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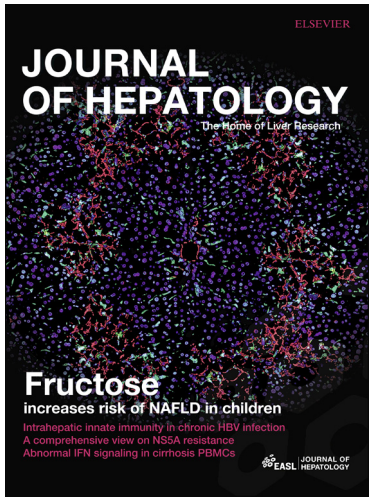

Grand Rounds

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Grand Round

Ursodeoxycholic acid in pregnancy ?

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Summary

The case of a 34-year-old woman with primary biliary cholangitis (PBC) before, during and after pregnancy is described. The use of ursodeoxycholic acid during and after pregnancy is discussed. UDCA has not been approved by the drug regulatory authorities as a pregnancy-safe drug; therefore, reluctance of clinicians to prescribe UDCA during pregnancy is comprehendible. This Grand Round aims to provide a detailed analysis of the current evidence, safety data and clinical experience with ursodeoxycholic acid (and alternative drugs) during pregnancy and lactation. Based on this analysis, an advice for clinicians regarding the use of UDCA during pregnancy and lactation is given.

Clinical case

A 34-year-old woman with an uneventful medical history presented to her general practioner with recent complaints of fatigue and intermittent mild to moderate pruritus (3-4/10), mainly in the late evening. Physical examination was unremarkable besides a few skin excoriations on her forearms and ankles secondary to scratching. Routine laboratory tests disclosed an elevated alkaline phosphatase (ALP) of 402 U/l (upper limit of normal (ULN) 120), gamma-glutamyl transferase (GGT) of 270 U/l (ULN 40), aspartate aminotransferase (AST) of 55 U/l (ULN 40) and alanine aminotransferase (ALT) of 72 U/l (ULN 34), whereas bilirubin was 15 µmol/L (ULN 17). Other laboratory analyses, including a complete blood count, serum creatinine, HbA1c, and lactate dehydrogenase (LDH) showed no abnormalities and could not disclose alternative causes of her itch sensations. The patient was referred to a local hospital for further investigation. Abdominal ultrasonography showed normal liver parenchyma, no intra- or extrahepatic bile duct dilatations, open portal and hepatic veins with normal flow, two slightly enlarged (>1 cm) lymph nodes in the liver hilum, and normal findings for pancreas, spleen (9.5 cm) and kidneys. Serum immunoglobulin M (IgM) was 5.95 g/l (ULN 2.3). Serum immunoglobulin G and immunoglobulin A levels were in the normal range. The patient was tested positive for anti-mitochondrial antibodies (AMA, antibody titer 1:80) and was negative for antinuclear antibodies (ANA). The clinical, biochemical and imaging findings were regarded as diagnostic for primary biliary cholangitis (PBC).

According to EASL and AASLD clinical practice guidelines standard treatment with ursodeoxycholic acid (UDCA) was initiated. A low starting dosage of 7 mg/kg daily was prescribed in the first week to avoid transient worsening of itch sensations. The therapeutic dose of 14 (13-15) mg/kg daily was administered from the second week on.

Six months after start of UDCA treatment, the patient reported improvement of fatigue and itch, but not yet complete relief. The serum liver tests showed improvement, but still a persistent elevation of alkaline phosphatase (183 U/l), gamma-glutamyl transferase (122 U/l) and the aminotransferases (AST 45 U/l, ALT 57 U/l) was observed.

The patient had the desire to conceive already for a while. Therefore, she asked her physician if using UDCA is contraindicated in pregnancy and if teratogenic hazards from UDCA have been observed in humans. Her physician advised her to interrupt UDCA intake until the end of the first trimester of gestation. As the patient felt better since start of UDCA treatment and her serum liver tests had markedly improved, she was reluctant to interrupt UDCA treatment. Therefore, she was referred to an Academic Centre for a second opinion about UDCA treatment during pregnancy.

Experience with management of young female patients with PBC as well as other cholestatic liver diseases who wish to get pregnant is scarce among clinicians. Since UDCA is currently not approved by the drug regulatory authorities for use during pregnancy and breastfeeding, there are various clinical questions that are prompted by this case, including:

1) Is it safe to use UDCA in general?
2) What is the clinical course of pregnancy in women who have an indication for use of UDCA during pregnancy?
3) Is it safe for mother and fetus to use ursodeoxycholic acid during pregnancy?
4) Are there alternative or additional therapeutic options for pregnant women with PBC or other cholestatic liver diseases?
5) Is it safe to use UDCA during lactation?

