European Journal of Obstetrics & Gynecology and Reproductive Biology 189 (2015) 59–63

Contents lists available at ScienceDirect

European Journal of Obstetrics & Gynecology and Reproductive Biology

journal homepage: www.elsevier.com/locate/ejogrb

Rifampicin in the treatment of severe intrahepatic cholestasis of pregnancy

Victoria Geenes [a], Jenny Chambers [b], Rshmi Khurana [c], Elisabeth Wikstrom Shemer [d], Winnie Sia [c], Dalvinder Mandair [e], Elwyn Elias [e], Hanns-Ulrich Marschall [f], William Hague [g], Catherine Williamson [a,*]

[a] Women's Health Academic Centre, King's College London, London, United Kingdom
[b] Women's Health Research Centre, Imperial College London, London, United Kingdom
[c] Royal Alexandra Hospital, University of Alberta, Edmonton, Canada
[d] Department of Women's and Children's Health, Akademiska Hospital, Uppsala University, Uppsala, Sweden
[e] Liver Unit, University of Birmingham Trust Hospital, Birmingham, United Kingdom
[f] Sahlgrenska Academy, University of Gothenburg, Gothenburg, Sweden
[g] Robinson Research Institute, University of Adelaide, Adelaide, South Australia, Australia

ARTICLE INFO

Article history:
Received 9 October 2014
Received in revised form 23 February 2015
Accepted 19 March 2015

Keywords:
Bile acids
Pregnancy
Obstetric cholestasis
Ursodeoxycholic acid
Rifampicin

ABSTRACT

Objective: To describe the use of combined ursodeoxycholic acid (UDCA) and rifampicin treatment in intrahepatic cholestasis of pregnancy (ICP).
Study design: A questionnaire survey of 27 women with 28 affected pregnancies identified via the UK and International Obstetric Medicine forum. The clinical case notes of women with ICP treated with combined UDCA and rifampicin therapy were reviewed, and data regarding maternal and perinatal outcomes extracted.
Results: Serum bile acids remained high whilst taking UDCA as monotherapy. In 14 pregnancies (54%) serum bile acids decreased following the introduction of rifampicin. In 10 pregnancies (38%), there was a 50% reduction in serum bile acids. There were no adverse effects reported with either drug.
Conclusions: This is the first report of the use of rifampicin in ICP. The data suggest that combined treatment with UDCA and rifampicin is an effective way of treating women with severe ICP who do not respond to treatment with UDCA alone.

Introduction

Intrahepatic cholestasis of pregnancy (ICP) is a pregnancy-specific liver disease, associated with an increased risk of adverse fetal outcomes, including preterm delivery, meconium staining of the amniotic fluid and stillbirth [1,2]. It is characterised by maternal pruritus and elevated transaminases and serum bile acids. The most sensitive and specific biochemical marker for the diagnosis and monitoring of ICP is the concentration of serum bile acids. Recent studies have shown an increased risk of adverse perinatal outcomes in women with severe ICP (i.e. in those with serum bile acids >40 μmol/L) [1,2]. ICP is commonly treated with ursodeoxycholic acid (UDCA), which has been shown to improve pruritus and serum biochemistry, including serum bile acid levels [3–5]. The mechanisms of action of UDCA are not fully understood, but are proposed to include improved bile acid transport and detoxification [6]. Evidence from in vitro studies of the developing fetal heart and the placenta suggest that UDCA may also have a direct protective effect on the fetal compartment in ICP [7]. However, not all women treated with UDCA have a biochemical response or an improvement in symptoms.

Rifampicin has been used in the treatment of several cholestatic liver diseases. In primary biliary cirrhosis it has been shown to reduce bilirubin, enhance hepatic efflux of organic anions, including serum bile acids, and improve pruritus. The mechanisms of its action in such diseases are complementary to those of UDCA, and include enhanced bile acid detoxification and elimination [6]. Combination therapy with rifampicin and UDCA might therefore be more effective than UDCA treatment alone, but there have been no reports of the use of rifampicin in ICP. The aim of this study was

* Corresponding author at: Women's Health Academic Centre, 10th floor North Wing, St Thomas' Hospital, London SE1 7EH, United Kingdom.
Tel.: +44 0207 188 3639.
E-mail address: catherine.williamson@kcl.ac.uk (C. Williamson).

http://dx.doi.org/10.1016/j.ejogrb.2015.03.020
0301-2115/

to evaluate the impact of the addition of rifampicin to UDCA in the treatment of ICP.

