Arch Gynecol Obstet
DOI 10.1007/s00404-010-1506-1

MATERNO-FETAL MEDICINE

Obstetrical and fetal outcomes of a new management strategy in patients with intra-hepatic cholestasis of pregnancy

Hani A. Al Shobaili · Hossam O. Hamed · Ahmad Al Robaee · Abdullateef A. Alzolibani · Ahmad F. Amin · Salah R. Ahmad

Received: 3 March 2010 / Accepted: 3 May 2010

Abstract
Purposes To determine the incidence, obstetrical, and fetal complication rates of intrahepatic cholestasis of pregnancy (ICP) in patients managed expectantly to 40-weeks gestation.
Methods In a prospective cohort study conducted between February 2008 and January 2010, a total of 21,960 pregnant women in Qassim Region of Saudi Arabia were screened for ICP using specific criteria for diagnosis. The course of pregnancy was monitored to 40-weeks gestation or spontaneous onset of labor, whichever comes first. The measured outcomes were compared with a cross-matched group of healthy pregnant women. Continuous variables were analyzed with t test, while χ^2 test was used for comparing percentages.
Results The incidence of ICP was 0.35% (76/21,960). There was no significant difference between groups in gestational age at delivery, preterm labor, intrauterine fetal death, cesarean section, or respiratory distress syndrome. There was significantly higher intrapartum non-reassuring fetal heart rate patterns and meconium-stained amniotic fluid in ICP group ($P < 0.01$ and <0.0001, respectively).
Conclusions The incidence of ICP in this region is low compared to worldwide range. Expectant management to 40-weeks gestation is associated with obstetrical and fetal outcomes comparable to normal pregnancy; however, intrapartum fetal asphyxia is more likely.

Keywords Pregnancy · Pruritus · Intrahepatic cholestasis · Obstetrical outcome

H. A. Al Shobaili · A. Al Robaee · A. A. Alzolibani
Department of Dermatology, Qassim University, Qassim, Saudi Arabia

H. O. Hamed (✉) · A. F. Amin
Department of Obstetrics and Gynecology, College of Medicine, Qassim University, Qassim, Saudi Arabia
e-mail: Hossam_omar@yahoo.com

H. O. Hamed
College of Medicine, Assiut University, Assiut, Egypt

H. O. Hamed
P.O. Box 30109, Buraidah, Qassim 51477, Saudi Arabia

S. R. Ahmad
Department of Obstetrics and Gynecology, Maternity-Childhood Hospital, Qassim, Qassim Region, Saudi Arabia

Introduction

The endocrine, metabolic, and vascular changes during pregnancy can lead to development of a heterogeneous group of strongly pruritic inflammatory dermatoses that exclusively associated with pregnancy and immediate postpartum period [1, 2]. Intrahepatic cholestasis of pregnancy (ICP), called pruritus and prurigo gravidarum, is the commonest of these pregnancy dermatoses. It is defined as generalized pruritus late in pregnancy that tends to resolve following delivery and recur in future pregnancy [1, 2]. It is associated with raised serum bile acids in absence of pre-existing liver disease [3, 4]. The incidence of ICP varies widely from 0.1 to 24% based on geographical location and ethnicity [3, 5]. While the highest incidence (24%) is recorded in South American women, Europe and USA have the lowest figures (0.1–1.5%) [3, 4]. The epidemiological studies addressing the incidence of ICP in Saudi Arabia are lacking. The etiology of ICP is complex and not fully understood; however, genetic [3, 4, 6, 7], hormonal

Published online: 04 June 2010

[4, 8, 9], and dietary factors [3, 10, 11] are highly postulated.

The adverse maternal, obstetrical, and fetal effects encountered in ICP are varied. Most of patients complain of mild pruritus, however, sever itching and jaundice could complicate up to 10–15% of cases [1, 3, 4]. On obstetrical side, there is much debate in literature regarding existence, frequency, and onset of adverse effects of ICP with a possible over consideration of the disease magnitude. While many authors [3, 12] had reported increased risks of preterm labor (PTL), intrauterine fetal death (IUFD), meconium-stained amniotic fluid (MSAF), and respiratory distress syndrome (RDS), others had reported no [13] or increased risk of unspecified or iatrogenic preterm labor [14–16]. On the other hand, there are some reports linking the adverse obstetrical outcome to higher levels of maternal serum bile acids only [17–20].