Is it safe to use ursodeoxycholic acid in general?

Ursodeoxycholic acid (UDCA) is during recent decades increasingly being used for the treatment of chronic cholestatic liver diseases [1]. UDCA is a natural component of human bile, amounting to 1-3% of bile acids in healthy individuals [2]. Currently, the use of UDCA has been approved for the treatment of primary biliary cholangitis (PBC) [3], cholesterol gallstones and for prevention of gallstone formation in obese patients undergoing rapid weight reduction, e.g. after bariatric surgery. Moreover, anticholestatic effects of UDCA treatment have extensively been reported in primary sclerosing cholangitis (PSC), intrahepatic cholestasis of pregnancy (ICP), cystic fibrosis-associated liver disease and cholestatic pediatric disorders such as progressive familial intrahepatic cholestasis type 3 (PFIC3), PFIC2 (in part), Alagille syndrome and biliary atresia [1].

Since the underlying molecular mechanisms differ in part between these cholestatic diseases, extensive research has been performed concerning the potential mechanisms and sites of action of UDCA. In PBC, PSC, liver disease in cystic fibrosis or biliary obstruction (e.g. by gallstones or tumor), biliary secretion can be reduced both from hepatocytes and cholangiocytes [4]. However, in ICP, particularly bile secretion from hepatocytes seems to be impaired. UDCA has marked anticholestatic and also antiapoptotic effects under both conditions, hepatocellular and cholangiocellular cholestasis. It is assumed that protection of cholangiocytes against the toxic effects of human biliary bile acids might prevail in early-stage PBC and PSC [2]. This may at least in part be explained by activation of biliary bicarbonate secretion [5-7] and, thereby, stabilization of a biliary bicarbonate umbrella against uncontrolled invasion of hydrophobic bile acids into cholangiocytes and periportal hepatocytes [8, 9, 10]. UDCA conjugates are potent post-transcriptional signaling molecules and secretagogues in hepatocytes and cholangiocytes [11, 12]. They can stimulate impaired hepatocellular and cholangiocellular secretion by Ca^{++}-, protein kinase Cα (PKCα)-, and protein kinase A (PKA)-dependent post-transcriptional mechanisms via stimulation of targeting and apical membrane insertion of key transporters (Figure 1) [13, 14, 15, 16]. Stimulation of impaired hepatocellular secretion by UDCA could be key for fast relief of pruritus and improvement of serum liver tests in ICP and in some forms of drug-induced cholestasis. Stimulation of cholangiocellular chloride and bicarbonate secretion mediated by the Ca^{++}-sensitive Cl^- channel, TMEM16A, and independent of CFTR could have a major impact in cystic fibrosis-associated liver disease. Inhibition of bile-acid induced hepatocyte and cholangiocyte apoptosis can have a role in all states of cholestasis that are characterized by intracellular bile acid accumulation (Figure 1) [17].

UDCA is considered as a safe and well-tolerated drug at recommended daily doses. No serious adverse effects of UDCA treatment are reported so far in controlled clinical trials in patients with

gallstone disease (10-12 mg/kg/day) or in long-term, large-scale, placebo-controlled trials in patients with PBC (13-15mg/kg/day) and other cholestatic liver diseases at recommended doses [18]. In contrast, a placebo-controlled trial in PSC patients, using very high doses of UDCA (28–30 mg/kg/day) showed that UDCA was not only ineffective regarding long-term outcome, but PSC patients under UDCA also reached more predefined study endpoints. In particular, more patients developed varices or were listed for liver transplantation in this high-dose group [18]. The mechanisms behind this are not entirely known, but increased serum and biliary levels of a UDCA metabolite, the toxic monohydroxy bile salt lithocholate (LCA), after very high doses of UDCA in a disease with partial bile duct obstructions has been discussed as a potential cofactor [19]. Therefore, very high doses of UDCA should be avoided not only in PSC, but also in various other forms of chronic cholestasis.

In a small minority of patients, side effects of UDCA have been reported, particularly gastrointestinal complaints like diarrhea and dyspepsia.

Diarrhea is the single most frequent described side effect during UDCA treatment and has been reported in 2-9% of patients with gallstone disease [20] and up to 5% in ICP [21]. Remarkably, in patients with PBC diarrhea is rarely observed under UDCA and was only incidentally reported [22]. Also in patients with PSC and inflammatory bowel disease (IBD), no diarrhea was reported in early randomized, placebo-controlled trials, including 119 PSC patients, mostly with IBD [23, 24].