Materials and methods

Women diagnosed with ICP and treated with a combination of ursodeoxycholic acid (UDCA) and rifampicin were identified via the UK and international Obstetric Medicine Discussion Forum, an online organisation for obstetricians and physicians with a specialist interest in Obstetric Medicine. Between 2009 and 2012 consultants with an interest in maternal medicine were asked to submit the details of any woman in their care with severe ICP treated with these drugs. ICP was diagnosed in women presenting with pruritus and elevated liver enzymes, including raised serum bile acids. Women with other causes of pregnancy specific liver dysfunction, including pre-eclampsia, the HELLP (haemolysis, elevated liver enzymes and low platelets) syndrome and acute fatty liver of pregnancy, were excluded. Clinical case notes were reviewed and data regarding drug treatment, serum biochemistry, pregnancy and fetal outcomes collated in an anonymised database. Blood test results from the 24-h period before either treatment was started were used for analysis. Blood tests were performed according to local hospital policy, and further information regarding whether individual women were fasted or not is not available. Statistical analysis was performed using Stata (StataCorp, Texas).

Results

Twenty-eight ICP pregnancies treated with both UDCA and rifampicin were identified in twenty-seven women (one woman had two pregnancies during the study period). Two pregnancies were excluded from subsequent analysis as rifampicin had been started before UDCA, based on the woman's previous history of severe ICP responding to rifampicin (see Table 1 and supplementary Figure 1). Of the remaining 26 pregnancies, two (8%) were twin gestations. 14 (54%) of the women had a previous history of ICP, and four (15%) had a history of stillbirth associated with ICP. Two women (8%) had a history of gallstones and six (23%) had a history of pruritus when taking the combined oral contraceptive pill. The mean gestational age at onset of pruritus was 21^{+0} weeks (Interquartile range [IQR] 13^{+3} to 28^{+6} weeks) and at diagnosis 24^{+5} weeks (IQR 18^{+6} to 30^{+0} weeks). Further clinical details can be found in Table 1.

The mean gestational age at which UDCA treatment was commenced was 26^{+1} weeks (IQR 22^{+0} to 31^{+1} weeks) and the starting dose of UDCA ranged from 500 to 1500 mg in divided doses daily. The maximum doses of UDCA ranged from 1500 to 3500 mg in divided doses daily. The mean gestational age at which rifampicin treatment was added was 30^{+2} weeks (IQR 29^{+6} to 34^{+0} weeks), and the doses used ranged from 300 to 1200 mg in divided doses daily. The mean number of weeks which women received combined UDCA and rifampicin treatment for was 2^{+2} weeks (IQR 0^{+6} to 6^{+3} weeks). Further details regarding doses and duration of treatment with each drug are given in Table 1. No adverse side

Table 1
Clinical features of women with intrahepatic cholestasis of pregnancy treated with combined UDCA and rifampicin therapy.

