholecystitis. Routine ultrasound showed gallstones in 3.5% of pregnancies, but it has not been shown whether pregnancy increases the risk of cholecystitis. The incidence of cholecystectomies in pregnant women is lower than in non-pregnant women. This is not due to lower incidence of cholecystectomies in pregnant women, as doctors tend to refrain from performing any surgery during pregnancy. Although there are few reports of patients

undergoing cholecystectomy surgeries during pregnancy, there is no evidence that laparoscopic surgery increases any risk to the mother or fetus [42].

Diagnostics and treatment

Several differential diagnoses should be considered in patients with suspected cholelithiasis: peptic ulcer disease, gastroesophageal reflux disease, irritable bowel syndrome, pancreatitis, appendicitis, hepatitis, myocardial infarction and kidney stones [13]. Ultrasound has introduced a highly sensitive, highly specific, non-invasive method to detect gallstones without exposure to radiation [23]. Ultrasonography has a specificity of 98%, a sensitivity of 95% and a false-negative rate of 1% to 4% [13]. X-ray diagnosis is of limited use, as only 10% of stones are calcified. Both Computed Tomography and Magnetic Resonance can be used to assess the condition of the biliary tract [43].

Conclusions

1. Cholelithiasis is a multi-factoral diseses affecting more often females.

2. The factors can be divided in non-modifying and modifying factors.

Ethical approval

This conducted study is not related to either human or animal use.

Acknowledgments

Not applicable.

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Conflict of interest

The authors declare no conflict of interest.

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