The cause of diarrhea as a result of UDCA treatment is not well known. 'Bile acid diarrhea' due to limited capacity or even a molecular defect of ileal bile acid reuptake is the most commonly discussed mechanism. Bacterial conversion of UDCA to chenodeoxycholic acid (CDCA), a bile acid which promotes colonic fluid and electrolyte secretion, might also contribute to the diarrhea [25]. Overall, the diarrhea is mild and uncommonly a reason to stop UDCA treatment. Other gastrointestinal complaints associated with UDCA treatment such as abdominal complaints in the right upper quadrant, flatulence, nausea and vomiting are reported very rarely in randomized placebo-controlled trials in chronic cholestatic diseases [18].

Transient worsening of pre-existing pruritus after initiation of UDCA treatment has been observed in a minority of patients in some trials [26,27,28]. The pathophysiology of this phenomenon remains unknown so far, but unfolding the anticholestatic effect of UDCA conjugates in cholestatic disorders may take some days. Before that, UDCA conjugates may compete with endogenous bile acid derivatives for biliary secretion and may rather lead to transient accumulation of endogenous bile acid conjugates and additional formation of pruritogenic cholephiles. Alternatively, the efficient bacterial conversion of UDCA conjugates in the colon to the strong TGR5 agonist lithocholic acid (LCA) might lead to transient TGR5-mediated aggravation of pruritus . Therefore, in patients with

substantial pruritus and patients with markedly elevated levels of alkaline phosphatase (AP) and gamma-glutamyl transferase (γGT), UDCA treatment should be started at low doses and should be slowly increased to the desired weight-based dose. Other skin related side effects, like toxoallergic exanthema [21], lichenoid and fixed drug eruption [29] and morbiliform eruption [30] are only published in single case reports and it is debatable whether the natural compound UDCA or drug adjuvants are responsible for these reactions. The same may hold true for complaints of thinning of the hair. Whether reported weight gain during UDCA treatment is a mirror of reduced inflammatory activity in the liver or a direct effect of UDCA, remains to be determined.

Pharmacokinetics of UDCA, dosage, absorption, tissue distribution, biotransformation and excretion have been extensively studied. Experience with drug interactions has expanded over several decades which are mainly related to drug absorption, but not clinically relevant drug metabolism.

The anion exchange resins cholestyramine and colesevelam bind UDCA like other bile acids in the small intestine and may, thereby, interfere with its absorption mainly in the terminal ileum [31]. Anion exchange resins should, therefore, never be administered together with UDCA, but only with an adequate interval to UDCA of at least 4 hours [32].

Reported drug-drug interactions are otherwise scarce. CYP3A4 is important for phase 1 biotransformation of a majority of currently available drugs. Some drugs prescribed in literature as having a potential drug-interaction with UDCA are mainly metabolized by CYP3A4 in the gut and liver. Previously it was hypothesized based on *in vitro* observations that UDCA might induce CYP3A4, but in humans *in vivo* UDCA was clearly disproved to be a relevant inducer of CYP3A isoforms [33, 34]. Case reports of drug-interactions with dapsone[35] and ciprofloxacin[36] are published as are pharmacokinetic interactions of midazolam with UDCA[34,37], but the mechanisms of the potential interactions remain unclear. Patients treated with cyclosporine should be closely monitored when UDCA is administered, since co-administration reduced the bioavailability in some patients but also led to a lower demand for cyclosporine in others [18].

We conclude that UDCA has an excellent safety profile when administered to patients with cholestatic liver diseases at recommended doses.

What is known about the clinical course of pregnancy in women who have an indication for use of ursodeoxycholic acid during pregnancy?

Liver diseases during pregnancy can be divided in pregnancy-related liver diseases and liver diseases unrelated to pregnancy. Pregnancy-related liver diseases include hyperemesis gravidarum (1st trimenon), intrahepatic cholestasis of pregnancy (ICP; 2nd to 3rd trimenon), pre-eclampsia, HELLP syndrome and the very rare acute fatty liver of pregnancy (mainly 3rd trimenon) and affect up to 3% of pregnant women. They are the most frequent cause of liver dysfunction during pregnancy at least in Europe [38]. Pre-existing liver diseases unrelated to pregnancy such as chronic viral hepatitis B or C, autoimmune hepatitis or the immune-mediated chronic cholestatic liver diseases PBC and PSC may first be detected and/or may first become symptomatic during pregnancy at an age of 20 to 40 years and are in that situation often misdiagnosed as ICP [1].