Case number	Gestation at diagnosis (weeks + days)	UDCA started (weeks + days)	Rifampicin started (weeks + days)	Duration of combined UDCA and rifampicin treatment (weeks + days)	Dose range of UDCA (mg)	Dose range of rifampicin (mg)	Gestational age at delivery (weeks + days)	Mode of delivery	Birthweight (g)	Adverse perinatal outcomes
1[a]	16^{+6}	17^{+4}	16^{+4}	16^{+3}	600–2500	600	34^{+1}	IOL/VD	1928	NNU
2[a]	9^{+2}	8^{+6}	6^{+5}	23^{+5}	1000–3000	300–900	32^{+5}	IOL/VD	2240	Mec
3	24^{+0}	25^{+1}	25^{+5}	8^{+2}	1000–2000	300–600	34^{+1}	IOL/VD	2260	Mec
4	29^{+2}	30^{+4}	35^{+2}	0^{+3}	1000–2000	600	35^{+6}	SVD	2990	–
5	33^{+1}	33^{+4}	33^{+5}	2^{+1}	1000	300	36^{+0}	IOL/SVD	n/a	–
6[b]	30^{+6}	31^{+4}	35^{+1}	0^{+1}	1000–2000	300	35^{+3}	ELCS	2548/2442	–/–
7	18^{+5}	19^{+1}	32^{+2}	0^{+6}	1000–2000	600	33^{+2}	IOL/VD	n/a	–
8	29^{+3}	30^{+5}	34^{+4}	0^{+6}	1000–2000	300	35^{+4}	IOL/VD	3080	Mec
9	30^{+5}	31^{+1}	33^{+6}	2^{+4}	1000–1500	300	36^{+4}	IOL/VD	2896	–
10	21^{+0}	21^{+6}	31^{+6}	0^{+5}	1000–2000	300	32^{+5}	EMCS	2214	NNU; Mec
11	30^{+1}	31^{+2}	34^{+2}	2^{+4}	1000–1750	600	37^{+0}	IOL/VD	3246	–
12	22^{+0}	30^{+0}	32^{+0}	2^{+4}	1500–2500	300	34^{+5}	IOL/VD	2180	Mec
13	34^{+1}	35^{+4}	36^{+4}	0^{+4}	1000–1500	300	37^{+2}	IOL/VD	2792	–
14	24^{+6}	25^{+4}	33^{+6}	0^{+1}	1000–2000	300	34^{+0}	ELCS	2640	NNU; Mec
15	29^{+1}	29^{+1}	34^{+1}	0^{+5}	1000–1500	1200	35^{+0}	IOL/VD	n/a	n/a
16	17^{+5}	20^{+0}	23^{+0}	12^{+3}	1000–2000	450–900	35^{+4}	ELCS	1191	NNU
17	14^{+6}	8^{+0}	25^{+0}	9^{+6}	750–2000	600	35^{+0}	IOL/VD	n/a	n/a
18	27^{+0}	28^{+0}	30^{+0}	3^{+3}	500–2250	600–1200	33^{+4}	EMCS	1965	NNU; Mec
19	28^{+0}	28^{+0}	30^{+0}	7^{+0}	n/a	300	37^{+1}	IOL/VD	3100	NNU
20[b]	29^{+0}	29^{+0}	32^{+0}	1^{+1}	1500–3500	300	33^{+2}	ELCS	2100/2110	NNU; Mec
21	26^{+0}	27^{+0}	28^{+0}	4^{+4}	1500–3000	300	32^{+5}	IOL/VD	2280	NNU
22	33^{+0}	33^{+0}	33^{+0}	1^{+0}	1500	300	34^{+1}	ELCS	2290	NNU
23	25^{+0}	29^{+0}	31^{+0}	6^{+3}	1000–3000	300	37^{+4}	IOL/VD	2770	NNU
24	30^{+0}	32^{+0}	32^{+0}	2^{+2}	1500–2250	300	34^{+3}	ELCS	2300	–
25	8^{+0}	24^{+0}	27^{+0}	1^{+3}	1500–3000	300	28^{+4}	EMCS	1260	NNU
26	30^{+0}	32^{+0}	36^{+0}	1^{+2}	1500–3000	300	37^{+3}	ELCS	2980	n/a
27	16^{+2}	20^{+0}	31^{+1}	0^{+4}	1000–2000	300	31^{+6}	SVD	1940	NNU
28	12^{+0}	26^{+0}	27^{+0}	6^{+3}	1500	300	33^{+4}	IOL/VD	n/a	n/a

Key:
IOL, induction of labour; VD, vaginal delivery; SVD, spontaneous vaginal delivery; ELCS, elective caesarean section; EMCS, emergency caesarean section; n/a, data not available; NNU, neonatal unit admission; Mec, meconium staining of the amniotic fluid; –, no adverse perinatal outcomes.

