Diagnose and Mngement of PSC

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Reference list :

- ✓ **EASL** - Journal of Hepatology - Primary sclerosing cholangitis – a comprehensive review
- ✓ **EASL -** Journal of Hepatology - Update on primary sclerosing cholangitis
- ✓ **Harrison's** Principles of Internal Medicine, 20e
- ✓ **Sleisenger and Fordtran** – 11th edition -2021
- ✓ **UpToDate -** 202008 edition
- ✓ **ACG** Clinical Guideline: Primary Sclerosing Cholangitis 2015
- ✓ **British Society** of Gastroenterology and UK-PSC guidelines for the diagnosis and management of primary sclerosing cholangitis 2019
- ✓ **the lancet** Primary sclerosing cholangitis – Vol 391 June 23, 2018
- ✓ **Journal of Hepatology** - Management of primary sclerosing cholangitis and its complications

INTRODUCTION

- **Primary sclerosing cholangitis (PSC)** is a rare chronic cholestatic disease of the liver and bile ducts that is frequently progressive and can lead to end-stage liver disease

- Primary or idiopathic sclerosing cholangitis (PSC) is characterized by a progressive, inflammatory, sclerosing, and obliterative process with multifocal bile duct stricture affecting the extrahepatic and/or the intrahepatic bile ducts.

Etiology

- The cause of PSC is unknown, and multiple mechanisms are likely to play a role.

a. suggests an autoimmune process

b. An inflammatory reaction

c. Ischemic damage

- Approximately 70 percent of patients with PSC are men, with a mean age at diagnosis of 40 years

PSC and IBD

- The disorder occurs up to 90% in association with inflammatory bowel disease, especially ulcerative colitis
- Ulcerative colitis (UC) has been reported in 25 to 90 percent of patients with PSC
- PSC also occurs in patients with Crohn disease
- The IBD associated with PSC is phenotypically and genetically. distinct from patients with IBD in the absence of PSC. Since pathognomonic features of IBD in PSC do not exist, standard IBD definitions should still be used, whilst making sure particular features (e.g. ‘‘**backwash" ileitis, rectal sparing** etc.) are adequately captured and described
- It may also be associated with autoimmune pancreatitis; multifocal fibrosclerosis syndromes such as retroperitoneal, mediastinal, and/or periureteral fibrosis; Riedel's struma; or pseudotumor of the orbit.

IgG4-associated sclerosing cholangitis

- All newly diagnosed PSC patients should have a serum IgG4 level checked
- The distinction between IAC and PSC with elevated IgG4 is important as the cholangiographic changes of IAC may resolve completely upon corticosteroid treatment and IAC is not pre-malignant
- PSC patients with elevated IgG4 are less responsive and data suggest they may progress more rapidly than other PSC patients

- slight elevations up to 5 g/L or 4ULN occur in patients with PSC not fulfilling IAC criteria. Additional evaluation of IgG4/IgG1-ratio (>0.24 indicates IAC) or blood IgG4/IgG RNA ratio using real-time PCR (elevated in IAC) has been reported to improve delineation of IgG4 disease and could enhance the diagnostic algorithm

Autoimmune hepatitis in patients with PSC

- Biochemical and histological features of autoimmune hepatitis are apparent in 7–14% of patients with PSC
- This poorly demarcated patient group has previously been denominated ‘‘overlap patients”
- Elevated transaminases and IgG may indicate autoimmune hepatitis, but may also be elevated as part of the biliary disease, meaning histological evidence is generally required for the diagnosis of the combined entity and therapeutic decision-making
- Immunosuppressive therapy following standard guidelines for treatment of autoimmune hepatitis is recommended for patients with PSC and features of autoimmune hepatitis

CLINICAL MANIFESTATIONS

- PSC may be asymptomatic and diagnosed as part of the evaluation of abnormal laboratory tests, or they may have symptoms

Symptoms

- Approximately half of the patients with PSC are asymptomatic at the time of diagnosis
- Among patients who have symptoms, **fatigue and pruritus** are common
- Pruritus is a common symptom of PSC that can be extremely disabling, leading to severe excoriations and a decreased quality of life
- Fevers, chills, night sweats, and right upper quadrant pain can also be present; These features may represent episodic bacterial cholangitis from biliary obstruction rather than advanced disease.

