The differential diagnosis of intra and extra-hepatic cholestasis: Causes and diagnosis of intrahepatic cholestatic disorders

Edite Sadiku[1], Stela Taci[1], Arvin Dibra[2], Ergita Nela[3], Adriana Babameto[1]

[1]Gastro-Hepatology Service, University Hospital Center "Mother Teresa", Tirana, Albania;
[2]Surgery Service, University Hospital Center "Mother Teresa", Tirana, Albania;
[3]Internal Medicine Service, University Hospital Center "Mother Teresa", Tirana, Albania.

Corresponding author: Edite Sadiku, MD;
Address: Rr. "Dibres", No. 371, Tirana, Albania;
Telephone: +355682020275; E-mail: editesadiku@gmail.com

Abstract

Cholestasis is defined both clinically and biochemically, with varying degrees of jaundice, pruritus, and elevated levels of conjugated bilirubin, alkaline phosphatase, γ-glutamyl transpeptidase, 5'-nucleotidase, bile acids, and cholesterol. A conventional categorization of cholestatic liver diseases has divided these factors into intrahepatic and extrahepatic causes. Intrahepatic cholestasis may result from hepatocellular functional defects or from obstructive lesions of the intrahepatic biliary tract distal from bile canaliculi. Cholestasis may also be related to mixed mechanisms in diseases such as lymphoma.

By convention, cholestasis is considered chronic if it lasts more than months. Most chronic cholestatic diseases are purely intrahepatic, whereas sclerosing cholangitis may affect small and large intrahepatic and/or extrahepatic bile ducts.

The differential diagnosis of cholestatic disorders can be wide. The first critical step is to differentiate intra-and extrahepatic cholestasis. A careful patient history and a detailed physical examination are essential in the diagnostic process.

Keywords: extra-hepatic cholestasis, hepatology, intrahepatic cholestatic disorders.

Introduction

The term *cholestasis* originally derives from the Greek and literally means "a standing still of bile". This disruption of bile flow can occur on a cellular level in the hepatocyte, at the level of the intrahepatic biliary ductules, or from an extrahepatic mechanical obstruction of the bile ducts. Commonly, bile flow is only partially disrupted, giving rise to anicteric cholestasis, or cholestasis without jaundice. Cholestasis is defined, therefore, both clinically and biochemically, with varying degrees of jaundice, pruritus, and elevated levels of conjugated bilirubin, alkaline phosphatase, γ-glutamyl transpeptidase, 5'-nucleotidase, bile acids, and cholesterol. A conventional categorization of cholestatic liver diseases has divided these factors into intrahepatic and extrahepatic causes (T 1).

Intrahepatic cholestasis may result from hepatocellular functional defects or from obstructive lesions of the intrahepatic biliary tract distal from bile canaliculi. Cholestasis may also be related to mixed mechanisms in diseases such as lymphoma (1).

By convention, cholestasis is considered chronic if it lasts >6 months. Most chronic cholestatic diseases are purely intrahepatic, whereas sclerosing cholangitis may affect small and large intrahepatic and/or extrahepatic bile ducts.

The differential diagnosis of cholestatic disorders can be wide (Table 1).

The first critical step is to differentiate intra- and extrahepatic cholestasis. Careful patient history and physical examination are essential in the diagnostic process.

Presence of extrahepatic diseases has to be recorded. A thorough occupational and drug history is imperative and any medications taken within 6 weeks of presentation may be incriminated (and discontinued); this includes herbal medicines, vitamins and other substances. A history of fever, especially when accompanied by rigors or right upper quadrant abdominal pain is suggestive of cholangitis due to obstructive diseases (particularly choledocholithiasis), but may be seen in alcoholic disease and rarely,in viral hepatitis. A history of prior biliary surgery also increases the likelihood that biliary obstruction is present.

