JOURNAL OF HEPATOLOGY

Ursodeoxycholic acid in pregnancy?

Elsemieke de Vries[1], Ulrich Beuers[1,*]

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 (UDCA) during and after pregnancy is discussed. UDCA has not been approved by the drug regulatory authorities as a pregnancy-safe drug; therefore, the reluctance of clinicians to prescribe UDCA during pregnancy is understandable. This Grand Round aims to provide a detailed analysis of the current evidence, safety data and clinical experience with UDCA (and alternative drugs) during pregnancy and lactation. Based on this analysis, advice for clinicians regarding the use of UDCA during pregnancy and lactation is given.

Keywords: Lactation; Primary biliary cholangitis; PBC; Primary sclerosing cholangitis; PSC; Stillbirth; UDCA.

Received 26 May 2019; received in revised form 19 August 2019; accepted 26 August 2019

Clinical case

A 34-year-old woman with an uneventful medical history presented to her general practitioner 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 did not reveal any alternative causes of her pruritus. 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, 2 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 tested positive for antimitochondrial antibodies (AMA, antibody titre 1:80) but 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 pruritus. The therapeutic dose of 14 (13–15) mg/kg daily was administered from the second week on.

Six months after the start of UDCA treatment, the patient reported improvement of fatigue and itch, but not complete relief. The serum liver tests showed improvement, but ALP (183 U/L), GGT (122 U/L) and the aminotransferases (AST 45 U/L and ALT 57 U/L) remained elevated.

The patient had wanted to conceive for a while. Therefore, she asked her physician if 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 had felt better since starting 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 regarding UDCA treatment during pregnancy.

Experience in managing young female patients with PBC, or other cholestatic liver diseases, who wish to get pregnant is scarce among clinicians. Since UDCA is not currently approved by the drug regulatory authorities for use during pregnancy and breastfeeding, this case prompts various clinical questions, 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 foetus to use UDCA 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?

UDCA has increasingly been used for the treatment of chronic cholestatic liver diseases in recent

[1]*Department of Gastroenterology and Hepatology and Tytgat Institute for Liver and Intestinal Research, Amsterdam University Medical Centers, Location AMC, Amsterdam, The Netherlands*

* Corresponding author. Address: Department of Gastroenterology and Hepatology, Tytgat Institute for Liver and Intestinal Research, Amsterdam University Medical Centers, Location AMC, C2-327, Meibergdreef 9, 1100 DE Amsterdam, The Netherlands.

E-mail address: u.h.beuers@amsterdamumc.nl (U. Beuers).

decades.[1] UDCA is a natural component of human bile, accounting for 1–3% of bile acids in healthy individuals.[2] Currently, the use of UDCA has been approved for the treatment of PBC,[3] cholesterol gallstones and for prevention of gallstone formation in obese patients undergoing rapid weight reduction, *e.g.* after bariatric surgery. Moreover, the anticholestatic effects of UDCA treatment have been reported extensively in primary sclerosing cholangitis (PSC), intrahepatic cholestasis of pregnancy (ICP), cystic fibrosis-associated liver disease and cholestatic paediatric 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 on the potential mechanisms and sites of action of UDCA has been performed. In PBC, PSC, liver disease in cystic fibrosis or biliary obstruction (*e.g.* by gallstones or tumour), biliary secretion can be reduced both from hepatocytes and cholangiocytes.[4] However, in ICP, bile secretion from hepatocytes seems to be particularly impaired. UDCA has marked anticholestatic and anti-apoptotic effects under both 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, stabilisation of a biliary bicarbonate umbrella against uncontrolled invasion of hydrophobic bile acids into cholangiocytes and periportal hepatocytes.[8–10] UDCA conjugates are potent post-transcriptional signalling molecules and secretagogues in hepatocytes and cholangiocytes.[11,12] They can stimulate impaired hepatocellular and cholangiocellular secretion by Ca^{2+}-, protein kinase C (PKC)-, and protein kinase A (PKA)-dependent post-transcriptional mechanisms, via stimulation of targeting and apical membrane insertion of key transporters (Fig. 1).[13–16] 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 characterised by intracellular bile acid accumulation (Fig. 1).[17]

Key point

UDCA has an excellent safety profile when used at recommended doses in patients with cholestatic liver diseases.