[a] Excluded from subsequent analysis as rifampicin started before UDCA (see supplementary Figure 1).

[b] Twin pregnancy.

effects were reported by women for either treatment. None of the women in this study recieved any other treatments specifically for ICP. However, six women (23%) received vitamin K, four women (15%) received an antihistamine, and 10 women (38%) were given steroids (either betamethasone or dexamethasone) to promote fetal lung maturity.

The serum biochemistry values for women before commencing UDCA treatment, before commencing rifampicin treatment and prior to delivery are shown in Figs. 1–3. In all women, serum bile acids remained high following the commencement of UDCA therapy (Fig. 1). In 14 (54%) women, serum bile acids reduced following the commencement of rifampicin treatment (Fig. 1). Ten women (38%) had a 50% or greater reduction in serum bile acids following the introduction of rifampicin. Subgroup analysis of these women did not identify any clinical or biochemical factors that could be used to predict a response to rifampicin treatment (Table 2). In particular, compared with women who did not respond to rifampicin treatment, women who responded were not more likely to have a history of pruritus when taking the oral contraceptive pill (30%, 3/10 vs. 19%, 3/16), nor a previous history of ICP (80%, 8/10 vs. 43%, 7/16). Furthermore, there was no difference in the dose of rifampicin used or in the number of weeks of treatment (1^{+0} weeks (IQR 0^{+4} to 3^{+2} weeks) vs. 2^{+3} weeks (IQR 1^{+0} to 5^{+4} weeks)). Of note, the two women with a history of gallstones both had a greater than 50% reduction in serum bile acids following the introduction of rifampicin.

The biochemical response to rifampicin for the other markers of liver dysfunction was less clear (Figs. 2 and 3). 15% (4 women) had a 50% or greater reduction in serum ALT, and 12% (3 women) had a 50% or greater reduction in serum bilirubin. Similar reductions were seen in serum AST (23%, 4 of 17 women) and GGT (4.5%, 1 of 22 women) (data not shown). Clinical case notes were reviewed for evidence of a subjective improvement in symptoms. Of the 15 pregnancies in which comment on symptoms was made in the clinical notes, 10 recorded a reduction in pruritus following the introduction of rifampicin.

The mean gestational age at delivery was 34^{+4} weeks (IQR 33^{+3} to 35^{+6} weeks) (Table 1). 16 (62%) women had vaginal deliveries, of whom 14 (54%) had labour induced for worsening serum biochemistry and/or symptoms. Of the ten women who required caesarean section, seven (27%) were delivered electively and three (12%) were delivered as an emergency procedure. There were no post-partum haemorrhages reported. Twelve babies (46%) were admitted to the neonatal unit, mainly for prematurity. Meconium staining of the amniotic fluid was reported in 8 cases (31%). There were no stillbirths or congenital abnormalities.

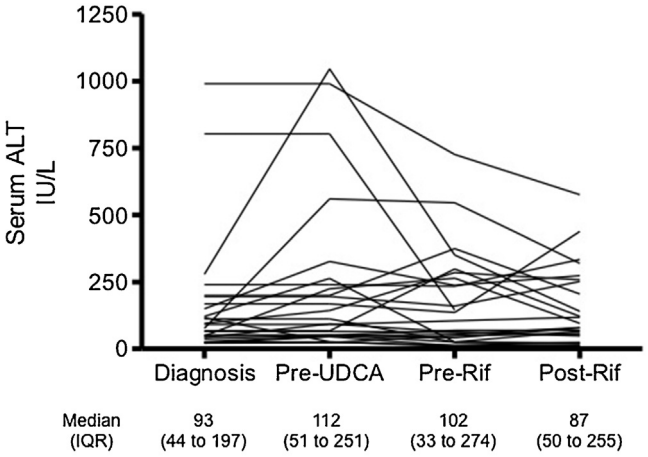

Fig. 2. Graph representing the serum ALT of women with intra-hepatic cholestasis of pregnancy (ICP) at diagnosis, prior to starting UDCA (pre-UDCA), before starting combined UDCA and rifampicin treatment (pre-rif) and at delivery (post-rif) are shown. Each line represents one woman.