Finally, a family history of cholestatic liver disease suggests a possibility of a hereditary disorder. Some cholestatic disorders are observed only under certain circumstances (e.g., pregnancy, childhood, liver transplantation, HIV-infection), and may require specific investigations that are not relevant in other populations.

Abdominal ultrasonography is usually the first step to exclude dilated intra- and extrahepatic ducts and mass lesions because it is rather sensitive and specific, non-invasive, portable and relatively inexpensive. Its disadvantages are that its findings are operator-dependent and abnormalities of bile ducts such as those observed in sclerosing cholangitis may be missed. Furthermore, the lower common bile duct and pancreas are usually not well depicted.

Computed tomography of the abdomen is less interpreter-dependent, but is associated with radiation exposure and may be not as good as ultrasound at delineating the biliary tree.

If bile duct abnormalities are present, further work-up depends on the presumed cause. From a purely diagnostic perspective, magnetic resonance cholangiopancreatography (MRCP) is a safe option to explore the biliary tree. Its accuracy for detecting biliary tract obstruction approaches that of endoscopic retrograde cholangiopancreatography (ER CP) when performed in experienced centres with state-of-the-art technology. Endoscopic ultrasound (EUS) is equivalent to MRCP in the detection of bile duct stones and lesions causing extrahepatic obstruction and may be preferred to MRCP in endoscopic units.

Extrahepatic biliary obstruction may be caused by stones, tumours, cysts, or strictures. The gold standard for visualizing the biliary tract and treating extrahepatic biliary obstruction is endoscopic retrograde cholangiopancreatography (ERCP), but even in experienced hands it carries a significant complication rate (pancreatitis in 3–5% of cases;

when combined with sphincterotomy, bleeding 2%, cholangitis 1%, procedure-related mortality 0.4%). Thus, when extrahepatic obstruction is considered and the need for endoscopic intervention is unclear, MRCP or EUS should be performed in order to avoid ERCP if it is not needed (2).

If imaging studies do not demonstrate mechanical obstruction, a diagnosis of intrahepatic cholestasis can be reasonably made. However, in an individual whose history suggests an extrahepatic cause (like early pancreatic or ampullary carcinoma), clinical judgment should be pursued and repeat ultrasound or another imaging procedure should be performed (3). When extrahepatic obstruction has been reasonably excluded, further work-up of intrahepatic cholestasis (Table 2) depends on the clinical setting. In adult patients with chronic intrahepatic cholestasis, the next step is testing for serum antimitochondrial antibodies (AMA) since the diagnosis of PBC, which is the major cause of small-duct biliary diseases (4), can be made with confidence in a patient with high-titer AMA (P1/40) and a cholestatic serum enzyme profile in the absence of an alternative explanation (5). A liver biopsy may still be appropriate in selected patients. If AMA and PBC-specific antinuclear antibodies (ANA) are negative, MRCP (in a specialized centre) may be the next diagnostic step for most patients with chronic intrahepatic cholestasis of unknown cause. Subsequently, a liver biopsy should be performed when the diagnosis is still unclear. Particular attention to the condition of bile ducts is critical in the histologic evaluation and a biopsy of adequate quality should contain P10 portal fields because of the high degree of sampling variability in patients with small bile duct disease.

Biopsy findings should be classified under (i) disorders involving bile ducts the main causes being AMA-negative PBC, isolated small duct PSC, ABCB4 deficiency, sarcoidosis, idiopathic ductopenia or prolonged drug-induced cholestasis; (ii) disorders not involving bile ducts, the main causes being a variety of storage or infiltrative liver diseases,hepatic granulomas (without cholangitis), nodular regenerative hyperplasia, peliosis, sinusoidal dilatation and cirrhosis; and (iii) hepatocellular cholestasis with only minimal histologic abnormalities as observed in benign recurrent intrahepatic cholestasis (BRIC), estrogen or anabolic steroid therapy, sepsis, total parenteral nutrition or as a paraneoplastic phenomenon.

Recommendations

- A detailed history and physical examination are essential (III/C1).