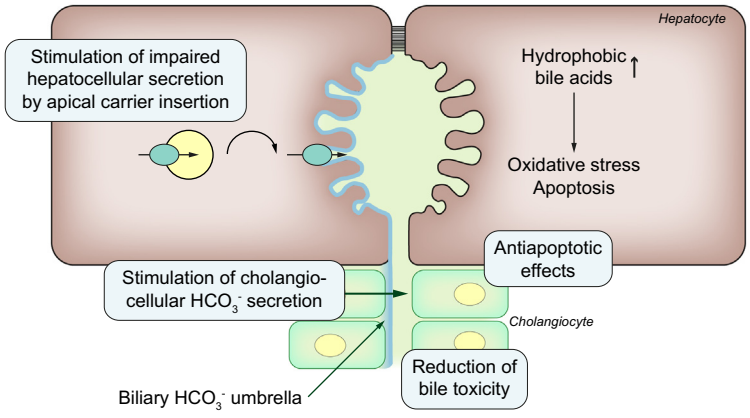

Fig. 1. Major mechanisms and sites of action of UDCA in cholestatic liver diseases.[2,10,57] Reproduced from[10] under the CCBY license. UDCA, ursodeoxycholic acid.

UDCA is considered a safe and well-tolerated drug at recommended daily doses. No serious adverse effects of UDCA treatment have been reported 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 (13–15 mg/kg/day) and other cholestatic liver diseases at recommended doses.[18] In contrast, a placebo-controlled trial in patients with PSC, using very high doses of UDCA (28–30 mg/kg/day), showed that UDCA was not only ineffective with respect to long-term outcome, but also led to more patients reaching 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 toxic UDCA metabolite, the monohydroxy bile salt lithocholate (LCA), after very high doses of UDCA, in a disease with partial bile duct obstructions, could be a cofactor.[19] Therefore, very high doses of UDCA should be avoided not only in PSC, but also in other forms of chronic cholestasis.

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

Diarrhoea is the single most frequently 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, diarrhoea is rarely observed under UDCA and was only incidentally reported.[22] Also in patients with PSC and inflammatory bowel disease (IBD), no diarrhoea was reported in early randomised, placebo-controlled trials, including 119 patients with PSC, mostly with IBD.[23,24]

The cause of diarrhoea following UDCA treatment is not well known. 'Bile acid diarrhoea' 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 diarrhoea.[25] Overall, the diarrhoea is mild and not usually 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,

have been reported very rarely in randomised placebo-controlled trials of patients with 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.[26–28] The pathophysiology of this phenomenon remains unknown, but elucidating the anticholestatic effect of UDCA conjugates in cholestatic disorders may take some time. Before that, UDCA conjugates may compete with endogenous bile acid derivatives for biliary secretion and may 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 LCA might lead to transient TGR5-mediated aggravation of pruritus. Therefore, in patients with substantial pruritus and patients with markedly elevated levels of ALP and GGT, 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 toxo-allergic exanthema,[21] lichenoid and fixed drug eruption[29] and morbiliform eruption[30] have only been published in single case reports; 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 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.

The pharmacokinetics of UDCA, dosage, absorption, tissue distribution, biotransformation and excretion have been studied extensively. Experience with drug interactions has expanded over several decades, with interactions 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 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 h.[32]

Reported drug-drug interactions are otherwise scarce. CYP3A4 is important for phase 1 biotransformation of a majority of currently available drugs. In the literature, some of the drugs that have been described as having potential interactions with UDCA are mainly metabolised by CYP3A4 in the gut and liver. Previously, it was hypothesised 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] have been published as have reports of a pharmacokinetic interaction with midazolam,[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 into pregnancy-related liver diseases and liver diseases unrelated to pregnancy. Pregnancy-related liver diseases include hyperemesis gravidarum (1st trimester), intrahepatic cholestasis of pregnancy (ICP; 2nd to 3rd trimester), pre-eclampsia, HELLP syndrome and the very rare acute fatty liver of pregnancy (mainly 3rd trimester). Pregnancy-related liver diseases 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 PBC (see case report above) or PSC (at least in Central Europe) and women who develop ICP (as defined by EASL Clinical Practice Guidelines[1]), or are known to have 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 at a recommended dose of 13–15 mg/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 controversial 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 have been carried out. 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 which regularly prescribe UDCA at recommended doses in PSC, such as the Netherlands (21 years) and France

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

Authors/year	PBC/PSC	No. of patients/pregnancies	No. of pregnancies with documented UDCA treatment during pregnancy	No. 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

PBC, primary biliary cholangitis; PSC, primary sclerosing cholangitis; UDCA, ursodeoxycholic acid.