A policy of early induction of labor at 36–37 weeks gestation has been adopted by many investigators [21, 22] to avoid risk of IUFD. However, there has been a marked debate regarding the gestational week at which IUFD occurs [15, 16, 23–25]. On the other hand, there are some concerns whether this clinical practice itself could be the cause of increased perinatal mortality as elective delivery at that age carries the risks of prematurity including RDS [26]. There have been no large prospective studies that address whether early delivery prevents adverse fetal outcome or not, and hence, the most effective intervention for ICP has not currently been established [3]. We hypothesize that allowing pregnancy to continue in ICP patients until expected date of delivery (EDD) or spontaneous onset of labor, could be associated with lower risks of iatrogenic preterm labor and respiratory distress syndrome without an additional increase in risk of IUFD. The aim of this study is to determine the incidence of ICP in Qassim Region of Saudi Arabia, and compare the obstetrical and fetal outcomes in patients managed expectantly to 40-weeks gestation to a group of healthy pregnant women.

Patients and methods

This is a prospective cohort hospital-based study conducted through cooperation between Obstetrics and Dermatology Departments, College of Medicine, Qassim University and the Tertiary Maternity-Childhood Hospital (MCH) in Qassim Region, Saudi Arabia. The study was carried out in February 2008 through January 2010 and approved by the research committees of Qassim University and Ministry of Health.

All patients complaining of recently onset generalized pruritus in the 2nd half of pregnancy were candidates for further searching of ICP. The inclusion criteria used to establish the diagnosis of ICP included generalized pruritus that usually presents in the 2nd half of pregnancy, becomes progressively more severe as the pregnancy advances, and typically resolves within 48 h of delivery. It most frequently starts at the palms and soles then it becomes generalized. Apart from skin scratch marks, there are no skin lesions [1–3]. Serum bile acid $\geq$14 μmol/L was considered a confirmatory laboratory test [3]. The exclusion criteria were those with known pre-gestational skin disease, other causes of pruritus, gall bladder, or liver diseases. Patients diagnosed having ICP after 40-weeks gestation were included for counting of ICP incidence, but excluded from the rest of the study. Another group of cross-matched women with uncomplicated pregnancy and no history of pruritus were recruited as a control group. Written informed consent was obtained from each participant which allows for further clinical and laboratory evaluation to establish the diagnosis of ICP and follow up of pregnancy to 40-weeks gestation. Patients who refused participation were not denied the full usual clinical care offered by the hospital.

At initial enrollment to the study, a detailed obstetric and medical history, and careful clinical examination was done in all eligible patients. The gestational age was calculated according to reliable LMP and/or early trimester ultrasound examination report. Clinical evaluation by a dermatologist was done to exclude primary skin diseases or other causes of itching. Gall stones or maternal liver pathology were excluded by history, trans-abdominal ultrasound, and liver function tests. A fasting blood sample was withdrawn from all patients who clinically suspected to have ICP for measurement of fasting serum total bile acids, alanine transaminase (ALT), and serum bilirubin. Hepatitis B surface antigen and hepatitis C antibody were also measured using ELISA techniques to exclude positive cases. The pregnancy course in ICP patients was carefully monitored to 40-weeks gestation or spontaneous onset of delivery, whichever comes first, provided no recorded maternal or fetal compromise. All excluded patients who had non-ICP causes of pruritus had received medical consultation and specific treatment according to the underlying cause.

The schedule of follow up and arrangement for hospital delivery was provided for both ICP and control groups. In ICP group, maternal evaluation included observation for development of jaundice, any change in urine or stool color, or bleeding tendency. Maternal liver function test was repeated every 2–3 weeks. Fetal well being was evaluated by weekly biophysical profile (BPP) and electronic fetal heart rate (FHR) monitoring which increased to twice weekly after 37 weeks gestation. Doppler ultrasound measurement of umbilical cord blood flow was done in both groups for first time at a gestational age between 34

and 36 weeks for a baseline comparison. If the sonogram was normal, it was repeated only in ICP group at 38 weeks, otherwise repeated weekly until delivery. Ultrasound and Doppler blood flow velocity waveform examination used a device combining B-mode-imaging and a bidirectional pulsed color Doppler technique with real-time spectral analysis (Sonoline G60 S ultrasound imaging system, Siemens, Germany). The fetal umbilical artery assessed in the fetal umbilical artery at a free loop of the cord near its attachment to the umbilicus using a convex 3.5 MHz probe while the patient was in a recumbent position with a slight left lateral tilt. Blood flow velocity waveforms were studied using the Doppler indices: systolic/diastolic ratio and pulsatility index.

