Cohort Study of Suspected Obstetric Cholestasis — What have We Learned?

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Objectives: To re-determine the local prevalence of obstetric cholestasis, and to study the presentations, diagnosis, and maternal and neonatal outcomes of obstetric cholestasis in a local cohort.
Methods: All the case records for patients with suspected obstetric cholestasis from 2003 to 2010 in the Department of Obstetrics and Gynaecology, Kwong Wah Hospital were identified and reviewed. The cases were separated into confirmed obstetric cholestasis and non–obstetric cholestasis. Comparison was then made between the two groups for maternal characteristics and neonatal outcomes. Maternal and neonatal outcomes were also compared with the annual departmental statistics for all deliveries from 2003 to 2010. Further subgroup analysis was performed for those women diagnosed with obstetric cholestasis by the higher cut-off level of serum bile acids at 40 μmol/L.
Results: Fifteen cases of obstetric cholestasis were confirmed among 41 suspected cases. When compared with the departmental statistics for all deliveries, obstetric cholestasis was significantly associated with high risk of maternal pre-eclampsia, higher rates of induction of labour and emergency Caesarean section delivery, prematurity of <37 weeks of gestation, and special baby care unit admission. Bile acid level of ≥40 μmol/L was associated with preterm delivery of <37 weeks.
Conclusions: The incidence of obstetric cholestasis was low in this locality and was associated with a high risk of prematurity and pre-eclampsia. However, obstetric cholestasis seems to run a more benign course in this population than in other regions, and management should be individualised. Conservative management can be considered, especially if the bile acid level is <40 μmol/L.
Hong Kong J Gynaecol Obstet Midwifery 2014; 14(1):51-6

Keywords: Bile acids and salts; Cholestasis; Infant, premature; Pre-eclampsia

Introduction

Obstetric cholestasis, also referred to as intrahepatic cholestasis of pregnancy, is characterised by unexplained pruritus and abnormal liver function tests (LFT), and / or raised bile acids and their resolution after delivery[1]. Other causes of pruritus and liver dysfunction should be excluded. Postnatal resolution of pruritus and abnormal LFT should be confirmed[1]. Obstetric cholestasis has been linked to maternal morbidity and adverse fetal outcomes. It has been reported that up to 60% of patients may deliver preterm and up to 2% of pregnancies result in intrauterine death[2,3]. However, it has also been reported that there is no increase in fetal risk in patients with bile acid levels of <40 μmol/L in a Scandinavian Caucasian study[4]. The prevalence of obstetric cholestasis is influenced by genetic and environmental factors and varies between populations worldwide, with the highest prevalences reported from Chile and Bolivia (6-27%)[4]. Data for Chinese or Asian populations are scarce. Reports from Sichuan, China showed a prevalence of 5.2% from 1991 to 2000 and 6.0% from 1999 to 2003[5]. A Hong Kong maternal fetal medicine (MFM) group from the Department of Obstetrics and Gynaecology, Kwong Wah Hospital, Hong Kong has published the first report on the local incidence of obstetric cholestasis of 0.05%[6] from a series of eight patients in 2003 to 2005. Since that report, this group has a heightened awareness of obstetric cholestasis and a low threshold for requesting serum bile acid level tests. It would thus be interesting to revisit this topic by including all patients with suspected obstetric cholestasis from 2003 to 2010.

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This retrospective cohort study aimed to re-determine the local incidence of obstetric cholestasis, and to re-study the presentations and diagnosis, as well as maternal and neonatal outcomes from a larger number of patients.