Examination findings

- Approximately half of patients with PSC will have a normal physical examination at the time of diagnosis. Abnormalities that may be detected on physical examination include jaundice, hepatomegaly, splenomegaly, and excoriations

- Patients may also have findings related to inflammatory bowel disease.

- Patients may also have findings related to end-stage liver disease

Laboratory tests

- Liver biochemical tests usually demonstrate a **cholestatic pattern**, with elevation of the serum alkaline phosphatase predominating in most patients

- The serum alkaline phosphatase and bilirubin may fluctuate substantially, possibly indicating transient blockage of strictured bile ducts by biliary sludge or small stones. The serum aminotransferases are typically less than 300 international unit/L. The serum albumin concentration is normal in patients with early stage disease, although those with active inflammatory bowel disease may have hypoalbuminemia

- Additional serologic findings in patients with PSC include:

a) Hypergammaglobulinemia
b) increased serum immunoglobulin M (IgM) levels
c) Atypical perinuclear antineutrophil cytoplasmic antibodies (P-ANCA)
d) Human leukocyte antigen DRw52a

- Hepatic and urinary copper levels are increased, and serum ceruloplasmin is reduced in most patients with PSC

DIAGNOSIS

General diagnostic approach

- PSC should be considered in patients with a cholestatic pattern of liver test abnormalities (particularly an elevated alkaline phosphatase), especially those with underlying inflammatory bowel disease.
- The diagnosis is then made by showing cholangiographic evidence of characteristic bile duct changes (multifocal strictures, segmental dilations) and excluding secondary causes of sclerosing cholangitis
- Imaging of the biliary tract is the most important initial step

Cholangiography

- The diagnosis of PSC is typically established by the demonstration of characteristic multifocal stricturing and dilation of intrahepatic and/or extrahepatic bile ducts on cholangiography .

- A cholangiogram may be obtained using magnetic resonance cholangiopancreatography (MRCP), Endoscopic retrograde cholangiopancreatography (ERCP), or percutaneous transhepatic cholangiography (PTC).
- We recommend that MRCP should be the principal imaging modality for the investigation of suspected PSC. ERCP should be reserved for patients with biliary strictures requiring tissue acquisition (eg, cytological brushings) or where therapeutic intervention is indicated
- The continuous improvement in MRC technology (e.g. the use of higher magnetic fields) means that the likelihood of an abnormal ERC in patients with normal MRC is small. If MRC is normal and PSC is suspected, it is reasonable to consider patient referral to centres with known technical expertise in MRC as a first step.
- If high-quality MRC is normal, most experts would perform a liver biopsy, unless ERC is indicated (e.g. suspected gallstone disease).

Liver biopsy

- A percutaneous liver biopsy may support the diagnosis of PSC, but is rarely diagnostic
- Liver biopsy is now seldom done to establish the diagnosis of PSC and is generally not considered necessary to establish the diagnosis.
- **We reserve liver biopsy** for patients with suspected small duct PSC or if other conditions such as an overlap syndrome with autoimmune hepatitis are suspected.

Classic PSC

- The biliary strictures in patients with PSC may be focal, with normal intervening areas, or diffuse, involving long segments. Strictures can occur in any part of the biliary tree;

a. intrahepatic and extrahepatic bile ducts – 87 percent

b. Intrahepatic bile ducts alone – 11 percent

c. Extrahepatic bile ducts alone – 2 percent

- The gallbladder and cystic duct may also be involved
- In contrast to the characteristic strictures, shallow ulcerations of the bile ducts may be the only cholangiographic finding in patients with early stage disease. ERCP is typically required to detect such changes

Small duct PSC

Small duct PSC makes up ~5% of the entire spectrum of patients with PSC.