Comment

This is the first report of the use of combined UDCA and rifampicin treatment in ICP. This study shows that rifampicin may be a useful adjunct to treatment in pregnant women with increasing serum bile acids despite maximal UDCA therapy. Following the addition of rifampicin, over half of women had some improvement in bile acids, and in 38% of women there was a reduction of greater than 50%. There were no adverse effects reported from either treatment and there were no stillbirths.

This study is that it is the first report of its kind, although rifampicin has been used with good effect in other cholestatic liver disorders, including primary biliary cirrhosis and childhood cholestatic syndromes [8–14]. In primary biliary cirrhosis it has been shown to improve both pruritus and serum biochemistry, including serum bile acids [8,12]. It is therefore biologically plausible that it would have a similar effect in ICP. Rifampicin has

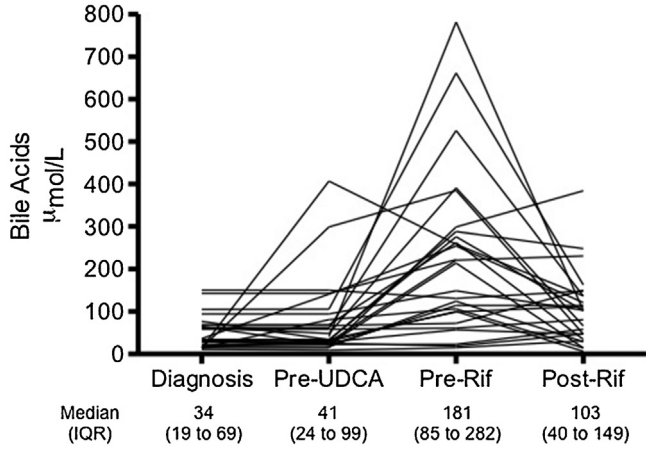

Fig. 1. Graph representing the serum bile acids of women with intra-hepatic cholestasis of pregnancy (ICP) at diagnosis, prior to starting UDCA (pre-UDCA), before starting combined UDCA and rifampicin treatment (pre-rif) and at delivery (post-rif) are shown. Each line represents one woman.

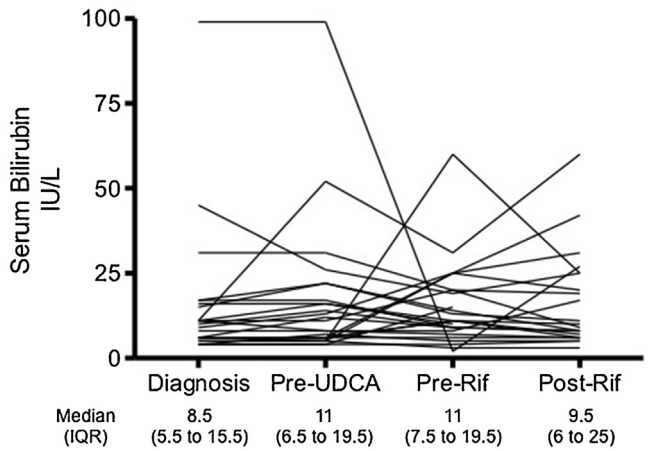

Fig. 3. Graph representing the serum bilirubin of women with intra-hepatic cholestasis of pregnancy (ICP) at diagnosis, prior to starting UDCA (pre-UDCA), before starting combined UDCA and rifampicin treatment (pre-rif) and at delivery (post-rif) are shown. Each line represents one woman.

Table 2
Clinical and biochemical features of women with intrahepatic cholestasis of pregnancy (ICP) who responded to UDCA and rifampicin combination therapy (*N* and proportions; median and inter-quartile ranges).