Methods

Pregnant women with suspected obstetric cholestasis underwent a standard panel of investigations that were endorsed by specialists in the Department of Obstetrics and Gynaecology, Kwong Wah Hospital. Suspicion was usually raised because of skin itchiness and / or deranged liver function. The investigations included LFT, fasting serum bile acid levels, and complete blood count. Standard investigations were undertaken to exclude other diagnoses. These included viral screen for hepatitis A, B, and C, liver autoimmune screen (anti-smooth muscle and antimitochondrial antibodies), and liver ultrasound. All tests for fasting serum bile acids were performed by the clinical biochemistry laboratory in Queen Mary Hospital. The blood and serum samples were light-shielded to minimise photodegradation of bile acids. Input from physicians and dermatologists was noted. For diagnosis of obstetric cholestasis, the following criteria had to be fulfilled: (1) presence of unexplained pruritus; (2) deranged LFT and / or raised bile acids; (3) resolution of pruritus and biochemistry abnormalities postpartum; and (4) exclusion of other causes of itching and of liver dysfunction. The upper limit of normal bile acid level in pregnancy is 11 μmol/L, which is two standard deviations above the mean value (reference range, 0.73-5.63 μmol/L)[7]. Bile acid levels are consistent throughout gestation, and are not elevated in pregnancy[8]. For transaminase and bilirubin, the upper limit of normal level throughout pregnancy is 20% lower than the range for non-pregnant women[9].

Approval from the Hospital Authority Kowloon West Cluster Ethics Committee on Clinical Research was obtained. All the case records of patients with suspected obstetric cholestasis from 2003 to 2010 were identified by tracing all the pregnant women who had fasting bile acid levels checked from the database of the biochemistry laboratory in Queen Mary Hospital and cross-checking with a registry in the Department of Obstetrics and Gynaecology, Kwong Wah Hospital. All the case records were first reviewed by the chief investigator followed by a panel of three MFM subspecialists. The MFM panel reviewed the case records and made the diagnosis using the strict criteria listed above. In order to make the diagnosis of obstetric cholestasis, three members of the panel had to agree, but they were not blinded to the decisions of the other members. The cases were then separated into two groups of confirmed obstetric cholestasis and non–obstetric cholestasis. Comparison was then made between the two groups for maternal characteristics and neonatal outcomes. Maternal and neonatal outcomes were also compared with the departmental statistics covering all deliveries from 2003 to 2010. Maternal outcomes included pre-eclampsia and postpartum haemorrhage. Postpartum haemorrhage referred to primary postpartum haemorrhage and was defined as blood loss of >500 mL for vaginal deliveries and 1000 mL for Caesarean section deliveries. Neonatal outcomes included prematurity (<37 weeks of gestation), small for gestational age (<10th centile from the local growth chart), Apgar score of <7 at 5 minutes, meconium-stained liquor, and admission to the neonatal intensive care unit (NICU) or special care baby unit (SCBU). Further subgroup analysis was performed for those women diagnosed with obstetric cholestasis with the higher cut-off level of serum bile acids at 40 μmol/L[4].

Statistical analysis was performed using the Statistical Package for the Social Sciences Windows version 17 (SPSS Inc., Chicago [IL], US). Statistical analysis was performed with Student's *t* test for continuous variables that were normally distributed, the Mann-Whitney *U* test for continuous variables that were not normally distributed, and Fisher's exact test for dichotomous variables. A two-tailed p value of <0.05 was considered significant.

Results

From 2003 to 2010, 46 pregnancies with fasting serum bile acids tested were identified. Pregnancies that were not singleton (two pairs of twins), with no regular antenatal care (two pregnancies), or no neonatal outcomes available (one woman who delivered in Australia) were excluded. The final cohort consisted of 41 pregnancies, all were singleton pregnancies with regular antenatal care and delivery in the department (Figure).

The eight cases of obstetric cholestasis from the previous case series in 2007[6] were included in the cohort of the current study and discussed in the MFM panel. Among these eight cases, six were retained in the obstetric cholestasis group, one was reclassified as non–obstetric cholestasis, and the other was excluded as the patient had no regular antenatal care. The case that was reclassified as non–obstetric cholestasis was deemed to be severe pre-eclampsia with coagulopathy. There was no pruritus and the bile acid level was normal in the postnatal period.