In this Grand Round we will focus on patients who have an indication for UDCA treatment during pregnancy such as pregnant women with primary biliary cholangitis (PBC; see case report above) or – at least in Central Europe - primary sclerosing cholangitis (PSC) and women who develop intrahepatic cholestasis of pregnancy (ICP as defined by EASL Clinical Practice Guidelines [1]) or are known with the low phospholipid associated cholelithiasis syndrome (LPAC syndrome as one manifestation of ABCB4 deficiency). In non-pregnant patients UDCA is approved for treatment of PBC in a recommended dose of 13-15mg/kg per day. In patients with PSC, UDCA treatment exerts marked anticholestatic effects, but is apparently less (or not?) effective with regard to disease progression (and development of hepatobiliary and intestinal malignancies which affect prognosis), and its general use is controversially discussed in different parts of the world. A benefit of UDCA on transplant-free survival in PSC has never been proven, but no placebo-controlled trials in PSC with adequate population size, adequate dose (15-20 mg/kg/d) and adequate follow-up period exist until today. Liver transplantation rates over the last decades have clearly decreased in PBC, but not in PSC. Still, reported transplant-free survival is highest in countries with regular prescription of UDCA at recommended doses in PSC such as the Netherlands (21 years) or France (17 years) [39, 40]. The current EASL guidelines consider use of UDCA in PSC at therapeutic doses (15-20 mg/kg per day) due to documented improvement of surrogate biomarkers of prognosis such as serum alkaline phosphatase or bilirubin [1].

In intrahepatic cholestasis of pregnancy (ICP), when defined according to EASL Clinical Practice Guidelines, UDCA (10-20mg/kg per day) is widely regarded as the first-line treatment [1].

Pregnant patients with chronic cholestatic liver diseases should be followed by the obstetrician in close cooperation with an experienced hepatologist for careful monitoring and regular reassessments throughout pregnancy and delivery. It is important to identify PBC and PSC patients with cirrhosis or severe fibrosis and portal hypertension since medical risks during pregnancy are relevant in this subgroup. Management is not different from that of other cirrhotic patients. The risk of variceal bleeding rises as a consequence of pregnancy related increase in portal pressure. It is advised to perform an elective endoscopy in the second trimester to evaluate varices and to accomplish appropriate treatment with nonselective betablockers or rubberband ligation if needed. Pregnancy in cirrhotic patients has been associated with increased risk of spontaneous abortions, premature births and perinatal deaths [3,41].

As pregnancy may affect maternal liver disease and maternal liver disease may affect fetal outcome, careful consideration of this topic is crucial while caring for women of childbearing age with a liver disease.

PBC and pregnancy (Table 1)

PBC is a chronic cholestatic liver disease caused by granulomatous destruction of interlobular bile ducts (< 100 μm) resulting in progressive ductopenia, liver fibrosis and cirrhosis when left untreated. Although PBC is most often diagnosed in middle-aged to elderly women, up to 25% of the patients are of childbearing age when PBC is diagnosed [42]. Younger patients tend to be more symptomatic than older PBC patients [43].

Patients with other chronic liver diseases often have anovulatory cycles, yet a large population-based PBC study showed no association with decreased fertility [39]. Pregnancies in auto-immune and immune-mediated diseases are categorized as high risk because of the potential complications, like disease exacerbation and increased fetal mortality. Depending on the expert's view, PBC is regarded as an immune mediated disorder with an underlying secretory defect of biliary epithelia or an auto-immune disease. (This discussion is out of the scope of this grand round.) Notably, disappearance of serum antimitochondrial antibodies (AMA) and improvement of serum liver tests has been described during pregnancy in PBC, suggesting that pregnancy may have immunosuppressive effects on liver and bile duct inflammation [44]. There are limited and conflicting data on the clinical course of PBC during pregnancy and maternal and fetal consequences. While case reports and small cohort studies published more than 20 years ago, described considerable rates of maternal and fetal complications,

the recent literature provides a more encouraging view. Still, pruritus as a first clinical manifestation of PBC during late pregnancy and post-partum flares of PBC are noteworthy.

A small French study described results of nine pregnancies in six PBC patients. During pregnancy all women remained asymptomatic and no complains of itching were reported. Notably, three months after delivery all patients experienced a flare with elevated serum liver tests. In these nine pregnancies no fetal complications were described [44].

A Turkish retrospective cohort study described the outcome of 9 pregnancies in 7 PBC patients and provided a literature search including 72 PBC patients with 98 pregnancies [45]. 70% of these women showed stable disease or even clinical and biochemical improvement during pregnancy. No pregnancy specific or serious hepatic complications were observed. However, development or worsening of pruritus during pregnancy was a common phenomenon, reported in 49% of the reported pregnancies. After delivery disease progression or exacerbation was noted in 60% of patients. Severe disease progression was reported in two patients, one was referred for liver transplantation. Notably, a relatively low 65% rate of live births was reported in this cohort of pregnant PBC patients, and 24 miscarriages and 3 stillbirths were described [45].

A Canadian population based study reported 50 pregnancies in 32 PBC patients. Pregnancies were mainly uneventful regarding maternal complications and incidence of hepatic decompensation with stable disease reported in 70%. Still, pruritus was reported in 53% and flares post-partum in 70% [46]. Strikingly again, a lower live birthrate of 58% was reported compared to AIH (73%), PSC (88%), and healthy individuals.