Ultrasound is the first-line non-invasive imaging procedure in order to differentiate intra- from extrahepatic cholestasis (III/C1).

- Testing for serum antimitochondrial antibodies (AMA) is mandatory in adults with chronic intrahepatic cholestasis (III/C1).
- Magnetic resonance cholangiopancreatography (MRCP) is the next step to be considered in patients with unexplained cholestasis (III/C1).
- Endoscopic ultrasound (EUS) is an alternative to MRCP for evaluation of distal biliary tract obstruction (II-2/B1).
- Diagnostic endoscopic retrograde cholangiopancreatography (ERCP) should be reserved for highly selected cases (II-2/A1). If the need for a therapeutic maneuver is not anticipated, MRCP or EUS should be preferred to ERCP because of the morbidity and mortality related to ERCP (II-2/A1).
- A liver biopsy should be considered in patients with otherwise unexplained intrahepatic cholestasis and a negative AMA test (III/C1).
- Genetic testing for ABCB4 (encoding the canalicular phospholipid export pump), when available, should be considered in patients with a negative AMA test and biopsy findings that might be compatible with PBC or PSC.

Table 1. Causes of Cholestasis

Intrahepatic Cholestasis
Primary biliary cirrhosis
Primary sclerosing cholangitis
Drugs and toxins
Sepsis
Malignancy
Granulomatous liver disease
Intrahepatic cholestasis of pregnancy
Hepatitis (viral and alcoholic)
Genetic disorders
Graft-versus-host disease
Post-liver transplantation
Extrahepatic Biliary Tract Diseases
Choledocholithiasis
Bile duct tumors, benign and malignant
Ampullary tumors, benign and malignant
Pancreatic carcinoma
Mirizzi's syndrome
AIDS cholangiopathy
Parasites
Primary sclerosing cholangitis

Table 2a. Causes of intrahepatic cholestasis in adulthood

Hepatocellular cholestasis
Sepsis-, endotoxemia-induced cholestasis
Cholestatic variety of viral hepatitis
Alcoholic or non-alcoholic steatohepatitis
Drug- or parenteral nutrition-induced cholestasis
Genetic disorders: e.g., BRIC, PFIC, ABCB4 deficiency, intrahepatic cholestasis of pregnancy (ICP), erythropoietic protoporphyria
Malignant infiltrating disorders: e.g., hematologic diseases, metastatic cancer
Benign infiltrating disorders: e.g., amyloidosis, sarcoidosis hepatis and other granulomatoses, storage diseases
Paraneoplastic syndromes: e.g., Hodgkin disease, renal carcinoma
Ductal plate malformations: e.g., congenital hepatic fibrosis
Nodular regenerative hyperplasia
Vascular disorders: e.g., Budd–Chiari syndrome, veno-occlusive disease, congestive hepatopathy
Cirrhosis (any cause)
Cholangiocellular cholestasis
Primary biliary cirrhosis (AMA+/AMA_)
Primary sclerosing cholangitis
Overlap syndromes of PBC and PSC with AIH
IgG4-associated cholangitis
Idiopathic adulthood ductopenia
Ductal plate malformations: biliary hamartoma, Caroli syndrome
Cystic fibrosis
Drug-induced cholangiopathy
Graft vs. host disease
Secondary sclerosing cholangitis: e.g., due to various forms of cholangiolithiasis, ischemic choangiopathies (hereditary hemorragic telangiectasia, polyarteritis nodosa and other forms of vasculitis), infectious cholangitis related to AIDS and other forms of immunodepression, etc.

