

Obstetric Cholestasis: Current Opinions and Management

L K Tan,**FAMS, MRCOG, M Med (O&G)*

Abstract

Obstetric cholestasis (OC) is a pregnancy-specific liver condition that typically presents with generalised pruritis in the absence of a rash in the late second trimester or third trimester. It is more common in certain ethnic groups, particularly those from South Asian, South American, Nordic and Scandinavian regions, and has a familial and genetic basis. Recent research suggests that the pathophysiology may reside in mutations in genes that code for bile acid transporter proteins. Mutations involving the bile acid transporters may impair maternal excretion and influence transplacental passage of bile acids. It is hypothesised that the surge in pregnancy steroid hormones may result in genetically predisposed women developing cholestasis. The condition is also associated with increased perinatal morbidity and mortality, particularly from preterm labour, fetal distress and intrauterine deaths. Animal studies have shown that bile acids are cardiotoxic, which may help explain the condition's association with fetal distress and stillbirths. Accurate diagnosis relies on a high index of suspicion, and the findings of abnormal liver function tests and raised serum bile acid levels after the exclusion of other organic causes of liver disease. Ursodeoxycholic acid helps relieve symptoms, improve serum bile acid levels and possibly has a cardioprotective effect. Active management, in the form of close antepartum fetal monitoring and delivery before 37 weeks, helps to decrease the risk of intrauterine deaths, though possibly at the expense of increased obstetric intervention. Following delivery, there is usually a dramatic improvement of symptoms and resolution of the condition. Women should be counselled about the high recurrence risk of OC in subsequent pregnancies.

Ann Acad Med Singapore 2003; 32:294-8

Key words: Bile acids, Liver function tests, Obstetric cholestasis (OC), Pregnancy, Pruritis, Stillbirths, Ursodeoxycholic acid (UDCA)

Introduction

Obstetric cholestasis (OC) is a pregnancy-specific liver disorder. It is also known by other names, such as pruritus gravidarum, recurrent intrahepatic cholestasis of pregnancy and obstetric hepatitis.

It is by no means a newly recognised disorder and, indeed, was previously known as benign intrahepatic cholestasis of pregnancy. Fetal complications associated with OC were reported as early as the mid-1970s.^{1,2} It is now widely acknowledged that the condition is no longer as benign as was once thought, and the diagnosis of the condition does portend significant perinatal morbidity and mortality, in particular, meconium-stained amniotic fluid (45%), acute onset of fetal compromise (22%), spontaneous preterm labour (44%), and intrauterine fetal demise (2%).³⁻⁶

Maternal morbidity is not as significantly increased, although the pruritis is often distressing and there is a predisposition to postpartum haemorrhage.⁷ It is, therefore, important that clinicians looking after pregnant women should have an increased awareness of the condition.

Epidemiology

OC has a geographically variable prevalence, being

relatively uncommon in most European populations (0.02%), significantly more common in South Asian (0.8% to 1.46%)^{8,9} and South American populations (9.2% to 15.6%), and is particularly prevalent in the native Araucanian population in Chile (28%).¹⁰ There are anecdotal reports, but little published data, on the incidence of OC in Oriental populations such as China, and efforts should be made to study the incidence locally. Among Europeans, the incidence of OC is higher in Nordic or Scandinavian countries. However, it is now thought that the low incidence in European populations may be an underestimation, as growing awareness has increased the incidence from 0.1% in the early 1960s to 0.7% after 2 decades.³

The condition occurs more frequently in women above the age of 35 years,⁵ with multiple pregnancies, and those with a previous history of OC in their previous pregnancies. Women with a family history of OC and whose male members suffer from gallstones also have an increased risk.

Aetiology

The underlying aetiology is multifactorial, with contributions from genetic, environmental and hormonal factors.

* Associate Consultant

Department of Obstetrics and Gynaecology

Singapore General Hospital

Address for Reprints: Dr Tan Lay Kok, Department of Obstetrics and Gynaecology, Singapore General Hospital, Outram Road, Singapore 169608.