A small Italian retrospective case series showed results of 8 pregnancies in 6 PBC patients. In two of the pregnancies, pruritus developed, and in four an increase of serum liver tests was reported after delivery. No fetal complications were described.[47]

PSC and pregnancy (Table 1)

PSC is a chronic cholestatic disease affecting both intra- and extrahepatic bile ducts. It can present at any age with a diagnostic peak at 30–40 years. The male to female ratio is approximately 2:1. Although women tend to be diagnosed later at an average age of approximately 45 years, women of childbearing age can be affected.[48] Studies on fertility and pregnancy in PSC are limited. Knowledge whether pregnancy might affect PSC and if PSC influences birth outcome is scarce. In contrast to PBC,

the majority of PSC patients (60-80%) has inflammatory bowel disease (IBD).[49] IBD may independently be associated with adverse pregnancy outcome [50]. Thus, the presence of IBD might affect studies on pregnancy outcome in PSC.

A German cohort study showed no reduced fertility in patients with PSC compared to healthy controls. 25 pregnancies in 17 PSC patients were investigated in detail. In the majority of patients no alteration of PSC course during pregnancy was reported. In 1/5 of pregnancies increasing serum liver tests were reported during pregnancy and in 1/3 after delivery. No emergency ERCP had to be performed during these pregnancies. As in PBC, seven PSC patients suffered from worsening of pruritus during pregnancy. In contrast to PBC studies, improvement of pruritus during pregnancy was reported in this cohort of PSC patients. The rate of fetal loss was 16% without a clear relation with disease severity. All these patients had concomitant IBD. Of the 21 live births no impairment of fetal outcome was recorded. [51]

A nationwide Swedish population-based study of 229 pregnancies in patients with PSC showed no increase in stillbirth, neonatal death or congenital malformations. Maternal PSC was well associated with increased risk of preterm birth in 16% and cesarean section. The increased risk was observed also in women without IBD. The preterm birth rate may be explained in part by elective early induction of delivery due to severe pruritus [52].

Intrahepatic cholestasis of pregnancy

Intrahepatic cholestasis of pregnancy (ICP) is the most common pregnancy-related liver disease and usually presents in the (second to) third trimester. ICP is characterized by pruritus, elevated levels of serum bile acids and/or elevated levels of serum transaminases, spontaneous resolution of all abnormalities soon after delivery, and absence of any other underlying liver disease [1]. The prevalence varies worldwide but in Western countries ICP complicates approximately 0.2% to 2% of pregnancies. The exact etiology is not fully understood, but genetic, environmental and hormonal factors play a role in its pathogenesis, and continuously rising levels of placenta-derived estrogen and progesterone metabolites during the (second and) third trimenon of pregnancy may unmask the hepatocellular secretory disease in genetically predisposed women [38].

Although symptoms like pruritus can be truly invalidating and may dramatically diminish quality of life, maternal prognosis is otherwise generally good. In contrast, ICP can lead to increased fetal risks. Spontaneous preterm delivery (most studies report rates of 30-40%), fetal distress (as indicated by

meconium-stained amniotic fluid in 16-58% of cases) and even stillbirth (up to 3.5%) are associated with the disease [53]. The risk of fetal complications seems to correlate with the level of maternal serum bile acids with a critical threshold of 40 μmol/l in the fasted state [54] and 100 μmol/L in the postprandial state [55]. Elevated levels of bile acids in amniotic fluid, cord blood and meconium have been reported. The pathophysiology of these fetal complications is not yet unraveled, but, based on experimental studies, cardiotoxic and arrhythmogenic effects of accumulating endogenous bile acids such as cholic acid conjugates are discussed as potential pathogenic factors leading to stillbirth in ICP [38,56].

At present, it is unclear whether the degree of elevation of serum bile acids, like in ICP, has a prognostic value for the outcome of pregnancy including the risk of preterm delivery, fetal anoxia and stillbirth (9, 19, 22) also in the pregnant patient with a chronic cholestatic liver disease such as PBC or PSC, sarcoidosis hepatis, cystic fibrosis associated liver disease or progressive familial intrahepatic cholestasis. Considering that serum bile acids do not only represent a biomarker for pregnancy outcome in ICP, but may also be a culprit initiating deleterious events in the fetus, a therapeutic strategy aiming at lowering serum endogenous bile acids would be highly desirable during pregnancy in patients with an underlying cholestatic liver disease not only for the mother, but also for the fetus in his/her unfriendly cholestatic environment. UDCA lowers the serum levels of endogenous bile acids mainly by improving impaired biliary secretion of endogenous bile acids [2, 10 57].