- Cholangiography is normal in a small percentage of patients who have a variant of PSC known as "small duct primary sclerosing cholangitis." This variant (sometimes referred to as "pericholangitis") is probably a form of PSC involving small caliber bile ducts
- Cholangiography will not be revealing. Diagnosis of small duct PSC requires liver biopsy, to demonstrate the characteristic microscopic disease
- A diagnosis of small-duct PSC is made upon histological findings characteristic of PSC and concurrent clinical and biochemical abnormalities strongly suggestive of PSC
- it has similar biochemical and histologic features to classic PSC
- It appears to have a significantly better prognosis than classic PSC
- It may evolve into classic PSC

DIFFERENTIAL DIAGNOSIS

- PSC needs to be differentiated from secondary causes of sclerosing cholangitis and IgG4-associated cholangitis/autoimmune pancreatitis

1. Chronic bacterial cholangitis
2. Infectious or ischemic cholangiopathy
3. Cholangiocarcinoma
4. Choledocholithiasis
5. Diffuse intrahepatic metastases
6. Intra-arterial chemotherapy
7. Portal hypertensive biliopathy
8. Recurrent pyogenic cholangitis
9. Surgical biliary trauma

COMPLICATIONS OF PRIMARY SCLEROSING CHOLANGITIS

- Fat-soluble vitamin deficiencies (A, D, E, and K)
- Metabolic bone disease
- Dominant biliary strictures
- Cholangitis and cholelithiasis
- Cholangiocarcinoma
- Gallbladder cancer
- Hepatocellular carcinoma (in patients with cirrhosis)
- Colon cancer (in patients with concomitant ulcerative colitis)

Management

- There are two major goals of treatment in PSC:

1. Retardation and reversal of the disease process
2. Management of progressive disease and its complications

- there is **no** proven treatment that slows progression of the disease
- excellent outcomes may be achieved after liver transplantation for advanced disease

DRUG THERAPY

A variety of immunosuppressive and anti-inflammatory agents have been studied in patients with primary sclerosing cholangitis (PSC):

1. Ursodeoxycholic acid
2. Glucocorticoids
3. Cyclosporine
4. Methotrexate
5. Vancomycin
6. Azathioprine and 6-mercaptopurine
7. Tacrolimus
8. D-penicillamine
9. Etanercept
10. FMT
11. Vedulizumab

Unfortunately, **none** has been conclusively proven to alter the natural history of this disorder

Ursodeoxycholic acid(UDCA)

- UDCA, a hydrophilic bile acid, is the most extensively studied of all medical treatments for PSC
- UDCA, at a dose up to **15 mg/kg per day**, is thought to exert its effects in cholestatic conditions via protection of cholangiocytes against cytotoxic hydrophobic bile acids, stimulation of hepatobiliary secretion, protection of hepatocytes against bile acid-induced apoptosis, and induction of antioxidants
- UDCA, at a dose up to 15 mg/kg/day, has shown some efficacy in **improving biochemical abnormalities and stabilizing hepatic inflammation** but has **NOT** resulted in a survival benefit or a delay in the need for liver transplantation
- We recommend that UDCA is **not used** for the prevention of colorectal cancer or cholangiocarcinoma

- Our approach is to not start UDCA in patients with PSC.
- In addition, we suggest stopping it in patients who are already taking it and offering to restart the drug at standard doses (13 to 15 mg/kg per day in divided doses) if any of the following occur:

1. The patient's bilirubin or alkaline phosphatase increases .
2. The patient has worsening pruritus.
3. The patient is concerned about his or her liver tests worsening and prefers to resume the drug.