A total of 26 pregnancies were not classified as obstetric cholestasis as they did not fulfil all the diagnostic

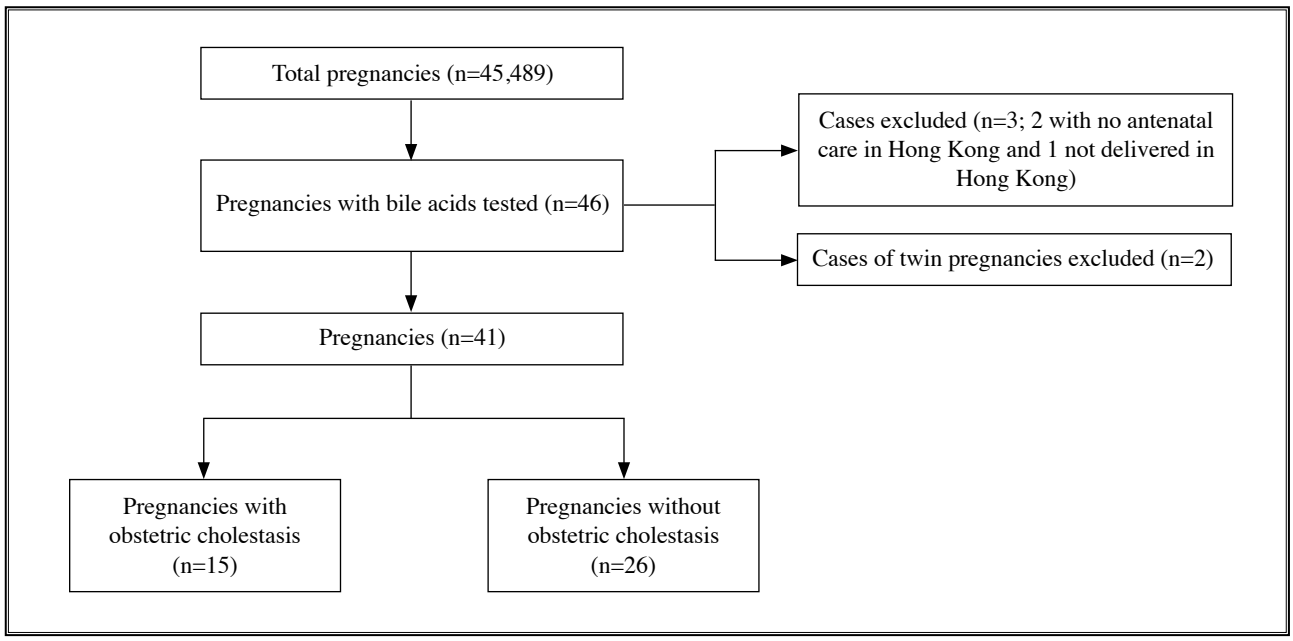

Figure. Suspected obstetric cholestasis among all deliveries at the Department of Obstetrics and Gynaecology, Kwong Wah Hospital, Hong Kong, from 2003 to 2010

Table 1. Comparison of maternal characteristics between patients with and without obstetric cholestasis

Characteristic	Median (interquartile range) or No. (%)		p Value
	Obstetric cholestasis (n=15)	Non–obstetric cholestasis (n=26)	
Age (years)	32 (29-36)	33 (28-35)	0.957*
Body mass index (kg/m^2)	20 (19.3-21.8)	20.35 (19.0-21.7)	0.968*
Tertiary education	3 (20.0)	11 (42.3)	0.186†
Smoking	0	2 (7.7)	0.524†
Alcohol consumption	1 (6.7)	0	0.366†
Multiparous	6 (40.0)	10 (38.5)	1.000†

* Mann-Whitney *U* test
† Fisher's exact test

criteria. The diagnoses were generalised pruritus (n=9), acute hepatitis (n=7), liver parenchymal disease (n=4), acute fatty liver (n=1), HELLP (haemolysis, elevated liver enzymes, and low platelet count) syndrome (n=1), pre-eclampsia (n=1), fetal arrhythmia (n=1), insect bite (n=1), and asymptomatic hypercholanaemia (n=1).