We conclude that the fetal risk of preterm delivery and stillbirth as well as the pregnant mother's impairment of quality of life, particularly due to increasing pruritus, might not be restricted to patients with ICP, but may also affect pregnant patients with chronic cholestatic liver diseases such as PBC. It remains to be determined whether serum levels of *endogenous* bile acids (rather than total bile acids including administered UDCA) can predict the fetal risk of preterm delivery and stillbirth not only in patients with ICP, but also in pregnant women with PBC and PSC.

Is it safe to use ursodeoxycholic acid during pregnancy?

Ursodeoxycholic acid (UDCA) has still not been approved by the regulatory authorities as a safe drug during pregnancy. Nevertheless, teratogenic effects of UDCA have never been reported in humans. In pregnant rats no significant fetal adverse effects were observed during daily administration of UDCA up to 2000 mg/kg (for comparison: the daily recommended therapeutic dose in humans with cholestatic disorders is about 100 times lower, ~15 mg/kg), except for tail malformation in the highest dose group [18].

As aforementioned, literature regarding pregnancy in PBC and PSC patients is scarce, data on UDCA treatment during pregnancy, especially in the first trimester, even more.

In a French case series of nine pregnancies in PBC patients UDCA treatment was withdrawn during the first trimester of pregnancy. UDCA was administered in the second and third trimester at a daily dosage of 12-15mg/kg. The pregnancies and delivery were unremarkable and no complications were reported for mothers and children. Notably, all patients were followed after pregnancy and none developed a disease flare within three months after delivery [44].

The above mentioned article from Turkey reported maintenance of UDCA treatment during all trimesters in three pregnancies and interruption in four pregnancies during the first trimester but re-administration later during pregnancy. During the second trimester one patient developed a biochemical flare after stop of UDCA, but all serum liver tests returned to normal after re-administration of UDCA. A post-partum flare was observed in five pregnancies. The three women who did not exhibit post-partum disease activity were all treated with UDCA during the course of all trimesters. A literature review identified 12 additional patients who received UDCA during the first trimester of pregnancy without any fetal side effects reported [45].

A small Italian case series reports 8 pregnancies of 6 PBC patients under continuous UDCA treatment. No clinical or biochemical exacerbation of PBC during pregnancy nor fetal or birth complications were reported. Still, three patients developed a marked increase in serum liver tests after delivery returning to normal within 6 months [47].

In the largest retrospective study, only a minority of six PBC patients used UDCA at various time points during pregnancy. No adverse fetal consequences were described. Still, five of six patients who were exposed to UDCA during pregnancy experienced a flare [46].

For PSC, a German retrospective analysis reported continuous UDCA administration during eight pregnancies and UDCA re-administration in another eight pregnancies after the first trimester. Women who used UDCA during pregnancy, at a mean dose of 16 mg / kg per day, more often experienced stable serum liver tests when compared with those who were not treated (13% vs 67%, $p<0.05$). Pregnancy and fetal outcome were uneventful in these patients and post-partum biochemical flares were not observed [51].

In these limited reports, all authors concluded that UDCA during pregnancy is safe and well tolerated and they advocated continuous use of UDCA throughout pregnancy to prevent PBC and PSC from progression.

A meta-analysis of 12 randomized controlled trials evaluated the effects and safety of UDCA in ICP, usually administered during the late second and/or third trimester of pregnancy [58, 59]. UDCA was found to improve maternal pruritus and serum liver tests and to reduce the risk of fetal and neonatal complications. UDCA was well tolerated in ICP and no adverse effects of UDCA in neonates were identified [58,59]. Long-term safety data of UDCA in later childhood were reported in one study indicating normal development [60].

We conclude that administration of the physiologic bile acid UDCA appears safe during pregnancy when provided at recommended doses, although available data for the first trimenon are limited. From a pathophysiological viewpoint, UDCA treatment appears highly useful in the cholestatic pregnant patient to beneficially modulate the unfriendly cholestatic milieu for the growing fetus which is dominated by hydrophobic endogenous bile acids. UDCA lowers serum levels of hydrophobic bile acids in cholestasis by stimulating their impaired biliary secretion.

Are there alternative or additional treatment options for pregnant women with PBC or other cholestatic liver diseases?

Treatment of chronic cholestatic liver diseases has advanced during the last decade, since a number of new therapies have been developed. Farnesoid X receptor (FXR) agonists like obeticholic acid, fibrates, FGF19 analogs like NGM282 and ASBT inhibitors have caught attention as second line treatment in PBC and possibly PSC, but also other cholestatic disorders.