- However, given the uncertainty regarding its benefits, an alternative approach is to start (or continue) UDCA in patients who want to take it despite the uncertain benefits . After six months, if the alkaline phosphatase normalizes or is decreased by at least 40 percent, or if the patient experiences symptomatic improvement, UDCA can be continued. Otherwise, it is stopped.
- **High-dose UDCA**

high-dose UDCA **should be avoided** in patients with PSC

Glucocorticoids

Cyclosporine and tacrolimus

Methotrexate

Azathioprine and 6-mercaptopurine

- No studies have demonstrated a long-term benefit from glucocorticoid therapy, either alone or in combination with other agents
- The value of combining one or more of the drugs discussed above is uncertain

Antibiotics

- An observational study :: oral vancomycin improved liver biochemical tests and symptoms, particularly in those without cirrhosis
- There are case series data and anecdotal reports that oral vancomycin has been associated with marked improvement in clinical symptoms and liver biochemistries in some patients, in particular in the pediatric age group
- Long-term prophylactic antibiotics are indicated for patients with recurrent cholangitis despite efforts to treat a dominant stricture
- Benefit with vancomycin has been reported in small studies in paediatric and adult populations with primary sclerosing cholangitis
- The use of a combination of ursodeoxycholic acid and metronidazole has shown an improvement in liver blood tests but not in disease progression.

ENDOSCOPIC THERAPY

- A subset of patients with primary sclerosing cholangitis (PSC) has a dominant extrahepatic biliary stricture that is potentially amenable to endoscopic therapy
- At cholangiography, dominant strictures are defined as stenosis measuring <1.5 mm in the common bile duct or <1.0 mm in the hepatic ducts
- Whether treatment of a dominant stricture improves outcomes has not been evaluated
- Therapeutic ERCP should only be performed at centers with highly experienced endoscopists.
- Balloon dilation is preferred to short-term stenting for management of symptomatic dominant strictures

- We suggest that patients with a dominant stricture and pruritus and/or cholangitis undergo endoscopic therapy to dilate and/or stent the stricture
- Efforts should be made to exclude cholangiocarcinoma, which may appear as a dominant stricture. Serum CA 19-9, brush cytology of the biliary tree, endobiliary biopsy and FISH as all used in the assessment of a dominant biliary stricture

- Therefore, all modalities should be used in attempting to differentiate benign from malignant strictures in PSC, including ERCP with brush cytology, endobiliary biopsies, FISH and cross-sectional imaging
- Antibiotic prophylaxis should be given, since patients with PSC are at increased risk for the development of cholangitis following biliary tract manipulation

British Society of Gastroenterology and UK-PSC guidelines for the diagnosis and management of primary sclerosing cholangitis 2019

- ERCP with balloon dilatation is recommended for PSC patients with dominant stricture and pruritus, and/or cholangitis, to relieve symptoms. (Strong recommendation, low quality of evidence)
- PSC with a dominant stricture seen on imaging should have an ERCP with cytology, biopsies, and fl uorescence in-situ hybridization (FISH), to exclude diagnosis of cholangiocarcinoma. (Strong recommendation, low quality of evidence)
- PSC patients undergoing ERCP should have antibiotic prophylaxis to prevent post-ERCP cholangitis. (Conditional recommendation, low quality of evidence)

ACG Clinical Guideline: Primary Sclerosing Cholangitis

SURGICAL THERAPY

- Surgical options for primary sclerosing cholangitis (PSC) include biliary reconstructive procedures, proctocolectomy (in patients with ulcerative colitis), and liver transplantation

- surgical therapies other than transplantation such as **biliary reconstructive procedures** should generally **be avoided** in patients with PSC.