Genetic Basis

A genetic predisposition to OC has been confirmed by a recent Finnish study which demonstrated that OC clusters within some families, with odds ratios and 95% confidence intervals for developing OC of 12.6 (5.6 to 28.1) for the sisters and 12.2 (6.2 to 24.2) for the mothers of women who had OC.¹¹

Although the precise genetic pattern remains obscure, some light has been shed in recent work in which carriership of long-chain 3-hydroxyacyl-coenzyme A dehydrogenase deficiency has been reported to be associated with an increased risk of OC. The gene is located in the p23 region of chromosome 2. Heinonen et al¹² reported finding a novel obstetric cholestasis-associated gene located in the vicinity of the 2p13 linkage disequilibrium region. These genetic predispositions may interact in some way with environmental factors. For example, clinical and experimental studies have suggested that a marginal selenium deficiency could be a dietary pathogenic factor,¹³ with Reyes et al¹⁴ demonstrating a remarkable seasonal variation in Chile in which the prevalence of OC has an inverse correlation with plasma selenium concentrations.

Steroid Hormones

Oestradiol metabolites, particularly 17- β oestradiol glucuronide, and even progesterone metabolites are known to have cholestatic effects. Meng et al¹⁵ showed that there is an increased ratio of urinary 3 α to 3 β hydroxysteroids and high levels of mono and disulphated progesterone metabolites in patients suffering from OC. It has been postulated that OC results from suboptimal metabolism and clearance of these substances. A prospective, observational study of 50 women with OC in France from 1989 to 1995 showed that orally administered micronised progesterone, given as prophylaxis against preterm labour, caused earlier onset of pruritis, and decreasing the dosage or removing progesterone altogether resulted in an improvement of symptoms, suggesting that progesterone might be an exogenous factor which triggers OC in predisposed women.¹⁶

Biliary Canalicular Transporters

Recent work has pointed out that the underlying pathophysiology may reside in the malfunction of biliary canalicular transporters, which are responsible for the transfer of these metabolites from the hepatocyte into the bile. Some of these transporters have been characterised as proteins responsible for bile canalicular secretion of bile acids (bile salt export pump), organic anions (multi-drug resistance protein 2) or phospholipids (multi-drug resistance protein 3).

OC is more common in mothers of patients with inborn

cholestatic syndromes such as recurrent familial intrahepatic cholestasis and progressive familial intrahepatic cholestasis type 3. These rare syndromes are related to dysfunction of biliary transporters. Specifically, progressive intrahepatic cholestasis type 3 is caused by a mutation associated with dysfunction of the bile canalicular phospholipid transporter multi-drug resistance protein 3, which results in increased levels of serum gamma glutamyl transpeptidase. Jacquemin et al¹⁷ reported a case whereby the maternal and paternal female relations of an infant with progressive familial intrahepatic cholestasis type 3, and who were heterozygous for the multi-drug resistance protein 3 mutation, had developed OC in pregnancy. This suggests that heterozygosity for the mutation in the genes coding for transporter proteins predisposes them to OC. Milkiewicz et al¹⁸ found that a third of all patients with OC had mutation of multi-drug resistance protein 3. Dixon et al¹⁹ reported a case of a woman with OC and raised gamma glutamyl transpeptidase who, although did not have a family history, was found to have a mis-sense mutation resulting from a single amino acid substitution, thereby causing a disruption in multi-drug resistance protein trafficking to the membrane of transfected cells.

The available evidence, therefore, suggests that clinical symptoms of OC arise when the secretory capacity of mildly malfunctioning canalicular transporters, which cause no problems outside pregnancy, are overwhelmed by the high levels of sex hormones produced in pregnancy, resulting in raised levels of bile acids and clinical features of cholestasis.

Fetal Effects

Stillbirths occurring in OC are associated with meconium-stained liquor. Prospective studies have shown that the incidence of meconium-stained liquor in women with OC before 37 weeks is significantly higher (17.9%), compared to the general obstetric population (2.9%).²⁰ This supports a hypoxic aetiology underlying the increased perinatal mortality.