Patients with mild to moderate itching had received symptomatic medical treatment in the form of oral 2nd generation antihistaminic, such as Cetirizine (VIP pharmaceuticals PVT, India) in dose of 10 mg tablet/once daily and/or local soothing agents, such as Menthol 2%. In severe cases, Ursodeoxycholic acid (UDCA) (Urdox^{TM}, Wockhardt UK Ltd.) was administered in dose of 600–900 mg/daily for 3 weeks as it has antipruritic effect and lowers the risk of adverse fetal outcome [27, 28]. Elective delivery was planned for patients extending beyond 40-weeks gestation to avoid additional fetal complications of post maturity. Induced preterm labor (<37 weeks) was reserved for patients with fetal surveillance and maternal lab tests indicated an earlier need for intervention. The definitions of normal and non-reassuring fetal heart rate (FHR) patterns were according to RCOG clinical guidelines [29]. All recordings were done by external cardiotocography performed using a Corometrics 170 monitor (GE Healthcare, Chalfont St Giles, UK).

After delivery, Apgar score was recorded for all newborns. Measurement of umbilical cord artery (UCA) pH was done only in newborns with suspected intrapartum fetal distress including those with MSAF, non-reassuring intrapartum CTG patterns, and low Apgar score. An UCA pH value of 7.13, which represents the 5th percentile of normal range, was used as cutoff point to differentiate between normal and hypoxic fetuses [30]. Postpartum hemorrhage was defined by bleeding loss >500 ml after vaginal delivery and >1,000 after CS [31].

The measured primary outcome was PTL. The secondary outcomes were gestational age at delivery, fetus viability, intrapartum CTG abnormalities, MSAF, mode of delivery, postpartum hemorrhage, neonatal outcome, maternal serum biochemical assays, and Doppler indices. The data were collected in a data collection sheet and entered onto a Microsoft access database and analyzed using the statistical package for social science (SPSS Inc., Chicago, version 16). The data were presented as mean ± 1SD or percentages. Unpaired Student t test was used to compare mean values while the χ^2 tests were used to compare the dichotomous variables in both groups. Logistic regression analysis was done to find the possible correlation between maternal serum biochemical assays and adverse obstetrical outcomes. P value <0.05 was considered to be statistically significant.

Results

A total of 21,960 pregnant women were booked for antenatal care and hospital delivery in the MCH during study period. Out of those, 804 women (3.7%) were complaining of generalized pruritus in pregnancy, and 76 had ICP as a definite cause of pruritus giving an incidence of 0.35% (76/21,960).

Table (1) shows no statistically significant difference between ICP group ($n = 76$) and controls ($n = 200$) regarding age, parity, history of abortion, previous CS delivery, current twin pregnancy, or body mass index (BMI). There were no other co-existing obstetrical or medical risk factors in both groups. During follow up of patients, there were no reported cases of clinical maternal jaundice or bleeding tendency. All patients in ICP group had received treatment with Cetirizine, while UDCA was used only in 31% (24/76) of patients who were complaining of severe itching.

The obstetrical and fetal outcomes in both groups are summarized in Table 2. There was no significant difference between groups in gestational age at delivery, IUFD, and iatrogenic or spontaneous PTL. The causes of iatrogenic preterm labor in ICP group were 2 cases of antepartum fetal distress, and one discordant growth in twin pregnancy. The only case of IUFD was seen in ICP group at 32 weeks. It was associated with MSAF and maternal bile acid level of 19 μmol/L, but no apparent congenital anomalies or oligohydramnios. During delivery, the ICP group had significantly higher non-reassuring intrapartum CTG patterns (10.5% vs. 3.0%, $P < 0.01$), meconium-stained amniotic fluid (23.6% vs. 2.5%, $P < 0.0001$), and neonatal care unit admission (15.7% vs. 4.9%, $P < 0.001$) compared to controls. The causes of neonatal care admission in ICP group included transient tachypnea of newborn ($n = 6$), meconium below vocal cords ($n = 4$), and RDS ($n = 2$). There was no significant difference between groups in total or elective CS rate. The indications of elective CS in ICP group (total $n = 6$) were 3 patients had iatrogenic PTL, one term twin pregnancy, one previous CS, and the last was for patient demand.