	Responder (>50% reduction in SBA) *N* = 10	Non-responder (<50% reduction in SBA) *N* = 16	*p*
Maternal medical history			
History of gallstones	2 (20%)	0 (0%)	ns
History of pruritus with oral contraceptives	3 (30%)	3 (19%)	ns
History of ICP	8 (80%)	7 (43%)	ns
Diagnosis of ICP			
Gestation at onset of pruritus	26^{+3} (14^{+5} to 29^{+6})	25^{+0} (12^{+6} to 28^{+3})	ns
Gestation at diagnosis of ICP	27^{+0} (19^{+1} to 31^{+3})	28^{+0} (19^{+6} to 30^{+0})	ns
Biochemistry at diagnosis			
Serum bile acids (μmol/L)	33 (17–73)	33.5 (17–65.5)	ns
Alanine transaminase (IU/L)	103.5 (62.5–194.5)	65 (27–195)	ns
Aspartate transaminase (IU/L)	52 (42.5–107.5)	47 (26–154.5)	ns
Bilirubin (μmol/L)	11 (8.5–23.5)	6 (5–11)	ns
Gamma glutamyl transferase (IU/L)	20 (16.5–36.5)	29 (16–44)	ns
Biochemistry at commencement of UDCA			
Serum bile acids (μmol/L)	58.5 (26.5–123.2)	33 (23.5–80.5)	ns
Alanine transaminase (IU/L)	184 (92–443.5)	65 (47–199)	ns
Aspartate transaminase (IU/L)	110.5 (40–216)	51 (35–154.5)	ns
Bilirubin (μmol/L)	13.5 (8–24)	6 (5–17)	ns
Gamma glutamyl transferase (IU/L)	25.5 (21–40)	30 (19–55)	ns
Biochemistry at commencement of rifampicin			
Serum bile acids (μmol/L)	258 (115–388)	122.5 (59–240)	ns 0.06
Alanine transaminase (IU/L)	237 (43.5–415)	62 (26–160)	ns
Aspartate transaminase (IU/L)	107.5 (34.5–192)	66.5 (35–145.5)	ns
Bilirubin (μmol/L)	14 (8.5–19.5)	10 (5–25)	ns
Gamma glutamyl transferase (IU/L)	24.5 (18.5–34)	24 (9–54)	ns

also been extensively used in the treatment of tuberculosis, including in the treatment of pregnant women, and there are encouraging safety data relating to its use in pregnancy.

The mechanism of action of rifampicin in cholestasis is not fully understood, but a study of the use of rifampicin in pre-operative patients with gallstones showed that it enhances bile acid detoxification, bilirubin conjugation and bilirubin excretion [6]. In the same study, these effects were complemented by the up-regulation of bile acid export pathways in the liver by UDCA [6]. Given the complementary effects of the two drugs seen in this study, we propose that UDCA should not be stopped prior to the commencement of rifampicin, but rather that both drugs should be continued together.

A limitation of this study is that it is a retrospective, observational study of a small number of cases. However, as the first report of the combination therapy in women with ICP, it adds to the current literature regarding the management of this still poorly understood condition, particularly in a group of women with ongoing severe disease with high serum bile acids despite treatment with UDCA.

The implications of the study are that treatment with rifampicin may be considered in women with ICP who do not have an adequate clinical or biochemical response to UDCA alone. Anecdotally, it is known that not all women with ICP have a clinical or biochemical improvement with UDCA treatment. Although the reasons for this are not known, the data presented here suggest that a sub-group of these women will respond to combined therapy with rifampicin. Given that there were no adverse effects reported in the study and that there is a well established safety profile for both drugs in pregnancy, it is reasonable to consider combined therapy in women with severe ICP who have not responded to treatment with UDCA alone.

Future research is needed to determine genetic or metabolomic features that will predict which women with ICP will respond to UDCA alone, or to UDCA in combination with rifampicin, so that treatment can be tailored to individuals. Furthermore, the data presented here warrant further investigation in the form of a prospective randomised and preferably placebo-controlled trial to assess whether combined treatment with UDCA and rifampicin is safe and effective in the management of severe cholestasis of pregnancy.