Fetal inheritance of the maternal gene mutation in bile acid transport may cause the normal fetal-to-maternal transfer of bile acids across the trophoblast to be impaired, resulting in the accumulation of excess bile acids toxic to the fetus. It has been shown that raised bile acids have a detrimental effect on the fetus in animal studies.²¹ More recent research on rat cardiomyocytes has demonstrated that exposure to elevated levels of the bile acid taurocholic acid affects the intracellular sarcoplasmic reticular calcium dynamics, causing a dose-related negative inotropic and chronotropic effect on the cardiomyocytes. The researchers postulate that elevated bile acids in OC may result in the development of a fetal dysrhythmia, leading to fetal hypoxia,

which explains the fetal distress and sudden intrauterine deaths observed in clinical practice.^{22,23} This may be the molecular basis for the increased perinatal mortality and morbidity associated with OC.

Clinical Features

OC usually presents in the late second trimester or third trimester of pregnancy with generalised and often distressing pruritis, which is especially pronounced over the palms and soles.²⁴ There is characteristically no accompanying rash, although dermatitis artefacta may be observed resulting from persistent scratching by the patient. Jaundice is not a usual clinical feature, appearing only in very severe cases.

Management

Diagnosis

A high index of suspicion is essential when encountering any expectant mother who complains of pruritis. The diagnosis of OC is one of exclusion and is supported by the presence of abnormal liver function tests. It is, therefore, necessary to exclude other forms of liver disease and cholestasis, and investigations should include screening for coincidental causes of liver disease, such as viral hepatitis and autoimmune liver disease, and imaging studies such as ultrasonography of the hepatobiliary tract. Pregnancy-specific causes of abnormal liver function include severe pre-eclampsia, the HELLP (haemolysis, elevated liver enzymes, low platelets) syndrome and acute fatty liver disease of pregnancy; however, women with these conditions are usually unwell and the diagnoses easily established on clinical grounds.

Typically, the main abnormality in OC is the mild elevation of liver enzymes (60% of patients), while hyperbilirubinaemia is present in only 25% of patients.²⁵ The transaminases are usually only mildly elevated (<100 IU/L), although more severe disease may have transaminases in excess of 100 IU/L. Serum alkaline phosphatase, a useful biochemical marker of cholestasis in non-pregnant cases, is less useful in pregnancy as it is raised in normal pregnancy due to placental production of the enzyme. There should also be no evidence of liver failure, haemolysis, thrombocytopaenia or disseminated intravascular coagulation.

An important caveat is that the clinician must also have a high index of suspicion in women who present with pruritis and have normal liver function initially, as delayed onset of abnormal liver function tests have been reported.²⁶ Serial liver function tests should, therefore, be done in these patients. Serum bile acids are also raised and this usually clinches the diagnosis, although the test may not be widely available. Raised serum bile acids have been shown to be a sensitive, but not specific, marker for OC.^{27,28}

Treatment

Treatment has been largely empiric as the pathophysiology is still yet to be fully resolved. There is presently increasing use of ursodeoxycholic acid (UDCA), the 7 β -epimer of chenodeoxycholic acid, which has multiple hepatoprotective activities. It modifies the bile acid pool, decreasing levels of endogenous, hydrophobic bile acids while increasing the proportion of non-toxic hydrophilic bile acids. It has a choleric effect, increasing hepatocellular bile acid excretion, as well as cytoprotective, anti-apoptotic and immunomodulatory properties.²⁹

UDCA helps to relieve the pruritis, decrease transaminases and serum bile acid levels,³⁰ although there is no correlation between pre- and post-UDCA serum bile acid levels.³¹ It is widely used outside pregnancy in the treatment of primary biliary cirrhosis, primary sclerosing cholangitis; it is also reportedly used in liver disease associated with cystic fibrosis.³² It is important to inform the mother that the drug is not licensed for use in pregnancy, but there has been no adverse fetal effects reported to date from early observational studies³³ to more recent randomised placebo-controlled trials.^{34,35} The only side effect noted so far is mild diarrhoea in the mother. Indeed, there are strong theoretical grounds for giving UDCA for fetal indications, as reduction of accumulation of serum bile acids in the fetus, particularly cholate, may be cardioprotective for the fetus. This has been convincingly demonstrated by an Italian study in which amniotic fluid levels and cord blood levels of cholic acid and chenodeoxycholic acid were significantly lower in babies whose mothers were treated with high doses of UDCA compared to untreated mothers.³⁶