The umbilical cord artery (UCA) pH was done in 21 and 8 newborns of ICP group and controls who were suspected to have intrapartum fetal distress (data not shown in tables). Out of them, 57% (12/21) and 37.5% (3/8) had

Table 1 Clinical characteristics of both groups

Characteristics	ICP ($n = 76$)	Controls ($n = 200$)	P value
Age (years)	29.18 ± 3.54 [18–35]	29.86 ± 4.37 [17–36]	0.91
>35 years	14 (18)	48 (24)	0.62
Parity	1.88 ± 1.6 [0-4]	2.11 ± 1.5 [0–5]	0.32
Primigravida	20 (26)	42 (21)	0.43
History of abortion	16 (21)	47 (23.5)	0.63
Previous one cesarean section	2 (2.6)	8 (4.0)	0.51
Current twin pregnancy	2 (2.6)	4 (2.0)	0.77
BMI (kg/m^2)	29.55 ± 3.15 [21–35]	30.23 ± 3.15 [11, 20–37]	0.34

Values are given as mean ± SD [range] or number (percentage)

ICP intrahepatic cholestasis of pregnancy, *BMI* body mass index

Table 2 Obstetrical and fetal outcomes in both groups

	ICP group ($n = 76$)	Controls ($n = 200$)	P value
Gestational age at delivery, mean ± SD	36.63 ± 2.57	37.24 ± 1.9	0.21
Preterm birth			
Spontaneous preterm labor	6 (7.8)	13 (6.5)	0.68
Iatrogenic preterm labor	3 (4.0)	5 (2.5)	0.29
Total	9 (11.8)	18 (9.0)	0.42
Intrauterine fetal death	1 (1.3)	2 (1.0)	0.82
Meconium-stained amniotic fluid	18 (23.6)	5 (2.5)	0.0001
Non-reassuring intrapartum CTG	8 (10.5)	6 (3.0)	0.01
Cesarean section			
Elective	6 (7.8)	12 (6.0)	0.65
Emergency	9 (11.8)	17 (8.5)	0.31
Total	15 (19.7)	29 (14.5)	0.15
Postpartum hemorrhage	4 (5.2)	9 (4.5)	0.41
Neonatal outcome[a]			
5 min-Apgar score median (range)	9 (6–10)	10 (8–10)	0.37
Pediatric care unit admission	12 (15.7)	10 (4.9)	0.001
Respiratory distress syndrome	2 (2.6)	3 (1.5)	0.28

Values are expressed as no. (%) unless otherwise indicated

ICP intrahepatic cholestasis of pregnancy, *CTG* cardiotocography

[a] After calculation of twin pregnancy and fetal death in both groups, $n = 77$ in ICP group and 202 in controls

proved fetal asphyxia with a mean of UCA pH 7.08 ± 0.02 and 7.07 ± 0.04, respectively.

Table 3 shows umbilical artery Doppler sonogram and maternal serum biochemical assays as near as delivery or before commencement of UDCA treatment. There was significantly higher total bilirubin, fasting bile acids, and ALT enzyme in ICP group. Doppler indices were comparable in both groups. In Table 4, logistic regression analysis shows a significant positive correlation between maternal fasting bile acids level and MSAF only ($P < 0.001$).