The 15 pregnancies with obstetric cholestasis were carried by 13 women for a local incidence of 0.033% (15/45,489 pregnancies). Among the 13 women, 11 were Chinese, and the other two was Indian and Nepalese, respectively. The maternal characteristics, including age, body mass index, education, smoking, and alcohol consumption were comparable between the obstetric cholestasis and non–obstetric cholestasis groups (Table 1).

The maternal outcomes of the obstetric cholestasis group were also similar to those of the non–obstetric cholestasis group. When compared with the departmental statistics covering all deliveries of 2003-2010, obstetric cholestasis was associated with a significantly higher risk of maternal pre-eclampsia (Table 2).

In the obstetric cholestasis group, 10 patients were given symptomatic treatment, including chlorpheniramine, aqueous cream, and crotamiton. Among these 10 patients, one was also given vitamin K, one was given combined ursodeoxycholic acid and vitamin K, and another one was given combined ursodeoxycholic acid and dexamethasone. Compared with the departmental statistics covering all deliveries of 2003-2010, higher rates of induction of

labour and emergency Caesarean delivery were observed in obstetric cholestasis group (Table 2). The indications for induction of labour in the obstetric cholestasis group were obstetric cholestasis (n=4, all of which were full-term pregnancies), preterm prelabour rupture of membrane and obstetric cholestasis (n=1), preterm prelabour rupture of membrane (n=1), pre-eclampsia (n=1), and deranged LFT (n=2). There was no case of iatrogenic prematurity solely due to obstetric cholestasis. Six patients underwent emergency Caesarean section — two for fetal distress, two for failed induction of labour, one for preterm labour with breech presentation, and the other for persistent occipito-posterior position.

Comparisons of neonatal outcomes among different groups are shown in Tables 3 and 4. There was no perinatal death in this cohort. Only one case from the obstetric cholestasis group required admission to the NICU for prematurity and low birth weight (1450 g at 32 weeks). Compared with the non–obstetric cholestasis

Table 2. Comparison of maternal outcomes among patients with and without obstetric cholestasis and all deliveries

Characteristic	No. (%)		p Value*	No. (%)	p Value*
	Obstetric cholestasis (n=15)	Non–obstetric cholestasis (n=26)		All deliveries (n=45,489)	
Postpartum haemorrhage	0	2 (7.7)	0.524	2413 (5.3)	1.0
Pre-eclampsia	2 (13.3)	3 (11.5)	1.000	345 (0.8)	0.006
Induction of labour	9 (60.0)	7 (26.9)	0.051	8481 (18.6)	<0.001
Emergency LSCS	6 (40.0)	9 (34.6)	0.749	6126 (13.5)	0.010

Abbreviation: LSCS = lower segment Caesarean section

* Fisher's exact test

Table 3. Comparison of neonatal outcomes between patients with and without obstetric cholestasis

Characteristic	Median (interquartile range) of No. (%)		p Value
	Obstetric cholestasis (n=15)	Non–obstetric cholestasis (n=26)	
Maturity (weeks)	37.29 (35.9-38.4)	38.93 (38.0-40.0)	0.003*
Birth weight (g)	2650 (2160-3120)	3225 (2868-3578)	0.005*
Apgar score <7 at 5 minutes	9 (9-10)	9 (9-9.3)	0.300*
Small for gestational age	4 (26.7)	2 (7.7)	0.168†

* Mann-Whitney *U* test

† Fisher's exact test

Table 4. Comparison of neonatal outcomes among patients with or without obstetric cholestasis and all deliveries