Another agent that has been used with some success in the early evolution of treatment options for OC is S-adenosyl-L-methionine (SAME). It has been shown to reverse oestrogen-induced cholestasis in animal studies and hepatic pathological changes induced by xenobiotics, such as tauroolithocholate in non-pregnant studies.³⁷ Frezza et al^{38,39} observed that 800 mg of SAME daily in women with OC for 18 days produced significantly decreased pruritis and improved liver function tests compared to using a lower dosage or placebo, with no maternal or fetal ill effects. However, Ribalta et al⁴⁰ challenged the therapeutic efficacy of SAME in their randomised, controlled double-blind trial, in which SAME failed to achieve any significant reduction of symptoms and raised transaminases compared to controls. In contemporary clinical practice, UDCA seems to have superseded SAME, and this is borne out by randomised controlled trials comparing the 2 agents in which UDCA was shown to be more effective than SAME in relieving pruritis and decreasing serum bile acid levels,⁴¹ although another randomised study, comparing the same 2 agents with 2 additional treatment arms comprising a

combination of both agents and placebo, interestingly showed that combination therapy was more effective than either drug alone.⁴² It is likely, however, that most patients would prefer single-agent therapy in clinical practice.

Dexamethasone has also been used to treat OC with effective relief of pruritis and improvement in liver function.⁴³ It should be considered as an alternative to UDCA in patients unable to tolerate the latter. The use of cholestyramine has been described in earlier reports,⁴⁴ but most women are unable to tolerate the unpleasant side effects. Likewise, guar gum^{45,46} and activated charcoal,⁴⁷ being agents that promote enteric binding and, therefore, faecal elimination of bile acids, have also been subjected to randomised controlled trials and shown promise as alternative therapies to UDCA for those intolerant to it.

In addition, antihistamines may be used for further symptomatic relief. As cholestasis affects vitamin K-dependent coagulation factors, it is also necessary to give vitamin K prophylaxis from 34 weeks to prevent postpartum haemorrhage.

Tests for fetal wellbeing, such as fetal cardiotocography (CTG) 2 to 3 times weekly, fetal movement monitoring, and fetal umbilical artery Doppler evaluation, are done once the diagnosis is made, although there is no strong data on the efficacy of these tests to predict intrauterine fetal death.⁴⁸

Delivery Considerations

Alsulyman et al⁴⁸ observed, in their case-controlled series in which women with OC were managed expectantly, that there was a significantly higher incidence of meconium passage in the OC group compared to controls (44.3% versus 7.6%). More importantly, there were 2 antepartum deaths observed in the OC group between 36 to 37 weeks' gestation in the OC group, both cases having had completely normal antepartum testing within 5 days before fetal demise. As the majority of unexplained fetal deaths occur at term, it is currently usual practice not to allow the pregnancy to go past 37 completed weeks of gestation, as the risk of prematurity then is minimal. OC is not an indication for caesarean section, which should continue to be dictated by obstetric indications. Roncaglia et al²⁰ showed that a policy of active intervention to induce deliveries at 37 weeks for patients with OC resulted in a dramatic reduction in stillbirths compared with conservative management (0/218 versus 14/888). Interestingly, such a policy did not result in an increased caesarean section rate in their series. This is in contrast to a more recent prospective observational study of 70 women with OC managed on a protocol of active management, which included delivery before 38 weeks: the caesarean section rate was 36% with 14% of babies admitted to the special neonatal care unit, of which 40%

required ventilation.²⁴ Again, there was no perinatal mortality in this series.

Post-delivery, there is usually a dramatic improvement in both symptoms and liver function tests, although there have been case reports of prolonged postpartum courses of OC refractory to standard treatments, and responding only after the administration of corticosteroids.⁴⁹ Generally, however, persistence of abnormalities should prompt investigations for other causes.