Key point

Pregnant women with chronic cholestatic liver diseases should be closely monitored by obstetricians in cooperation with an experienced hepatologist.

(17 years).[39,40] The current EASL guidelines consider the use of UDCA in PSC at therapeutic doses (15–20 mg/kg per day), because of the documented improvement in surrogate biomarkers of prognosis, such as serum ALP or bilirubin.[1]

In ICP, defined according to EASL Clinical Practice Guidelines, UDCA (10–20 mg/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, to provide 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 a pregnancy-related increase in portal pressure. An elective endoscopy is advised in the second trimester to evaluate varices and to carry out appropriate treatment with non-selective 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 foetal outcome, careful consideration of this topic is crucial while caring for women of childbearing age with a liver disease.

PBC and pregnancy

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 patients are of childbearing age when PBC is diagnosed.[42] Younger patients tend to be more symptomatic than older patients with PBC.[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 autoimmune and immune-mediated diseases are categorised as high risk because of the potential complications, like disease exacerbation and increased foetal 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 autoimmune disease. (This discussion is out of the scope of this Grand Round.) Notably, disappearance of serum AMA and improvement of serum liver tests have 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 the maternal and foetal consequences (Table 1). While case reports and small cohort studies published more than 20 years ago described considerable rates of maternal and foetal 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 the results of 9 pregnancies in 6 patients with PBC. During pregnancy all women remained asymptomatic and no complaints of itching were reported. Notably, 3 months after delivery all patients experienced a flare with elevated serum liver tests. In these 9 pregnancies, no foetal complications were described.[44]

A Turkish retrospective cohort study described the outcome of 9 pregnancies in 7 patients with PBC and provided a literature search including 72 patients with 98 pregnancies.[45] Of these women, 70% 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 2 patients, one of whom was referred for liver transplantation. Notably, a relatively low rate of live births (65%) was reported in this cohort of

pregnant patients with PBC, and 24 miscarriages and 3 stillbirths were described.[45]

A Canadian population-based study reported 50 pregnancies in 32 patients with PBC. Pregnancies were mainly uneventful regarding maternal complications and the 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 birth-rate of 58% was reported compared to that for AIH (73%), PSC (88%), and healthy individuals.

A small Italian retrospective case series showed the results of 8 pregnancies in 6 patients with PBC. In 2 of the pregnancies, pruritus developed, and in 4 an increase of serum liver tests was reported after delivery. No foetal complications were described.[47]

PSC and pregnancy

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 (Table 1). There is scarce knowledge regarding the potential effects of pregnancy on PSC and of PSC on birth outcomes. In contrast to PBC, the majority of patients with PSC (60–80%) have inflammatory bowel disease (IBD).[49] IBD may be independently associated with adverse pregnancy outcomes.[50] Thus, the presence of IBD might confound studies on pregnancy outcomes in patients with PSC.

A German cohort study showed no reduced fertility in patients with PSC compared to healthy controls. A total of 25 pregnancies in 17 patients with PSC were investigated in detail. In the majority of patients, no alteration of PSC course was reported during pregnancy. In one-fifth of pregnancies, increasing serum liver tests were reported during pregnancy and in one-third after delivery. No emergency endoscopic retrograde cholangiopancreatography had to be performed during these pregnancies. As in PBC, 7 patients with PSC suffered from pruritus during pregnancy, in part worsening during the third trimester. The rate of foetal loss was 16%, with no clear relation to disease severity. All these patients had concomitant IBD. Of the 21 live births, no impairment of foetal 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 associated with an increased risk of preterm birth (which occurred in 16% of patients) and caesarean section (performed in 30% of cases). The increased risk was also observed 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

ICP is the most common pregnancy-related liver disease and usually presents in the (second to) third trimester. ICP is characterised by pruritus, elevated levels of serum bile acids and/or elevated levels of serum aminotransferases, spontaneous resolution of all abnormalities soon after delivery, and an 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 aetiology is not fully understood, but genetic, environmental and hormonal factors play a role in its pathogenesis, and continuously rising levels of placenta-derived oestrogen and progesterone metabolites during the (second and) third trimester of pregnancy may unmask the hepatocellular secretory disease in genetically predisposed women.[38]