The FXR agonist obeticholic acid (OCA) was recently approved by American (FDA) and European (EMA) authorities as an add-on treatment in PBC patients incompletely responding (or in rare cases intolerant) to UDCA. Considering absence of data concerning OCA use in pregnancy, prescription of OCA should currently be avoided during pregnancy. Notably, animal studies did not suggest reproductive toxicity.

Fibrates such as the peroxisomal proliferator activating receptor (PPAR) agonist bezafibrate are registered as therapeutics of hypertriglyceridemia since decades. Therefore, limited data are available on fibrate use during pregnancy, suggesting safe use even during the first trimester [61]. Still,

it is advised to discontinue fibrates by the time pregnancy is considered, and safety of fibrates in pregnancy remains questionable.

Use of other FXR or PPAR agonists, FGF19 analogs and ASBT inhibitors has not been reported in pregnancy so far and can therefore not be recommended.

Cholestasis-associated pruritus may be aggravated or appear for the first time during the course of pregnancy in PBC, PSC and ICP, but also other cholestatic disorders, in part probably due to increasing serum and tissue levels of placenta-derived estrogen and progesterone metabolites. Scarce data are available concerning treatment of pruritus during pregnancy. Cholestyramine, an anion exchange resin, and rifampicin, a pregnane X-receptor (PXR) agonist, are considered relatively safe in pregnancy as pruritus-attenuating therapy [3].

In the stepwise therapeutic approach of pruritus in cholestasis, regardless of pregnancy, cholestyramine is still the first recommended drug. Cholestyramine is recommended as a 4 g sachet 1 h before and after breakfast up to a maximum dose of 16 g/day. [3] Precaution is warranted since high-dose cholestyramine can increase the risk of coagulopathy as a result of malabsorption of fat-soluble vitamins, especially vitamin K. Maternal vitamin K deficiency may lead to vitamin K deficiency and coagulopathy in the newborn as is hypothesized in a case report of severe fetal intracranial hemorrhage during cholestyramine treatment in ICP. [62] In ICP, a randomized controlled trial showed that pruritus is more effectively reduced by UDCA than cholestyramine, with less adverse effects on the mother and delivery of the babies closer to term.[63]

Rifampicin is part of the first line combination therapy in tuberculosis since decades. Its use in pregnancy is considered safe for the mother and the fetus [64]. Although rifampicin has been shown to be potentially teratogenic in rodents, no increase in the frequency of spontaneous abortion, congenital malformations, preterm delivery, or low birth weight has been observed in patients with tuberculosis associated with rifampicin use in pregnancy. Rifampicin has been associated with neonatal hemorrhage, especially when given in the last few weeks of pregnancy in severe refractory ICP, but the severity of cholestasis with impaired vitamin K absorption rather than use of rifampicin might have contributed to this complication [65]. In women suffering from severe cholestasis-associated pruritus caused by PBC, PSC, ICP, or other cholestatic diseases in whom UDCA therapy alone is ineffective, potential benefit and safety of add-on treatment with rifampicin is recommended [66].

We conclude that cholestasis-associated pruritus in pregnancy, if not adequately controlled by the anticholestatic effect of UDCA, can be treated with the anion exchange resin cholestyramine or, more effectively, the PXR agonist rifampicin in combination with UDCA.

Is it safe to use ursodeoxycholic acid during lactation?

There are no guideline recommendations for UDCA treatment during lactation since data on UDCA treatment and bile acid levels in breast milk are scarce, but toxicity of UDCA when administered at recommended doses in cholestatic neonates and infants is not known. Only a few case reports have addressed the issue of UDCA in breastmilk. One German case report analyzed patient's breast milk by high pressure liquid chromatography while she was treated with UDCA at a dose of 750mg/day. No UDCA was detected, in contrast to the more hydrophobic cholic acid, deoxycholic acid and lithocholic acid [67]. A more recent case report analyzed bile acids in breast milk at a UDCA dosage up to 1500mg/day and found no effect of UDCA at increasing doses on breast milk bile acid content; development of the child was normal [68]. The most relevant study on UDCA therapy and breast milk was performed in ICP patients [69]. Bile acid excretion in colostrum from 16 lactating ICP patients was compared to that in colostrum of five healthy lactating mothers. In ICP patients treated with UDCA compared to non-treated women excretion of total bile acid in colostrum was substantially decreased. Accumulation of UDCA in colostrum was very limited and the concentration ingested by the nursing infant irrelevant. The breastfeeding infant would be exposed to less than 0.01% of the UDCA administered to the mother with an estimated total daily dose of approximately 12 µg. No side effects were encountered in breastfeeding infants whose mothers continued UDCA treatment during lactation [45].

We conclude that UDCA treatment during breastfeeding is safe and will not harm the infant.