In summary, rifampicin may be a useful adjunct to the treatment with UDCA in women with severe ICP, and should be used in combination with UDCA, given that the two drugs act in a complementary fashion to enhance bile acid detoxification and increase bile acid excretion.

Conflict of interest

The authors have no conflict of interest to declare.

Role of funding source

This study was supported by the National Institute for Health Research (NIHR) Biomedical Research Centres based at Kings College London (grant number: guysbrc-2012-1) and Imperial College London. The views expressed are those of the authors and not necessarily those of the NHS, the NIHR or the Department of Health NIHR or the Department of Health. The funders had no role in study design, data collection and analysis, decision to publish, or preparation of the manuscript.

Acknowledgements

Paul Seed for help with statistical analysis.

Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.ejogrb.2015.03.020.

References

[1] Geenes V, Chappell LC, Seed PT, Steer PJ, Knight M, Williamson C. Association of severe intrahepatic cholestasis of pregnancy with adverse pregnancy outcomes: a prospective population-based case-control study. Hepatology 2014;59:1482–91.
[2] Glantz A, Marschall HU, Mattsson LA. Intrahepatic cholestasis of pregnancy: Relationships between bile acid levels and fetal complication rates. Hepatology 2004;40:467–74.
[3] Chappell LC, Gurung V, Seed PT, Chambers J, Williamson C, Thornton JG. Ursodeoxycholic acid versus placebo, and early term delivery versus expectant management, in women with intrahepatic cholestasis of pregnancy: semi-factorial randomised clinical trial. BMJ 2012;344:e3799.

[4] Glantz A, Marschall HU, Lammert F, Mattsson LA. Intrahepatic cholestasis of pregnancy: a randomized controlled trial comparing dexamethasone and ursodeoxycholic acid. Hepatology 2005;42:1399–405.
[5] Glantz A, Reilly SJ, Benthin L, Lammert F, Mattsson LA, Marschall HU. Intrahepatic cholestasis of pregnancy: amelioration of pruritus by UDCA is associated with decreased progesterone disulphates in urine. Hepatology 2008;47:544–51.
[6] Marschall HU, Wagner M, Zollner G, et al. Complementary stimulation of hepatobiliary transport and detoxification systems by rifampicin and ursodeoxycholic acid in humans. Gastroenterology 2005;129:476–85.
[7] Geenes VL, Lim YH, Bowman N, et al. A placental phenotype for intrahepatic cholestasis of pregnancy. Placenta 2011;32:1026–32.
[8] Bachs L, Pares A, Elena M, Piera C, Rodes J. Comparison of rifampicin with phenobarbitone for treatment of pruritus in biliary cirrhosis. Lancet 1989;1:574–6.
[9] Bachs L, Pares A, Elena M, Piera C, Rodes J. Effects of long-term rifampicin administration in primary biliary cirrhosis. Gastroenterology 1992;102:2077–80.
[10] Cynamon HA, Andres JM, Iafrate RP. Rifampin relieves pruritus in children with cholestatic liver disease. Gastroenterology 1990;98:1013–6.
[11] Ghent CN, Carruthers SG. Treatment of pruritus in primary biliary cirrhosis with rifampin. Results of a double-blind, crossover, randomized trial. Gastroenterology 1988;94:488–93.
[12] Hoensch HP, Balzer K, Dylewizc P, Kirch W, Goebell H, Ohnhaus EE. Effect of rifampicin treatment on hepatic drug metabolism and serum bile acids on patients with primary biliary cirrhosis. Eur J Clin Pharmacol 1985;28:475–7.
[13] Podesta A, Lopez P, Terg R, et al. Treatment of pruritus of primary biliary cirrhosis with rifampin. Dig Dis Sci 1991;36:216–20.
[14] Yerushalmi B, Sokol RJ, Narkewicz MR, Smith D, Karrer FM. Use of rifampin for severe pruritus in children with chronic cholestasis. J Pediatr Gastroenterol Nutr 1999;29:442–7.