Although symptoms like pruritus can be truly debilitating and may dramatically diminish quality of life, maternal prognosis is otherwise generally good. In contrast, ICP can lead to increased foetal risks. Spontaneous preterm delivery (most studies report rates of 30–40%), foetal 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 foetal complications seems to correlate with the level of maternal serum bile acids with a critical threshold of 40 μmol/L in the fasting 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 foetal complications is not yet clear, 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, also has prognostic value in predicting the outcome of pregnancy – including the risk of preterm delivery, foetal anoxia and stillbirth (9, 19, 22) – 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 not only represent a biomarker for pregnancy outcomes in ICP, but may also initiate deleterious events in the foetus, a therapeutic strategy aimed 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 foetus in his/her unfriendly cholestatic environment. UDCA lowers the serum levels of endogenous bile acids mainly by improving

Key points

Serum bile acids not only represent a biomarker for pregnancy outcomes but may also initiate deleterious events in the foetus. So, a therapeutic strategy aimed at lowering serum endogenous bile acids would be highly desirable during pregnancy in patients with an underlying cholestatic liver disease.

impaired biliary secretion of endogenous bile acids.[2,10,57]

We conclude that the foetal risk of preterm delivery and stillbirth, as well as the impairment to the pregnant mother's 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 foetal 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?

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 foetal adverse effects were observed during daily administration of UDCA up to 2,000 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 mentioned, literature regarding pregnancy in patients with PBC and PSC is scarce, data on UDCA treatment during pregnancy, especially in the first trimester, is even scarcer.

In a French case series of 9 pregnancies in patients with PBC, UDCA treatment was withdrawn during the first trimester of pregnancy. UDCA was administered in the second and third trimester at a daily dosage of 12–15 mg/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 3 months after delivery.[44]

The aforementioned article from Turkey reported maintenance of UDCA treatment during all trimesters in 3 pregnancies and interruption in 4 pregnancies during the first trimester but re-administration later during pregnancy. During the second trimester, 1 patient developed a biochemical flare after stopping UDCA, but all serum liver tests returned to normal after re-administration of UDCA. A post-partum flare was observed in 5 pregnancies. The 3 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 foetal side effects reported.[45]

A small Italian case series reported on 8 pregnancies in 6 patients with PBC under continuous UDCA treatment. No clinical or biochemical exacerbation of PBC during pregnancy, nor foetal or birth complications were reported. Still, 3 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 6 patients with PBC used UDCA at various time points during pregnancy. No adverse foetal consequences were described. Still, 5 of 6 patients who were exposed to UDCA during pregnancy experienced a flare.[46]

For PSC, a German retrospective analysis reported continuous UDCA administration during 8 pregnancies and UDCA re-administration in another 8 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 foetal 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 randomised 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 foetal 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 1 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 trimester are limited. From a pathophysiological viewpoint, UDCA treatment appears highly useful in the cholestatic pregnant patient, as it beneficially modulates the unfriendly cholestatic milieu for the growing foetus, which is dominated by hydrophobic endogenous bile acids. UDCA lowers serum levels of hydrophobic bile acids in cholestasis by stimulating their impaired biliary secretion.

Key point

The administration of UDCA appears to be safe during pregnancy when given at recommended doses.

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, with the development of a number of new therapies. Farnesoid X receptor (FXR) agonists (like obeticholic acid [OCA]), fibrates, FGF19 analogues (like NGM282)

and ASBT inhibitors have garnered attention as second-line treatment options in PBC and possibly PSC, but also other cholestatic disorders.

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

Fibrates such as the peroxisomal proliferator activating receptor (PPAR) agonist bezafibrate have been registered as therapeutics for hypertriglyceridemia for decades. Therefore, albeit limited, data are available on fibrate use during pregnancy, suggesting that its use is safe 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.

The use of other FXR or PPAR agonists, FGF19 analogues and ASBT inhibitors has not been reported in pregnancy to date 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, probably due, in part, to increasing serum and tissue levels of placenta-derived oestrogen 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, as 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 hypothesised in a case report of severe foetal intracranial haemorrhage during cholestyramine treatment in ICP.[62] In ICP, a randomised 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 has been part of the first-line combination therapy for tuberculosis for decades. Its use in pregnancy is considered safe for the mother and the foetus.[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 haemorrhage, 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, add-on treatment with rifampicin is recommended based on its potential benefit and safety.[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.

Key points

In patients with cholestasis-associated pruritus, cholestyramine or rifampicin can be given if UDCA cannot adequately control the pruritus.