Discussion

The current study measured the incidence, obstetrical, and fetal outcomes in patients with ICP. Among the total of 21,960 women booked for antenatal care and delivery, 76 patients had ICP giving an incidence of 0.35%. There is a widely geographical and ethnic variation of ICP in many studies all over the world. While the incidence in current study is comparable to others conducted in USA (0.32%) and Europe (0.2–1.5%), it is much lower than those reported from South America (6.5–27.6%) [3, 12, 17, 23, 27]. The low incidence in current study could be partially attributed to the more restrictive criteria that are used for diagnosis of ICP. In earlier studies, pruritus and/or jaundice with elevated liver enzymes or bilirubin rather than bile acids were the main tools of ICP diagnosis. The young age of our patients (29.18 ± 5.54) with only 18% of them above 35 years could be another explanation that was previously described in one study that reported higher rate of ICP with higher maternal age [32].

Genetic, racial, and environmental factors, such as diet and hot weather also have its contribution that could not be excluded. Investigators had proposed that hot weather and reduced dietary selenium intake, which has antioxidant effect against oxidative stress process mediated by bile acids and estrogens, may also contribute for this geographic variation of ICP [3]. This proposal had been strengthened by two studies demonstrated a lower serum selenium level in women with ICP compared to controls, and an increase of ICP peaks in cold weather [11, 33].

The course of pregnancy in ICP in the current study was comparable to controls. There is considerable debate in

Table 3 Maternal biochemical assays and umbilical artery Doppler sonogram in both groups

	ICP group ($n = 76$)	Controls ($n = 200$)	P value
Total bile acid (μmol/L)	28.95 ± 3.93 [19.2–36.3]	6.51 ± 0.8 [1.2–9.6]	0.001
ALT (IU/L)	182.21 ± 22.49 [134–229]	49.35 ± 18.36 [18–76]	0.001
Total serum bilirubin (μmol/L)	10.5 ± 2.19 [7.4–14.8]	4.77 ± 1.22 [2.4–7.8]	0.05
Doppler indices			
S/D ratio	2.43 ± 0.41 [1.88–3.72]	2.40 ± 0.43 [1.58–3.78]	0.43
Pulsatility index	0.92 ± 0.16 [0.66–1.27]	0.91 ± 0.19 [0.51–1.32]	0.79

Values are given as mean ± SD [range]

ICP intrahepatic cholestasis of pregnancy, *ALT* alanine transaminase enzyme, *S/D* systolic/diastolic ratio

Table 4 Correlation between maternal serum biochemical assays and adverse obstetrical and fetal outcomes in ICP group

	Total serum bilirubin		Serum bile acids		Alanine transaminase	
	r	P	r	P	r	P
Total preterm Labor ($n = 9$)	0.14	NS	0.24	NS	0.03	NS
Meconium-stained amniotic fluid ($n = 18$)	0.18	NS	0.47	0.001	0.21	NS
Pediatric care unit admission ($n = 12$)	0.08	NS	0.29	NS	0.11	NS

r correlation coefficient, *NS* not significant

literature about the magnitude of ICP risks. There are multiple reports of adverse fetal outcomes in association with ICP; however, these studies are not sufficiently large to allow accurate counting of frequency of complications [22, 25]. The mean of maternal fasting bile acids in current study is 28.95 ± 7.93 with a range of 19.2–36.3 μmoL/L. This range is low compared to others who reported a level as high as 100 times the upper limit of normal [34]. The uneventful pregnancy course that reported in this study is in agreement with others who reported more adverse obstetrical outcomes in higher maternal fasting bile acids [18–20]. In one study [17] the authors reported no increase in adverse outcomes if serum bile acid was <40 μmoL/L.

The low rate of PTL in current study is inconsistent with others who reported a wide range of 4–60% of PTL in ICP patients [14–17, 21–23, 32]. However, many of these studies did not differentiate between iatrogenic or spontaneous PTL [16, 17, 32]. Iatrogenic delivery was carried around 36–37 weeks that reflects the policy of early intervention in earlier studies aiming at reducing risk of fetal complications. There are some concerns whether this clinical practice itself could be the cause of increased perinatal mortality as elective delivery, namely CS, carries both risks of PTL and RDS [3]. Many factors could explain the low rate of PTL and RDS in current study including expectant management policy to 40-weeks gestation, low level of maternal bile acid [18–20], and treatment of one-third of patients by UDCA [27, 28]. However, the low rate of RDS is in disagreement with others attributed the syndrome to chemical pneumonitis and pulmonary edema due to accumulated bile acids in fetal circulation rather than PTL [35].