Table 1: Case series describing the course of pregnancies and treatment with UDCA in pregnant women with cholestatic liver diseases

Back to the clinical case

As this grand round shows there is no evidence for discontinuation of UDCA during pregnancy, the physician of the university hospital advised to continue the UDCA treatment during a potential future pregnancy. One year after start of treatment the patient became pregnant and after an uncomplicated pregnancy, at 38 weeks gestation, she delivered a healthy son with a birthweight of 3600 gram.

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Figure 1:

Major mechanisms and sites of action of ursodeoxycholic acid in cholestatic liver diseases [2, 10] modified, [57].

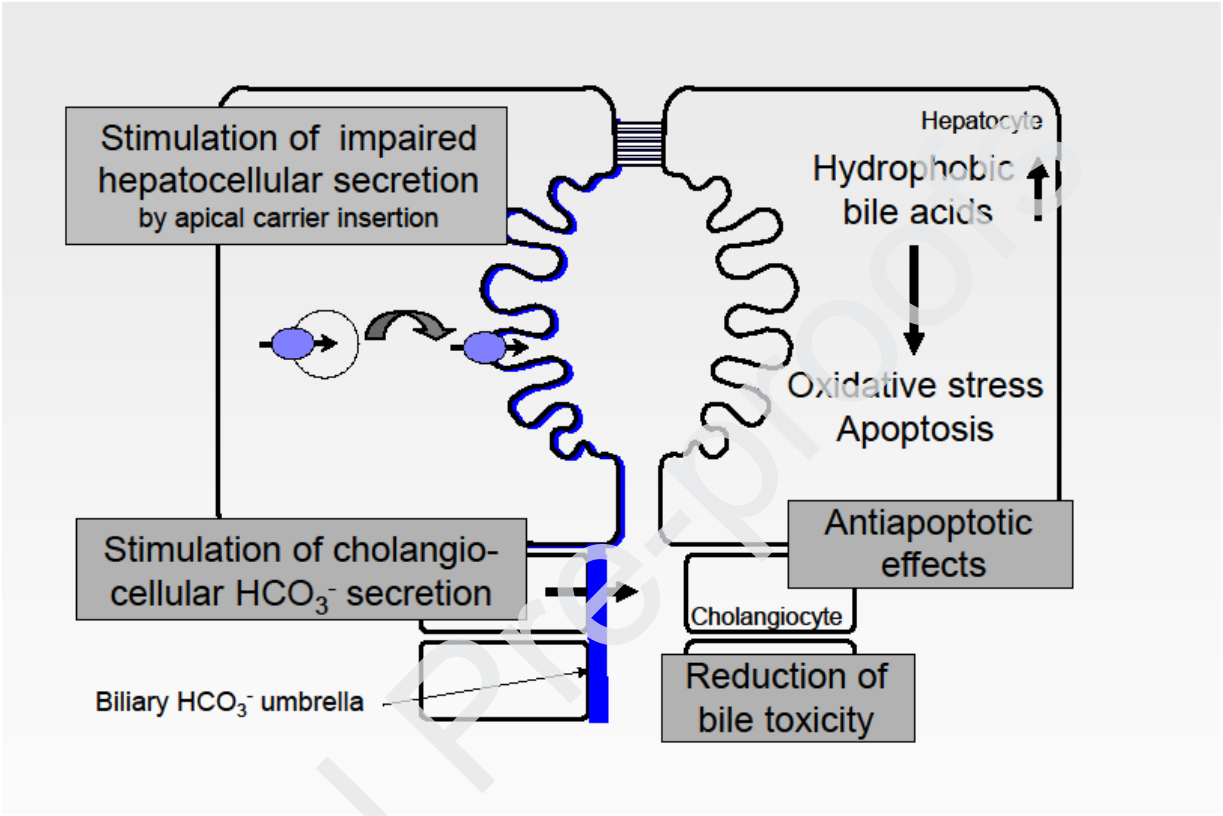

Table 1: Case series describing the course of pregnancies in patients with PBC and PSC and documentation regarding UDCA treatment

Authors / Year	**PBC PSC**	**Number of patients / pregnancies**	**Number of pregnancies with documented UDCA treatment during pregnancy**	**Number of pregnancies with documented UDCA treatment during the first trimester**
Poupon et al. 2005 [44]	PBC	6 / 9	9	0
Trivedi et al. 2014 [46]	PBC	32 / 50	6	4
Efe et al. 2014 [45]	PBC	72 / 98 (literature)	Unknown	12
		7/9 (local cases)	7	3
Floreani et al. 2015 [47]	PBC	6 / 8	8	8
Wellge et al. 2011 [51]	PSC	17 / 25	16	8
Ludvigsson et al. 2014 [52]	PSC	Unknown / 229	Unknown	Unknown
Janczewska et al [70]	PSC	10 / 13	0	0

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Janczewska et al [70]	PSC	10 / 13	0	0