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 analysed a patient's breast milk by high pressure liquid chromatography while she was being treated with UDCA at a dose of 750 mg/day. No UDCA was detected, in contrast to the more hydrophobic cholic acid, deoxycholic acid and lithocholic acid.[67] A more recent case report analysed bile acids in breast milk at a UDCA dosage up to 1,500 mg/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 patients with ICP.[69] Bile acid excretion in colostrum from 16 lactating patients with ICP was compared to that in the colostrum of 5 healthy lactating mothers. In patients with ICP treated with UDCA, excretion of total bile acid in colostrum was substantially decreased compared to non-treated women. 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.

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 starting treatment the patient became pregnant, and after an uncomplicated pregnancy, at 38 weeks gestation, she delivered a healthy son with a birthweight of 3.6 kg.

Financial support

The authors received no financial support to produce this manuscript.

Conflict of interest

EdV has no disclosures. UB actually receives research funding from a South-African PSC Patient Foundation, the Netherlands Gastroenterology and Hepatology Foundation (MLDS), the European Union LIVERHOPE project, investigator-initiated study support from Dr. Falk Pharma GmbH, Freiburg, Germany, and Intercept, San Diego, USA.

Please refer to the accompanying ICMJE disclosure forms for further details.

Authors' contribution

Both authors contributed equally to the manuscript.

Disclaimer

The educational clinical case contains elements of more than one 'real life' case in order to address most issues regarding treatment with UDCA during pregnancy.

Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.jhep.2019.08.020.

References

[1] European Association for the Study of the Liver. EASL Clinical Practice Guidelines: management of cholestatic liver diseases. J Hepatol 2009;51:237–267.

[2] Beuers U. Drug insight: mechanisms and sites of action of ursodeoxycholic acid in cholestasis. Nat Clin Pract Gastroenterol Hepatol 2006;3:318–328.

[3] European Association for the Study of the Liver. EASL Clinical Practice Guidelines: the diagnosis and management of patients with primary biliary cholangitis. J Hepatol 2017;67:145–172.

[4] Boyer JL. Bile formation and secretion. Compr Physiol 2013;3:1035–1078.

[5] Medina JF, Martinez A, Vazquez JJ, Prieto J. Decreased anion exchanger 2 immunoreactivity in the liver of patients with primary biliary cirrhosis. Hepatology 1997;25:12–17.

[6] Prieto J, Garcia N, Marti-Climent JM, Penuelas I, Richter JA, Medina JF. Assessment of biliary bicarbonate secretion in humans by positron emission tomography. Gastroenterology 1999;117:167–172.

[7] Banales JM, Saez E, Uriz M, Sarvide S, Urribarri AD, Splinter P, et al. Up-regulation of microRNA 506 leads to decreased Cl-/HCO3- anion exchanger 2 expression in biliary epithelium of patients with primary biliary cirrhosis. Hepatology 2012;56:687–697.

[8] Beuers U, Hohenester S, de Buy Wenniger LJ, Kremer AE, Jansen PL, Elferink RP. The biliary HCO_3 umbrella: a unifying hypothesis on pathogenetic and therapeutic aspects of fibrosing cholangiopathies. Hepatology 2010;52:1489–1496.

[9] Hohenester S, Wenniger LM, Paulusma CC, van Vliet SJ, Jefferson DM, Elferink RP, et al. A biliary HCO3- umbrella constitutes a protective mechanism against bile acid-induced injury in human cholangiocytes. Hepatology 2012;55:173–183.

[10] Beuers U, Trauner M, Jansen P, Poupon R. New paradigms in the treatment of hepatic cholestasis: from UDCA to FXR, PXR and beyond. J Hepatol 2015;62(1 Suppl):S25–S37.

[11] Beuers U, Nathanson MH, Boyer JL. Effects of tauroursodeoxycholic acid on cytosolic Ca2+ signals in isolated rat hepatocytes. Gastroenterology 1993;104:604–612.

[12] Bouscarel B, Fromm H, Nussbaum R. Ursodeoxycholate mobilizes intracellular Ca2+ and activates phosphorylase a in isolated hepatocytes. Am J Physiol 1993;264(2 Pt 1):G243–G251.

[13] Beuers U, Nathanson MH, Isales CM, Boyer JL. Tauroursodeoxycholic acid stimulates hepatocellular exocytosis and mobilizes extracellular Ca++ mechanisms defective in cholestasis. J Clin Invest 1993;92:2984–2993.

[14] Beuers U, Throckmorton DC, Anderson MS, Isales CM, Thasler W, Kullak-Ublick GA, et al. Tauroursodeoxycholic acid activates protein kinase C in isolated rat hepatocytes. Gastroenterology 1996;110:1553–1563.