Postpartum and Pre-pregnancy Counselling

The patient should be counselled that the recurrence risk in future pregnancies is high (80%), and that it may also be worthwhile to inform her female siblings of an increased risk of OC in their own pregnancies.

Conclusion

Pruritis is a common, and often wrongly considered unimportant, symptom in pregnancy. OC must always be suspected, especially if pruritis occurs in the later half of pregnancy. The pathophysiology of OC is incompletely understood, but the familial nature of the disease has been recognised. The aetiology is still unresolved, although increasing evidence points to a selective defect in the secretion of sulphated steroid metabolites and bile acids into bile caused by genetic polymorphism of canalicular transporter(s) for steroid sulphates or their regulation. Interaction with oestrogen metabolites and/or some exogenous compounds may further enhance the process, triggering OC in genetically predisposed individuals. OC must be suspected on clinical grounds in women presenting in the third trimester with pruritis, and the diagnosis established in the presence of abnormal liver function tests and raised serum bile acid levels after exclusion of other organic liver disease. Active management, including UDCA to relieve symptoms, close fetal monitoring and delivery before 38 weeks, should be employed to minimise the risk of intrauterine deaths, granted that this may result in a higher obstetric intervention rate.

REFERENCES

1. Reid R, Ivey K J, Rencoret R H, Storey B. Fetal complications of obstetric cholestasis. *BMJ* 1976; 1:870-2.
2. Laatikainen T, Ikonen E. Fetal prognosis in obstetric hepatitis. *Ann Chir Gynaecol Fenn* 1975; 64:155-64.
3. Lammert F, Marschall H U, Glantz A, Matern S. Intrahepatic cholestasis of pregnancy: molecular pathogenesis, diagnosis and management. *J Hepatol* 2000; 33:1012-21.
4. Palmer D G, Eads J. Intrahepatic cholestasis of pregnancy: a critical review. *J Perinat Neonatal Nurs* 2000; 14:39-51.
5. Heinonen S, Kirkinen P. Pregnancy outcome with intrahepatic cholestasis. *Obstet Gynecol* 1999; 94:189-93.
6. Fisk N M, Storey G N. Fetal outcome in obstetric cholestasis. *Br J Obstet Gynaecol* 1988; 95:1137-43.