Table 2b. Causes of intrahepatic cholestasis in infancy and childhood

Metabolic disease
– with biliary tract involvement: a1-antitrypsin storage disease, cystic fibrosis
– without biliary tract involvement: galactosemia, tyrosinemia, fatty acid oxidation defects, lipid and glycogen storage disorders, peroxisomal disorders
– specific defects in biliary function: disorders of bile acid biosynthesis and conjugation disorders of canalicular secretion (PFIC)
Paucity of bile ducts
– syndromic: Alagille syndrome (Jagged 1 defect)
– non-syndromic
Ductal plate malformations
Infections: bacterial, viral
Toxic: parenteral nutrition, drugs
Idiopathic neonatal hepatitis
Cirrhosis (any cause)

Primary biliary cirrhosis (PBC)

Primary biliary cirrhosis (PBC) is a chronic cholestatic liver disease predominantly affecting middle-aged women. It is hypothesized that PBC begins with loss of immune self tolerance, leading to damage of the biliary epithelial cells of small bile ducts. Ongoing immunologic events perpetuate the biliary epithelial cell destruction via direct cytotoxicity or lymphokine-mediated cell damage, leading to disease progression. PBC is most commonly diagnosed after the age of 40 years. Of patients with PBC, 90% are women. The prevalence is higher in northern European population groups and lower in Japan. Disease prevalence estimates have ranged from 40 to 400 cases per 1,000,000 population, with an incidence between 4 and 30 cases per 1,000,000 per year. Recent evidence has suggested that environmental factors, including infectious agents and chemicals, might play a role in inducing PBC in genetically predisposed patients (2).

Diagnosis of PBC

Patients with PBC may present with symptoms as fatigue, pruritus and/or jaundice, but the majority of them are asymptomatic at diagnosis.

The diagnosis of PBC is based on a combination of findings, including cholestatic liver enzyme levels, positive antimitochondrial antibody (AMA), and characteristic liver biopsy findings. An elevated serum alkaline phosphatase level of liver origin is the most common laboratory finding.

The most characteristic laboratory finding in PBC is the presence of the AMA, generally in a titer of 1:40 or higher. More than 95% of patients with PBC have a positive AMA. A confident diagnosis of PBC may be made in cases with typical clinical presentation of PBC in the setting of a positive AMA ($\geq$1:40), and a cholestatic pattern of liver enzymes with alkaline phosphatase at least 1.5 times the upper limit of normal and AST less than five times the upper limit of normal without the obligation to perform a liver biopsy (7,8). A liver biopsy should be performed in atypical cases, in cases where an alternative diagnosis is suspected, and to obtain staging information. The liver biopsy findings include portal hepatitis, with granulomatous destruction of bile ducts. The histologic changes are divided into four stages, ranging from stage 1, characterized by portal inflammation and bile duct destruction, through stage 4, characterized by histologic cirrhosis. Overlapping stages can be found in individual patients.

A subgroup of patients have a positive AMA with normal liver enzyme levels. Most of these patients ultimately develop biochemical evidence of cholestasis and symptomatic disease. Another subgroup, with cholestasis and histology suggesting PBC, are AMA negative (AMA-negative PBC) (9). The natural history

of AMA-positive and AMA-negative PBC appears to be similar. A positive AMA, usually in low titer, can be seen in patients with other autoimmune disorders (10).

Summary

- A diagnosis of PBC can be made with confidence in adult patients with otherwise unexplained elevation of AP and presence of AMA (P1:40) and/or AMA type M2. A liver biopsy is not essential for the diagnosis of PBC in these patients, but allows activity and stage of the disease to be assessed (III/A1).
- A liver biopsy is needed for the diagnosis of PBC in the absence of PBC specific antibodies. A liver biopsy may also be helpful in the presence of disproportionally elevated serum transaminases and/or serum IgG levels to identify additional or alternative processes (III/C1).
- AMA-positive individuals with normal serum liver tests should be followed with annual reassessment of biochemical markers of cholestasis (III/C2).

PBC–AIH overlap syndrome

The ‘‘overlap syndrome” is used to describe conditions of patients presenting with clinical, biochemical, serological, and/or histological features reminiscent of both diseases: primary biliary cirrhosis (PBC) and autoimmune hepatitis (AIH).