Inconsistent with current study which reported a low rate of IUFD (1.3%) in ICP group, others had reported a rate of 3.5–15% [16, 19, 23, 24]. The literature has marked debate regarding definite week for maximum risk [15, 16, 23–25] and mechanism of IUFD [24, 36, 37]. Although many studies showed that stillbirths in ICP tend to cluster around 37–39 weeks [15, 16, 23, 24] there have been reports of stillbirths even at lower gestational age [15, 25]. On the other hand, other studies had demonstrated a correlation between maternal bile acid level and IUFD [17, 19]. The risk had shown to increase by 1–2% for every 1 μmol/L of maternal bile acid above 40 μmol/L [17]. Others reported IUFD with maternal level as low as 15 μmol/L [19] that is in agreement with the current study which showed one case of IUFD with maternal bile acid level of 19 μmol/L. However, as no postmortem examination was done, the possibility of other etiologies for IUFD in current study could not be excluded completely. The mechanism of sudden IUFD is poorly understood. It is postulated that the associated MSAF and/or high amniotic fluid bile acid plays an important rule. Both bile acid [36] and meconium [37] has the ability to penetrate deep into the placenta and umbilical cord causing vasoconstriction of umbilical vessels and acute fetal anoxia [24].

When shifting to delivery events, the current study showed that ICP patients had significantly higher adverse

effects compared to controls. The high rate of MSAF (23.6% vs. 2.5%) is in agreement with previous studies that reported a range of 16–58% [13, 24] and up to 100% of cases associated with IUFD [25]. Although there is some reports that had linked the higher rate of MSAF to maternal serum bile acids level [17, 20] the definite cause is not completely clear. One accepted explanation is that accumulate fetal bile acid causes fetal distress and subsequent meconium passage. However, this could not explain all cases of MSAF in current study as 43% (9/21) of neonates with suspected fetal distress had normal umbilical cord artery pH. Another explanation could be postulated from animal data which showed that bile acids infusion in fetal sheep resulted in MSAF in 100% of treated lambs without any signs of fetal distress [38]. Alternatively, bile acids are suggested to increase colonic motility and meconium passage [39]. The positive correlation between maternal bile acids level and MSAF in this study is consistent with others [17–20]. Designing large clinical trials to evaluate the efficacy of maternal bile acids to be used as laboratory indicators of obstetrical and fetal outcomes are highly recommended.

The intrapartum non-reassuring FHR patterns that are encountered in this study in association with ICP are in agreement with others [19, 24]. These abnormalities could be explained by associated fetal distress in newborns with low UCA pH. It is suggested that placental perfusion may decrease along the course of the disease due to accumulation of bile acids in placental vasculature [3, 24, 36]. This effect, however, was not evident in the antenatal course of current ICP patients who showed normal umbilical Doppler indices. During delivery, we suggest that potentially compromised placental perfusion led to higher non-reassuring FHR patterns and MSAF and low UCA pH in ICP group compared to controls. In newborns with normal pH, however, the abnormal FHR could be explained through an animal model which showed a direct action of accumulated fetal bile acids on fetal heart contractility and rhythm rather than distress [40].

In addition to low rates of PTL and RDS, the current study showed low rate of elective CS which was comparable to controls. This could be explained by the adoption of expectant management policy and low rate of antenatal fetal distresses. This is in disagreement with others [21, 22] who reported a higher rate of elective CS as a result of their clinical practice of active management to avoid risk of IUFD. In addition, the higher rate of adverse intrapartum effects in current study did not translate to increased rate of emergency CS resulting in comparable total CS rate in both groups.

In summary, the incidence of ICP in Qassim Region of Saudi Arabia is low compared to worldwide figures. The expectant management of ICP to 40 weeks is associated with comparable pregnancy course to normal women provided good fetal monitoring, and moderate rise of maternal serum bile acids. Careful intrapartum fetal monitoring is necessary to avoid more likely birth asphyxia. Large randomized clinical trials to compare both early delivery and expectant management lines are highly recommended to establish an effective management strategy to reduce rates of adverse obstetrical and fetal outcomes.

Conflict of interest statement The authors have no a financial relationship with organizations that sponsored the research or any conflict of interest to be declared.