[15] Marzioni M, Francis H, Benedetti A, Ueno Y, Fava G, Venter J, et al. Ca2+-dependent cytoprotective effects of ursodeoxycholic and tauroursodeoxycholic acid on the biliary epithelium in a rat model of cholestasis and loss of bile ducts. Am J Pathol 2006;168:398–409.

[16] Beuers U, Bilzer M, Chittattu A, Kullak-Ublick GA, Keppler D, Paumgartner G, et al. Tauroursodeoxycholic acid inserts the apical conjugate export pump, Mrp2, into canalicular membranes and stimulates organic anion secretion by protein kinase C-dependent mechanisms in cholestatic rat liver. Hepatology 2001;33:1206–1216.

[17] Guicciardi ME, Gores GJ. Bile acid-mediated hepatocyte apoptosis and cholestatic liver disease. Dig Liver Dis 2002;34:387–392.

[18] Hempfling W, Dilger K, Beuers U. Systematic review: ursodeoxycholic acid–adverse effects and drug interactions. Aliment Pharmacol Ther 2003;18:963–972.

[19] Lindor KD, Kowdley KV, Luketic VA, Harrison ME, McCashland T, Befeler AS, et al. High-dose ursodeoxycholic acid for the treatment of primary sclerosing cholangitis. Hepatology 2009;50:808–814.

[20] Roda E, Bazzoli F, Labate AM, Mazzella G, Roda A, Sama C, et al. Ursodeoxycholic acid vs. chenodeoxycholic acid as cholesterol gallstone-dissolving agents: a comparative randomized study. Hepatology 1982;2:804–810.

[21] Parizek A, Simjak P, Cerny A, Sestinova A, Zdenkova A, Hill M, et al. Efficacy and safety of ursodeoxycholic acid in patients with intrahepatic cholestasis of pregnancy. Ann Hepatol 2016;15:757–761.

[22] Pares A, Caballeria L, Rodes J, Bruguera M, Rodrigo L, Garcia-Plaza A, et al. Long-term effects of ursodeoxycholic acid in primary biliary cirrhosis: results of a double-blind controlled multicentric trial. UDCA-Cooperative Group from the Spanish Association for the Study of the Liver. J Hepatol 2000;32:561–566.

[23] Beuers U, Spengler U, Kruis W, Aydemir U, Wiebecke B, Heldwein W, et al. Ursodeoxycholic acid for treatment of primary sclerosing cholangitis: a placebo-controlled trial. Hepatology 1992;16:707–714.

[24] Lindor KD. Ursodiol for primary sclerosing cholangitis. Mayo primary sclerosing cholangitis-ursodeoxycholic acid study group. N Engl J Med 1997;336:691–695.

[25] Kelly OB, Mroz MS, Ward JB, Colliva C, Scharl M, Pellicciari R, et al. Ursodeoxycholic acid attenuates colonic epithelial secretory function. J Physiol 2013;591:2307–2318.

[26] Lotterer E, Stiehl A, Raedsch R, Foelsch UR, Bircher J. Ursodeoxycholic acid in primary biliary cirrhosis: no evidence for toxicity in the stages I to III. J Hepatol 1990;10:284–290.

[27] Kneppelhout JC, Mulder CJ, van Berge Henegouwen GP, de Vries RA, Brandt KH. Ursodeoxycholic acid treatment in primary biliary cirrhosis with the emphasis on late stage disease. Neth J Med 1992;41:11–16.

[28] Heathcote EJ, Cauch-Dudek K, Walker V, Bailey RJ, Blendis LM, Ghent CN, et al. The Canadian Multicenter Double-blind randomized controlled trial of ursodeoxycholic acid in primary biliary cirrhosis. Hepatology 1994;19:1149–1156.

[29] Ozkol HU, Calka O, Dulger AC, Bulut G. Ursodeoxycholic acid induced generalized fixed drug eruption. Cutan Ocul Toxicol 2014;33:256–258.

[30] Ellul JP, Groves R, Walters JR, Murphy GM. Lichen planus associated with chenodeoxycholic acid and ursodeoxycholic acid for gallstone dissolution. Dig Dis Sci 1992;37:628–630.