Based on the major characteristics of PBC and AIH has been proposed the presence of at least 2 of the 3 accepted criteria of both diseases for diagnosing PBC–AIH overlap syndrome (Table 3) (10).

Table 3. Diagnostic criteria of PBC–AIH overlap syndrome

PBC criteria
1. AP >2_ ULN or cGT >5_ ULN
2. AMA P1:40
3. Liver biopsy specimen showing florid bile duct lesions AIH criteria
1. ALT >5_ ULN
2. IgG >2_ ULN or a positive test for anti-smooth muscle antibodies (ASMA)
3. Liver biopsy showing moderate or severe periportal or periseptal lymphocytic piecemeal necrosis

Histologic evidence of moderate to severe lymphocytic piecemeal necrosis (interface hepatitis) is mandatory for the diagnosis.

Primary sclerosing cholangitis

Primary sclerosing cholangitis (PSC) is a chronic, cholestatic liver disease that is characterized by an inflammatory and fibrotic process affecting both intra and extrahepatic bile ducts (13). The disease leads to irregular bile duct obliteration, including formation of multifocal bile duct strictures. PSC is a progressive disorder that eventually develops into liver cirrhosis and liver failure. The male to female ratio is approximately 2:1. PSC can be diagnosed in children as well as in the elderly, but mean age at diagnosis is around 40 years.

Up to 80% of PSC patients have concomitant inflammatory bowel disease (IBD) that in the majority of cases is diagnosed as ulcerative colitis (UC). Thus, the ‘‘typical” PSC patient is a young to middle-aged man with IBD who presents with biochemical and/or clinical signs of a cholestatic liver disease.

Diagnosis of PSC

A diagnosis of PSC is made in patients with elevated

serum markers of cholestasis (AP, cGT) not otherwise explained, when magnetic resonance cholangiopancreatography (MRCP) or endoscopic cholangiopancreatography (ERCP) show characteristic bile duct changes with multifocal strictures

and segmental dilatations, and causes of secondary sclerosing cholangitis (14) and other cholestatic disorders are excluded.

A variety of autoantibodies have been detected in PSC (15): perinuclear antineutrophil cytoplasmic antibodies (pANCA) (26-94%), antinuclear antibodies (ANA) (8-77%), and smooth muscle antibodies (SMA) (0-83%) (15).

Patients who present with clinical, biochemical and histological features compatible with PSC, but have a normal cholangiogram, are classified as Small duct PSC.

The term small duct PSC refers to a disease entity which is characterized by clinical, biochemical, and histological features compatible with PSC, but having a normal cholangiogram (16).

Differential diagnosis of PSC versus secondary forms of sclerosing cholangitis Before the diagnosis of PSC can be settled, causes of secondary sclerosing cholangitis such as previous biliary surgery, cholangiolithiasis and disorders mimicking PSC such as carcinoma of the bile ducts have to be excluded although cholangiolithiasis and cholangiocarcinoma may also be the consequence of PSC (14). Clinical and cholangiographic findings resembling those of PSC have most commonly been described in relation to intraductal stone disease, surgical trauma from cholecystectomy, abdominal injury, intra-arterial chemotherapy, and recurrent pancreatitis (14). A variety of other conditions have also been associated with features imitating those of PSC, including IgG4-associated cholangitis/autoimmune pancreatitis, hepatic inflammatory pseudotumor, eosinophilic cholangitis, mast cell cholangiopathy, portal hypertensive biliopathy, AIDS cholangiopathy, recurrent pyogenic cholangitis, ischemic cholangitis, as well as others (14). Differentiating between primary and secondary sclerosing cholangitis may be particularly difficult since PSC patients themselves may have undergone bile duct surgery or have concomitant intraductal stone disease or even cholangiocarcinoma (CCA). Factors like clinical history, the distribution of the cholangiographic abnormalities, as well as the presence of concomitant IBD, have to be taken into account when determining

whether a pathological cholangiogram is due to PSC or secondary to a benign or malignant bile duct stricture without PSC (14).