References

1. Ambros-Rudolph CM, Glatz M, Trauner M, Kerl H, Müllegger RR (2007) The importance of serum bile acid level analysis and treatment with ursodeoxycholic acid in intrahepatic cholestasis of pregnancy: a case series from central Europe. Arch Dermatol 143:757–762
2. Ambros-Rudolph CM, Müllegger RR, Vaughan-Jones SA, Kerl H, Black MM (2006) The specific dermatoses of pregnancy revisited and reclassified: results of a retrospective two-center study on 505 pregnant patients. J Am Acad Dermatol 54:395–404
3. Geenes V, Williamson C (2009) Intrahepatic cholestasis of pregnancy. World J Gastroenterol 15:2049–2066
4. Kroumpouzos G (2002) Intrahepatic cholestasis of pregnancy: what's new. JEADV 16:316–318
5. Lee RH, Goodwin TM, Greenspoon J, Incerpi M (2006) The prevalence of intrahepatic cholestasis of pregnancy in a primarily Latina Los Angeles population. J Perinatol 26:527–532
6. Ruetz S, Gros P (1994) Phosphatidylcholine translocase: a physiological role for the mdr2 gene. Cell 77:1071–1081
7. Smith AJ, Timmermans-Hereijgers JL, Roelofsen B, Wirtz KW, van Blitterswijk WJ, Smit JJ et al (1994) The human MDR3 P-glycoprotein promotes translocation of phosphatidylcholine through the plasma membrane of fibroblasts from transgenic mice. FEBS Lett 354:263–266
8. Yamamoto Y, Moore R, Hess HA, Guo GL, Gonzalez FJ, Korach KS et al (2006) Estrogen receptor alpha mediates 17alpha-ethynylestradiol causing hepatotoxicity. J Biol Chem 281:16625–16631
9. Rathi U, Bapat M, Rathi P, Abraham P (2007) Effect of liver disease on maternal and fetal outcome: a prospective study. Indian J Gastroenterol 26:59–63
10. Kroumpouzos G, Cohen LM (2001) Dermatoses of pregnancy. J Am Acad Dermatol 45:1–19
11. Reyes H, Báez ME, González MC, Hernández I, Palma J, Ribalta J et al (2000) Selenium, zinc and copper plasma levels in intrahepatic cholestasis of pregnancy, in normal pregnancies and in healthy individuals, in Chile. J Hepatol 32:542–549
12. Reyes H, Taboada G, Ribalta J (1979) Prevalence of intrahepatic cholestasis of pregnancy in La Paz, Bolivia. J Chronic Dis 32:499–504
13. Shaw D, Frohlich J, Wittmann BA, Willms MA (1982) Prospective study of 18 patients with cholestasis of pregnancy. Am J Obstet Gynecol 142:621–625
14. Lo TK, Lau WL, Lam HS, Leung WC, Chin RK (2007) Obstetric cholestasis in Hong Kong—local experience with eight consecutive cases. Hong Kong Med J 13:387–391
15. Williamson C, Hems LM, Goulis DG, Walker I, Chambers J, Donaldson O et al (2004) Clinical outcome in a series of cases of