[31] Rust C, Sauter GH, Oswald M, Buttner J, Kullak-Ublick GA, Paumgartner G, et al. Effect of cholestyramine on bile acid pattern and synthesis during administration of ursodeoxycholic acid in man. Eur J Clin Invest 2000;30:135–139.
[32] Glasova H, Beuers U. Extrahepatic manifestations of cholestasis. J Gastroenterol Hepatol 2002;17:938–948.
[33] Dilger K, Denk A, Heeg MH, Beuers U. No relevant effect of ursodeoxycholic acid on cytochrome P450 3A metabolism in primary biliary cirrhosis. Hepatology 2005;41:595–602.
[34] Yan D, Yang Y, Uchida S, Misaka S, Luo J, Takeuchi K, et al. Effects of ursodeoxycholic acid on the pharmacokinetics and pharmacodynamics of intravenous and oral midazolam in healthy volunteers. Naunyn Schmiedebergs Arch Pharmacol 2008;377:629–636.
[35] Stroubou E, Dawn G, Forsyth A. Ursodeoxycholic acid causing exacerbation of dermatitis herpetiformis. J Am Acad Dermatol 2001;45:319–320.
[36] Belliveau PP, Nightingale CH, Qunitiliani R, Maderazo EG. Reduction in serum concentrations of ciprofloxacin after administration of ursodiol to a patient with hepatobiliary disease. Clin Infect Dis 1994;19:354–355.
[37] Misaka S, Kurosawa S, Uchida S, Yoshida A, Kato Y, Kagawa Y, et al. Evaluation of the pharmacokinetic interaction of midazolam with ursodeoxycholic acid, ketoconazole and dexamethasone by brain benzodiazepine receptor occupancy. J Pharm Pharmacol 2011;63:58–64.
[38] Westbrook RH, Dusheiko G, Williamson C. Pregnancy and liver disease. J Hepatol 2016;64:933–945.
[39] Boonstra K, Weersma RK, van Erpecum KJ, Rauws EA, Spanier BW, Poen AC, et al. Population-based epidemiology, malignancy risk, and outcome of primary sclerosing cholangitis. Hepatology 2013;58:2045–2055.
[40] Garioud A, Seksik P, Chretien Y, Corphechot C, Poupon R, Poupon RE, et al. Characteristics and clinical course of primary sclerosing cholangitis in France: a prospective cohort study. Eur J Gastroenterol Hepatol 2010;22:842–847.
[41] Westbrook RH, Yeoman AD, O'Grady JG, Harrison PM, Devlin J, Heneghan MA. Model for end-stage liver disease score predicts outcome in cirrhotic patients during pregnancy. Clin Gastroenterol Hepatol 2011;9:694–699.
[42] Carbone M, Mells GF, Pells G, Dawwas MF, Newton JL, Heneghan MA, et al. Sex and age are determinants of the clinical phenotype of primary biliary cirrhosis and response to ursodeoxycholic acid. Gastroenterology 2013;144, 560–9 e7.
[43] Dyson JK, Wilkinson N, Jopson L, Mells G, Bathgate A, Heneghan MA, et al. The inter-relationship of symptom severity and quality of life in 2055 patients with primary biliary cholangitis. Aliment Pharmacol Ther 2016;44:1039–1050.
[44] Poupon R, Chretien Y, Chazouilleres O, Poupon RE. Pregnancy in women with ursodeoxycholic acid-treated primary biliary cirrhosis. J Hepatol 2005;42:418–419.
[45] Efe C, Kahramanoglu-Aksoy E, Yilmaz B, Ozseker B, Takci S, Roach EC, et al. Pregnancy in women with primary biliary cirrhosis. Autoimmun Rev 2014;13:931–935.
[46] Trivedi PJ, Kumagi T, Al-Harthy N, Coltescu C, Ward S, Cheung A, et al. Good maternal and fetal outcomes for pregnant women with primary biliary cirrhosis. Clin Gastroenterol Hepatol 2014;12, 1179–85 e1.
[47] Floreani A, Infantolino C, Franceschet I, Tene IM, Cazzagon N, Buja A, et al. Pregnancy and primary biliary cirrhosis: a case-control study. Clin Rev Allergy Immunol 2015;48:236–242.
[48] Marchioni Beery RM, Vaziri H, Forouhar F. Primary biliary cirrhosis and primary sclerosing cholangitis: a review featuring a women's health perspective. J Clin Transl Hepatol 2014;2:266–284.
[49] Chapman R, Fevery J, Kalloo A, Nagorney DM, Boberg KM, Shneider B, et al. Diagnosis and management of primary sclerosing cholangitis. Hepatology 2010;51:660–678.