Summary

- Cholangiography is the diagnostic test of choice.
- Cholangiographic features include areas of stricturing and dilation in the intrahepatic or extrahepatic biliary tree, or both.
- Liver enzyme studies typically show an elevation of the alkaline phosphatase level.

PSC–AIH overlap syndrome

PSC–AIH overlap syndrome is an ill-defined immune-mediated disorder which is predominantly found in children, adolescents and young adults (17,18-26). Its characteristics include clinical, biochemical, and histologic features of AIH as summarized in the modified AIH score defined by an international group of experts for study purposes (12) and cholangiographic features typical of PSC (11).

Immunoglobulin G4-associated cholangitis

Immunoglobulin G4-associated cholangitis (IAC) is a recently described biliary disease of unknown etiology that presents with biochemical and cholangiographic features indistinguishable from PSC, frequently involves the extrahepatic bile ducts, responds to anti-inflammatory therapy, is often associated with autoimmune pancreatitis and other fibrosing conditions, and is characterized by elevated serum IgG4 and infiltration of IgG4-positive plasma cells in bile ducts and liver tissue (27-33). In the largest cohorts of 53 and 17 IAC patients, respectively (33,31), median age at diagnosis of the mostly male patients (7/8) was around 60 years.

The diagnosis of IAC was recently proposed to be definitive if a patient with biliary stricture(s) in the intrahepatic, proximal extrahepatic and/or intrapancreatic bile ducts (i) has recently undergone pancreatic/biliary surgery or core biopsy of the pancreas showing diagnostic features of autoimmune pancreatitis (AIP)/IAC; or (ii) shows classical imaging findings of AIP and elevated IgG4; or (iii) fulfils two of the following criteria (elevated serum IgG4; suggestive pancreatic imaging findings; other organ manifestations including sclerosing sialadenitis, retroperitoneal fibrosis, or gastrointestinal involvement and abdominal lymphadenopathy with infiltration of IgG4-positive plasma cells; >10 IgG4-pos. plasma cells per high power field in bile duct biopsies) and shows an adequate response to a 4-week course of corticosteroid treatment to allow stent removal without relapse of obstructive cholestasis, to reach serum liver tests <2_ ULN, and to present decreasing IgG4 and CA 19-9 (33).

Genetic cholestatic liver diseases

• *Cystic fibrosis-associated liver disease:* Cystic fibrosis-associated liver disease (CFALD) was observed in up to 27% of patients with CF during longterm follow-up as defined by hepatomegaly, persistent elevation of at least two serum liver tests and abnormal findings on ultrasound and may manifest as neonatal cholestasis, hepatic steatosis, focal or multilobular cirrhosis. Complications of CFALD represent today the second most frequent cause of disease-related death in patients with CF. Ultrasound may reveal signs of CFALD such as hepatomegaly or bile duct alterations (34). Liver biopsy is controversially discussed due to the focal nature of fibrosis/cirrhosis in many cases.

• *Benign recurrent intrahepatic cholestasis:* Benign recurrent intrahepatic cholestasis (BRIC) type 1 and 2 are acute cholestatic disorders of adolescence and adulthood and represent the benign forms of PFIC1 and PFIC2 mainly caused by missense mutations in the ATP8B1 and ABCB11 genes (35,36). BRIC is characterized by acute episodes of cholestasis, jaundice and severe pruritus caused by unknown factors which after weeks or months completely resolve to start again after an asymptomatic period of months to years. BRIC1 like PFIC1 may be accompanied by pancreatitis, whereas BRIC2 may be accompanied by gallstone disease (35).