obstetric cholestasis identified via a patient support group. BJOG 111:676–681
16. Bacq Y, Sapey T, Bréchot MC, Pierre F, Fignon A, Dubois F (1997) Intrahepatic cholestasis of pregnancy: a French prospective study. Hepatology 26:358–364
17. Glantz A, Marschall HU, Mattsson LA (2004) Intrahepatic cholestasis of pregnancy: Relationships between bile acid levels and fetal complication rates. Hepatology 40:467–474
18. Laatikainen T, Ikonen E (1977) Serum bile acids in cholestasis of pregnancy. Obstet Gynecol 50:313–318
19. Laatikainen T, Tulenheimo A (1984) Maternal serum bile acid levels and fetal distress in cholestasis of pregnancy. Int J Gynaecol Obstet 22:91–94
20. Lee RH, Kwok KM, Ingles S, Wilson ML, Mullin P, Incerpi M, Pathak B, Goodwin TM (2008) Pregnancy outcomes during an era of aggressive management for intrahepatic cholestasis of pregnancy. Am J Perinatol 25:341–345
21. Fisk NM, Storey GN (1988) Fetal outcome in obstetric cholestasis. Br J Obstet Gynaecol 95:1137–1143
22. Roncaglia N, Arreghini A, Locatelli A, Bellini P, Andreotti C, Ghidini A (2002) Obstetric cholestasis: outcome with active management. Eur J Obstet Gynecol Reprod Biol 100:167–170
23. Rioseco AJ, Ivankovic MB, Manzur A, Hamed F, Kato SR, Parer JT et al (1994) Intrahepatic cholestasis of pregnancy: a retrospective case-control study of perinatal outcome. Am J Obstet Gynecol 170:890–895
24. Reid R, Ivey KJ, Rencoret RH, Storey B (1976) Fetal complications of obstetric cholestasis. Br Med J 1:870–872
25. Davies MH, da Silva RC, Jones SR, Weaver JB, Elias E (1995) Fetal mortality associated with cholestasis of pregnancy and the potential benefit of therapy with ursodeoxycholic acid. Gut 37:580–584
26. Morrison JJ, Rennie JM, Milton PJ (1995) Neonatal respiratory morbidity and mode of delivery at term: influence of timing of elective caesarean section. Br J Obstet Gynaecol 102:101–106
27. Laifer SA, Stiller RJ, Siddiqui DS, Dunston-Boone G, Whetham JC (2001) Ursodeoxycholic acid for the treatment of intrahepatic cholestasis of pregnancy. J Matern Fetal Med 10:131–135
28. Diaferia A, Nicastri PL, Tartagni M, Loizzi P, Iacovizzi C, Di Leo A (1996) Ursodeoxycholic acid therapy in pregnant women with cholestasis. Int J Gynaecol Obstet 52:133–140
29. Royal College of Obstetricians and Gynaecologists (2001) The use of electronic fetal monitoring. The use and interpretation of cardiotocography in intrapartum fetal surveillance. Evidence based clinical guideline 8
30. Nordstrom L, Marcus C, Persson B, Shimojod N, Westgren M (1996) Lactate in cord blood and its relationship to pH and catecholamines in spontaneous vaginal deliveries. Early Hum Dev 46:97–104
31. American College of Obstetricians and Gynecologists (2006) Postpartum hemorrhage. ACOG Practice Bulletin No. 76
32. Heinonen S, Kirkinen P (1999) Pregnancy outcome with intrahepatic cholestasis. Obstet Gynecol 94:189–193
33. Kauppila A, Korpela H, Mäkilä UM, Yrjänheikki E (1987) Low serum selenium concentration and glutathione peroxidase activity in intrahepatic cholestasis of pregnancy. Br Med J (Clin Res Ed) 294:150–152
34. Heikkinen J, Mäentausta O, Ylöstalo P, Jänne O (1981) Changes in serum bile acid concentrations during normal pregnancy, in patients with intrahepatic cholestasis of pregnancy and in pregnant women with itching. Br J Obstet Gynaecol 88:240–245
35. Porembka DT, Kier A, Sehlhorst S, Boyce S, Orlowski JP, Davis K Jr (1993) The pathophysiologic changes following bile aspiration in a porcine lung model. Chest 104:919–924
36. Sepúlveda WH, González C, Cruz MA, Rudolph MI (1991) Vasoconstrictive effect of bile acids on isolated human placental chorionic veins. Eur J Obstet Gynecol Reprod Biol 42:211–215
37. Miller PW, Coen RW, Benirschke K (1985) Dating the time interval from meconium passage to birth. Obstet Gynecol 66:459–462
38. Campos GA, Guerra FA, Israel EJ (1986) Effects of cholic acid infusion in fetal lambs. Acta Obstet Gynecol Scand 65:23–26
39. Falconer JD, Smith AN, Eastwood MA (1980) The effects of bile acids on colonic motility in the rabbit. Q J Exp Physiol Cogn Med Sci 65:135–144
40. Williamson C, Gorelik J, Eaton BM, Lab M, de Swiet M, Korchev Y (2001) The bile acid taurocholate impairs rat cardiomyocyte function: a proposed mechanism for intrauterine fetal death in obstetric cholestasis. Clin Sci (Lond) 100:363–369