- **Proctocolectomy**

this procedure should be performed only if it is indicated because of the colitis

Liver transplantation

- Liver transplantation is the treatment of choice for patients with advanced liver disease due to PSC, and patients should generally be referred for liver transplantation once their Model for End-stage Liver Disease **(MELD) score is ≥15**
- Outcomes for liver transplantation in PSC compare favorably to transplants for other indications
- Jaundice alone, in the absence of other signs of liver failure, is not an absolute indication for transplant
- There are special circumstances in which liver transplantation may be indicated despite a low priority MELD score. These may include:

1) Recurrent or refractory cholangitis
2) Intractable pruritus
3) Peripheral or hilar cholangiocarcinoma <3 cm in diameter (in the context of a clinical trial)

CANCER SCREENING

- In addition to age-appropriate cancer screening, patients with primary sclerosing cholangitis (PSC) typically undergo screening for :

a. gallbladder carcinoma
b. cholangiocarcinoma
c. colon cancer
d. hepatocellular carcinoma

Gallbladder carcinoma and cholangiocarcinoma

- Surveillance for cholangiocarcinoma and gallbladder cancer should be performed in **all adult patients ≥20 years** with PSC regardless of disease stage
- Ultrasound, abdominal computed tomography (CT) scan, or magnetic resonance imaging (MRI)/MRCP with or without serum levels of the tumor marker cancer antigen (CA) 19-9 every 6 to 12 months.
- MRI/MRCP is our imaging modality of choice because of the superior sensitivity of MRI compared with US for detection of cholangiocarcinoma
- Cholecystectomy in patients found to have a gallbladder polyp >8 mm
- Endoscopic retrograde cholangiopancreatography (**ERCP**) with brush cytology **should not be used routinely** for surveillance of cholangiocarcinoma in PSC

Colon cancer

- The prevalence of ulcerative colitis in patients with PSC approaches 90 percent and is associated with a high risk of colonic dysplasia
- patients with PSC and inflammatory bowel disease (IBD) should undergo surveillance colonoscopy every **one to two years** from the time of diagnosis of PSC
- patients with PSC without IBD should undergo surveillance colonoscopy every **three to five years**, including biopsies to look for previously undiagnosed colitis
- Several reports have suggested that the incidence of colon cancer is high in patients with ulcerative colitis and PSC who undergo liver transplantation
- we suggest that patients who have had a liver transplant for PSC who also have inflammatory bowel disease undergo routine **yearly** surveillance colonoscopy.

Hepatocellular carcinoma

- Patients with cirrhosis require screening for hepatocellular carcinoma
- For patients who require HCC surveillance, we suggest abdominal ultrasound as the primary modality.
- For patients who require HCC surveillance, the abdominal ultrasound is performed every six months.
- The addition of serum alpha-fetoprotein (AFP) to ultrasound for surveillance is optional