• *Alagille syndrome :* Alagille syndrome is an autosomal dominant multiorgan disease of children and adolescents which is characterized by chronic progressive cholestasis with ductopenia without relevant inflammatory changes in liver histology (37). The extrahepatic signs and symptoms with involvement of nearly every organ system including heart, kidney, skeleton, central nervous system and a typical facies with hypertelorism, deep-set eyes and a flat nasal bridge may lead to the diagnosis of Alagille syndrome in young cholestatic patients suffering from often severe itch. The disease is caused by mutations in the JAG1 gene in 70% of patients.

Drug-induced cholestatic liver disease

Drug-induced cholestasis can be categorized into acute and chronic forms. The acute forms are subdivided into cholestasis without inflammation (bland cholestasis), cholestasis with inflammation, and cholestasis with bile duct injury. Chronic forms include a vanishing bile duct syndrome and a sclerosing cholangitis-like syndrome.

Drug-induced cholestasis can be accompanied by nausea, anorexia, malaise, and pruritus (32). Symptoms can occur weeks to months after beginning treatment.

Drugs that cause cholestasis with bile duct injury often are accompanied by additional clinical features, such as fever, rigors, jaundice, and tender hepatomegaly mimicking acute cholangitis. Drugs that result in a vanishing bile duct syndrome can lead to progressive cholestasis, with prolonged

jaundice, pruritus, and, occasionally, cirrhosis and liver failure.

The most important tool in the diagnosis of drug-induced cholestasis is a careful medical history, eliciting a history of taking prescribed, over-the-counter, or alternative medications, including herbs. Biliary obstruction should be excluded with an imaging study, ultrasound, or computed tomography (CT) of the biliary tree. The mainstay of treatment is withdrawal of the drug. Management of symptoms associated with cholestasis are similar to those for PBC.

Most cholestatic hepatic injury resolves with withdrawal of the offending medication. A small subgroup of patients develop progressive liver disease, resulting in biliary cirrhosis and liver failure.

Various factors such as age, gender, dose, or co-administered medications may affect the risk to develop drug-induced hepatic injury (40).

Cholestatic disorders in pregnancy

Intrahepatic cholestasis of pregnancy (ICP, also known as obstetric cholestasis) is a reversible form of cholestasis characterized by (i) intense pruritus in pregnancy (starting in the second or third trimester of pregnancy in most patients), (ii) elevated serum ALT activities and fasting serum bile acid levels, and (iii) spontaneous relief of signs and symptoms after delivery (within 4–6 weeks) (41,42). In Europe, about 0.4–2.0% of pregnancies are affected. The clinical importance of ICP lies in the potential fetal risks (spontaneous or iatrogenic prematurity, asphyxia events during delivery, intrauterine death), albeit perinatal mortality rates from recent studies (9/1000) are comparable to whole population figures, most likely due to improvements in obstetric and neonatal care (44). Pruritus (typically worse at night) impairs the mother's quality of life. There appears to be a genetic component because it has been reported to occur in family members.

Table 4. Most frequent drugs causing hepatocellular or ductal cholestasis

Hepatocellular cholestasis	Ductular/ductal cholestasis
Sex hormones	Allopurinol
Carbamazepine	Amoxicillin-clavulanic acid
Chlorpromazine	Azathioprine
Amoxicillin-clavulanic acid	Barbiturates
Trimethroprim-sulfamethoxazole	Captopril
Erytromicin, Clarithromycin	Carbamazepine
Nitrofurantoin	Chlorpropamide
Chlorpropamide	Clindamycin
Azathioprine	Phenytoin
Cyclosporine	Sulpiride
Propafenone	Trimethroprim-sulfamethoxazole
Nifedipine	Medicinal herbs
Medicinal herbs	
NSAIDS, nimesulide	

Summary

Diagnosis of ICP is based on (i) pruritus in pregnancy, (ii) elevated serum ALT activities and fasting bile acid levels, and (iii) exclusion of other causes of liver dysfunction or itching (II-2/C2). ICP is confirmed when serum liver tests completely normalize after delivery.

Conflicts of interest: None declared.

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