7. Johnston W G, Baskett T F. Obstetric cholestasis. A 14 year review. *Am J Obstet Gynecol* 1979; 133:299-301.
8. Shanmugam S, Thappa D M, Habeebullah S. Pruritus gravidarum: a clinical and laboratory study. *J Dermatol* 1998; 25:582-6.
9. Abedin P, Weaver J B, Egginton E. Intrahepatic cholestasis of pregnancy: prevalence and ethnic distribution. *Ethn Health* 1999; 4:35-7.
10. Reyes H, Gonzalez M C, Ribalta J, Aburto H, Matus C, Schramm G, et al. Prevalence of intrahepatic cholestasis in Chile. *Ann Intern Med* 1978; 88:487-93.
11. Eloranta M L, Heinonen S, Mononen T, Saarikoski S. Risk of obstetric cholestasis in sisters of index patients. *Clin Genet* 2001; 60:42-5.
12. Heinonen S, Eloranta M L, Heiskanen J, Punnonen K, Helisalmi S, Mannermaa A, et al. Maternal susceptibility locus for obstetric cholestasis maps to chromosome region 2p13 in Finnish patients. *Scand J Gastroenterol* 2001; 36:766-70.
13. Reyes H. Review: intrahepatic cholestasis. A puzzling disorder of pregnancy. *J Gastroenterol Hepatol* 1997; 12:211-6.
14. Reyes H, Baez M E, Gonzalez M C, Hernandez I, Palma J, Ribalta J, et al. Selenium, zinc and copper plasma levels in intrahepatic cholestasis of pregnancy, in normal pregnancies and in healthy individuals, in Chile. *J Hepatol* 2000; 32:542-9.
15. Meng L J, Reyes H, Palma J, Hernandez I, Ribalta J, Sjoval J. Effects of ursodeoxycholic acid on conjugated bile acids and progesterone metabolites in serum and urine of patients with intrahepatic cholestasis of pregnancy. *J Hepatol* 1997; 27:1029-40.
16. Bacq Y, Sapey T, Brechot M C, Pierre F, Fignon A, Dubois F. Intrahepatic cholestasis of pregnancy: a French prospective study. *Hepatology* 1997; 26:358-64.
17. Jacquemin E, Cresteil D, Manouvrier S, Boute O, Hadchouel M. Heterozygous non-sense mutation of the MDR3 gene in familial intrahepatic cholestasis of pregnancy. *Lancet* 1999; 353:210-1.
18. Milkiewicz P, Gallagher R, Egginton E, Kilby M, Weaver J B, Elias E. Obstetric cholestasis with elevated GGT: incidence, presentation and treatment. *Hepatology* 2001; 34:A364.
19. Dixon P H, Weerasekera N, Linton K J, Donaldson O, Chambers J, Egginton E, et al. Heterozygous MDR3 missense mutation associated with intrahepatic cholestasis of pregnancy: evidence for a defect in protein trafficking. *Hum Mol Genet* 2000; 9:1209-17.
20. Roncaglia N, Arreghini A, Locatelli A, Bellini P, Andreotti C, Ghidini A. Obstetric cholestasis: outcome with active management. *Eur J Obstet Gynecol Reprod Biol* 2002; 100:167-70.
21. Campos G A, Guerra F A, Israel E J. Effects of cholic acid infusion in fetal lambs. *Acta Obstet Gynecol Scand* 1986; 65:23-6.
22. Williamson C, Gorelik J, Eaton B M, Lab M, de Swiet M, Korchev Y. The bile acid taurocholate impairs rat cardiomyocyte function: a proposed mechanism for intra-uterine fetal death death in obstetric cholestasis. *Clin Sci (Lond)* 2001; 100:363-9.
23. Gorelik J, Harding S E, Shevchuk A I, Koralage D, Lab M, de Swiet M, et al. Taurocholate induces changes in rat cardiomyocyte contraction and calcium dynamics. *Clin Sci (Lond)* 2002; 103:191-200.
24. Kenyon A P, Piercy C N, Girling J, Williamson C, Tribe R M, Shennan A H. Obstetric cholestasis, outcome with active management: a series of 70 cases. *BJOG* 2002; 109:282-8.
25. Milkiewicz P, Elias E, Williamson C, Weaver J. Obstetric cholestasis. *BMJ* 2002; 324:123-4.
26. Kenyon A P, Piercy C N, Girling J, Williamson C, Tribe R M, Shennan A H. Pruritus may precede abnormal liver function tests in pregnant women with obstetric cholestasis: a longitudinal analysis. *BJOG* 2001; 108:1190-2.
27. Walker I A, Nelson-Piercy C, Williamson C. Role of bile acid measurement in pregnancy. *Ann Clin Biochem* 2002; 39:105-13.
28. Lunzer M, Barnes P, Byth K, O'Halloran M. Serum bile acid concentrations during pregnancy and their relationship to obstetric cholestasis. *Gastroenterology* 1986; 91:825-9.
29. Angulo P. Use of ursodeoxycholic acid in patients with liver disease. *Curr Gastroenterol Rep* 2002; 4:37-44.