[50] Alstead EM, Nelson-Piercy C. Inflammatory bowel disease in pregnancy. Gut 2003;52:159–161.
[51] Wellge BE, Sterneck M, Teufel A, Rust C, Franke A, Schreiber S, et al. Pregnancy in primary sclerosing cholangitis. Gut 2011;60:1117–1121.
[52] Ludvigsson JF, Bergquist A, Ajne G, Kane S, Ekbom A, Stephansson O. A population-based cohort study of pregnancy outcomes among women with primary sclerosing cholangitis. Clin Gastroenterol Hepatol 2014;12, 95–100 e1.
[53] Geenes V, Williamson C. Intrahepatic cholestasis of pregnancy. World J Gastroenterol 2009;15:2049–2066.
[54] Glantz A, Marschall HU, Mattsson LA. Intrahepatic cholestasis of pregnancy: Relationships between bile acid levels and fetal complication rates. Hepatology 2004;40:467–474.
[55] Ovadia C, Seed PT, Sklavounos A, Geenes V, Di Ilio C, Chambers J, et al. Association of adverse perinatal outcomes of intrahepatic cholestasis of pregnancy with biochemical markers: results of aggregate and individual patient data meta-analyses. Lancet 2019;393:899–909.
[56] Brites D. Intrahepatic cholestasis of pregnancy: changes in maternal-fetal bile acid balance and improvement by ursodeoxycholic acid. Ann Hepatol 2002;1:20–28.
[57] Paumgartner G, Beuers U. Ursodeoxycholic acid in cholestatic liver disease: mechanisms of action and therapeutic use revisited. Hepatology 2002;36:525–531.
[58] Bacq Y, Sentilhes L, Reyes HB, Glantz A, Kondrackiene J, Binder T, et al. Efficacy of ursodeoxycholic acid in treating intrahepatic cholestasis of pregnancy: a meta-analysis. Gastroenterology 2012;143:1492–1501.
[59] Kong X, Kong Y, Zhang F, Wang T, Yan J. Evaluating the effectiveness and safety of ursodeoxycholic acid in treatment of intrahepatic cholestasis of pregnancy: a meta-analysis (a prisma-compliant study). Medicine (Baltimore) 2016;95 e4949.
[60] Zapata R, Sandoval L, Palma J, Hernandez I, Ribalta J, Reyes H, et al. Ursodeoxycholic acid in the treatment of intrahepatic cholestasis of pregnancy. A 12-year experience. Liver Int 2005;25:548–554.
[61] Sunman H, Canpolat U, Sahiner L, Aytemir K. Use of fenofibrate during the first trimester of unplanned pregnancy in a patient with hypertriglyceridemia. Ann Pharmacother 2012;46 e5.
[62] Sadler LC, Lane M, North R. Severe fetal intracranial haemorrhage during treatment with cholestyramine for intrahepatic cholestasis of pregnancy. Br J Obstet Gynaecol 1995;102:169–170.
[63] Kondrackiene J, Beuers U, Kupcinskas L. Efficacy and safety of ursodeoxycholic acid versus cholestyramine in intrahepatic cholestasis of pregnancy. Gastroenterology 2005;129:894–901.
[64] Loto OM, Awowole I. Tuberculosis in pregnancy: a review. J Pregnancy 2012;2012 379271.
[65] Liu J, Murray AM, Mankus EB, Ireland KE, Acosta OM, Ramsey PS. Adjuvant use of rifampin for refractory intrahepatic cholestasis of pregnancy. Obstet Gynecol 2018;132:678–681.
[66] Geenes V, Chambers J, Khurana R, Shemer EW, Sia W, Mandair D, et al. Rifampicin in the treatment of severe intrahepatic cholestasis of pregnancy. Eur J Obstet Gynecol Reprod Biol 2015;189:59–63.
[67] Rudi J, Schonig T, Stremmel W. Therapy with ursodeoxycholic acid in primary biliary cirrhosis in pregnancy. Z Gastroenterol 1996;34:188–191.
[68] Vitek L, Zelenkova M, Bruha R. Safe use of ursodeoxycholic acid in a breast-feeding patient with primary biliary cirrhosis. Dig Liver Dis 2010;42:911–912.
[69] Brites D, Rodrigues CM. Elevated levels of bile acids in colostrum of patients with cholestasis of pregnancy are decreased following ursodeoxycholic acid therapy [see comemnts]. J Hepatol 1998;29:743–751.
[70] Janczewska I, Olsson R, Hultcrantz R, Broome U. Pregnancy in patients with primary sclerosing cholangitis. Liver 1996;16:326–330.