Pregnancy and PSC

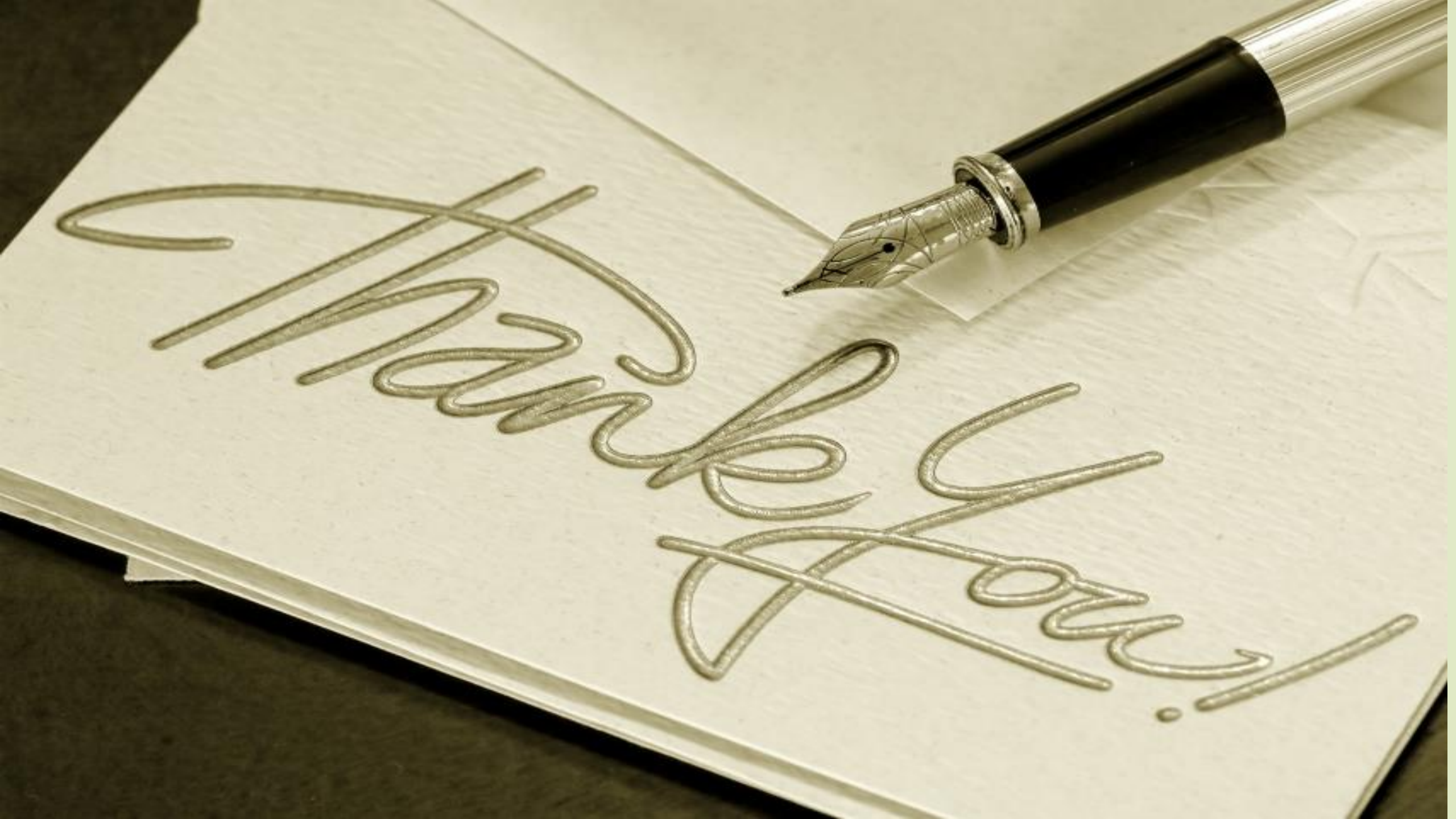
- Women should be counselled about the risk of preterm birth, which appears to be associated with peak maternal bile acids and serum maternal ALT at booking. The benefits to pregnancy outcome with the use of UDCA to ameliorate serum maternal bile acid concentration appears unclear, but it may have beneficial effects on liver transaminases and hepatic impairment, meaning that women should continue with its use in pregnancy(1)
- fertility does not seem to be reduced in PSC. We here report from the largest series of patients with PSC and pregnancy available to date, that successful pregnancies can be achieved by patients with PSC. No impairment of fetal outcome and no serious maternal complications were recorded. Pruritus is common in late pregnancy and the potential clinical and genetic overlap with ICP may warrant further study(2)
- UDCA treatment is presumed to be safe during the second and third trimester and may be safe earlier in pregnancy(2)

1.Pregnancy outcomes in women with primary biliary cholangitis and primary sclerosing cholangitis: cohort study

2.Pregnancy in primary sclerosing cholangitis - Gut

Health maintenance

- Patients with PSC have high rates of osteoporosis and non-vertebral fracture. Patients with PSC should be screened at the time of diagnosis and then at regular intervals .
- Patients with advanced liver disease should also be screened for fat-soluble vitamin deficiency
- Patients with advanced liver disease (evidence of cirrhosis, platelet count <250,000) should undergo screening for esophageal varices.


Thank You!