30. Laifer S A, Stiller R J, Siddiqui D S, Dunston-Boone G, Whetham J C. Ursodeoxycholic acid for the treatment of intrahepatic cholestasis of pregnancy. *J Matern Fetal Med* 2001; 10:131-5.
31. Reyes H, Sjoval J. Bile acids and progesterone metabolites in intrahepatic cholestasis of pregnancy. *Ann Med* 2000; 32:94-106.
32. Paumgartner G, Beuers U. Ursodeoxycholic acid in cholestatic liver disease: mechanisms of action and therapeutic use revisited. *Hepatology* 2002; 36:525-31.
33. Palma J, Reyes H, Ribalta J, Iglesias J, Gonzalez M C, Hernandez I, et al. Effects of ursodeoxycholic acid in patients with intrahepatic cholestasis of pregnancy. *Hepatology* 1992; 15:1043-7.
34. Palma J, Reyes H, Ribalta J, Hernandez I, Sandoval L, Almuna R, et al. Ursodeoxycholic acid in the treatment of cholestasis of pregnancy: a randomized, double-blind study controlled with placebo. *J Hepatol* 1997; 27:1022-8.
35. Diaferia A, Nicastrì P L, Tartagni M, Loizzi P, Iacovizzi C, Di Leo A. Ursodeoxycholic acid therapy in pregnant women with cholestasis. *Int J Gynaecol Obstet* 1996; 52:133-40.
36. Mazzella G, Rizzo N, Azzaroli F, Simoni P, Bovicello L, Miracolo L, et al. Ursodeoxycholic acid administration in patients with cholestasis of pregnancy: effects on primary bile acids in babies and mothers. *Hepatology* 2001; 33:504-8.
37. Almasio P, Bortolini M, Pagliaro L, Coltorti M. Role of S-adenosyl-L-methionine in the treatment of intrahepatic cholestasis. *Drugs* 1990; 40(Suppl 3):111-23.
38. Frezza M, Pozzato G, Chiesa L, Stramentinoli G, di Padova C. Reversal of intrahepatic cholestasis of pregnancy in women after high dose S-adenosyl-L-methionine administration. *Hepatology* 1984; 4:274-8.
39. Frezza M, Centini G, Cammareri G, Le Grazie C, Di Padova C. S-adenosylmethionine for the treatment of intrahepatic cholestasis of pregnancy. Results of a controlled clinical trial. *Hepatogastroenterology* 1990; 37(Suppl 2):122-5.
40. Ribalta J, Reyes H, Gonzalez MC, Iglesias J, Arrese M, Poniachik J, et al. S-adenosyl-L-methionine in the treatment of patients with intrahepatic cholestasis of pregnancy: a randomized, double-blind, placebo-controlled study with negative results. *Hepatology* 1991; 13:1084-9.
41. Floreani A, Paternoster D, Melis A, Grella P V. S-adenosylmethionine versus ursodeoxycholic acid in the treatment of intrahepatic cholestasis of pregnancy: preliminary results of a controlled trial. *Eur J Obstet Gynecol Reprod Biol* 1996; 67:109-13.
42. Nicastrì P L, Diaferia A, Tartagni M, Loizzi P, Fanelli M. A randomised placebo-controlled trial of ursodeoxycholic acid and S-adenosylmethionine in the treatment of intrahepatic cholestasis of pregnancy. *Br J Obstet Gynaecol* 1998; 105:1205-7.
43. Hirvioja M L, Tuimala R, Vuori J. The treatment of intrahepatic cholestasis of pregnancy by dexamethasone. *Br J Obstet Gynaecol* 1992; 99:109-11.
44. Lutz E E, Margolis A J. Obstetric hepatitis: treatment with cholestyramine and interim response to steroids. *Obstet Gynecol* 1969; 33:64-71.
45. Riikonen S, Savonius H, Gylling H, Nikkila K, Tuomi A M, Miettinen T A. Oral guar gum, a gel-forming dietary fiber relieves pruritus in intrahepatic cholestasis of pregnancy. *Acta Obstet Gynecol Scand* 2000; 79:260-4.
46. Gylling H, Riikonen S, Nikkila K, Savonius H, Miettinen T A. Oral guar gum treatment of intrahepatic cholestasis and pruritus in pregnant women: effects on serum cholesterol and other non-cholesterol sterols. *Eur J Clin Invest* 1998; 28:359-63.
47. Kaaja R J, Kontula K K, Raiha A, Laatikainen T. Treatment of cholestasis of pregnancy with peroral activated charcoal. A preliminary study. *Scand J Gastroenterol* 1994; 29:178-81.
48. Alsulyman O M, Ouzounian J G, Ames-Castro M, Goodwin T M. Intrahepatic cholestasis of pregnancy: perinatal outcome associated with expectant management. *Am J Obstet Gynecol* 1996; 175:957-60.
49. Olsson R, Tysk C, Aldenborg F, Holm B. Prolonged postpartum course of intrahepatic cholestasis of pregnancy. *Gastroenterology* 1993; 105:267-71.