Characteristic	No. (%)		p Value*	No. (%)	p Value*
	Obstetric cholestasis (n=15)	Non–obstetric cholestasis (n=26)		All deliveries (n=45,489)	
Admission to NICU	1 (6.7)	3 (11.5)	1.000	674 (1.5)	0.201
Admission to SCBU	12 (80.0)	14 (53.8)	0.177	12,473 (27.4)	<0.001
Preterm (<37 weeks)	7 (46.7)	3 (11.5)	0.022	2615 (5.7)	<0.001
Preterm (<34 weeks)†	1 (6.7)	1 (3.8)	1.000	284 (1.0)‡	0.09
MSL	5 (33.3)	5 (19.2)	0.453	6835 (15.0)	0.062

Abbreviations: NICU = neonatal intensive care unit; SCBU = special care baby unit; MSL = meconium-stained liquor

* Fisher's exact test

† n=28,976

‡ Only department statistics for 2006-2010 were available for prematurity <34 weeks

Table 5. Comparison of obstetric cholestasis cases by different bile acid levels

Characteristic	No. (%)		p Value*
	≥40 μmol/L (n=6)	<40 μmol/L (n=9)	
Preterm (<37 weeks)	6 (100)	1 (11)	0.001
Small for gestational age	2 (33)	2 (22)	1.000
Meconium-stained liquor	1 (17)	3 (33)	0.604
Pre-eclampsia	1 (17)	1 (11)	1.000

* Fisher's exact test

group, babies in the obstetric cholestasis group were delivered at slightly earlier gestations with lower birth weights. Babies of mothers with obstetric cholestasis were also more likely to be admitted to the SCBU than those from the departmental statistics covering all the deliveries for the same period.

In the obstetric cholestasis group, the extent of elevation of transaminase was not associated with preterm delivery (p=0.619). Bile acid blood level of ≥40 μmol/L was associated with preterm delivery <37 weeks of gestation (p=0.001), but not with other adverse neonatal outcomes (Table 5).

Among the 13 patients with obstetric cholestasis, two had recurrent obstetric cholestasis. One patient had three episodes of obstetric cholestasis. Her first pregnancy resulted in intrauterine death, which was managed at another hospital and no causes for the fetal death were found. In her second pregnancy, this patient was diagnosed with obstetric cholestasis at 34 weeks, and Caesarean section was performed for breech presentation after spontaneous onset of labour at 36 weeks. Obstetric cholestasis occurred again in her third pregnancy and she underwent elective Caesarean section at 37 weeks for previous Caesarean section and oligohydramnios. In her fourth pregnancy, she was diagnosed with obstetric cholestasis at 20 weeks. She subsequently underwent elective Caesarean section at 37 weeks for two previous Caesarean sections. Ursodeoxycholic acid was not given during any of the three pregnancies. For the second patient with recurrent obstetric cholestasis, the diagnosis was made in her first pregnancy, which was managed at another hospital. She was seen in the department in her second pregnancy. Diagnosis of recurrence of obstetric cholestasis was made at 13 weeks of gestation. She was given ursodeoxycholic acid and was subsequently admitted for premature prelabour rupture of membrane at 32 weeks of gestation. The baby was admitted to the NICU due to prematurity and low birth weight.

Discussion

The prevalence of obstetric cholestasis varies between populations, and growing awareness has increased the reported incidence[10]. In the present study conducted from case records over an 8-year period, the prevalence of obstetric cholestasis in a local regional hospital was 0.033%, which is comparable to the prevalence of 0.047% previously reported [6]. This might reflect the true situation in this locality. As the authors were quite liberal in suspecting obstetric cholestasis, the apparently low prevalence observed is unlikely to be due to underestimation as a result of unawareness by clinicians.

The findings of this paper concurred with the previous observation[11] that pre-eclampsia is more common in patients with obstetric cholestasis. These results also confirmed the increased risk of prematurity in women with obstetric cholestasis, which is consistent with the previous study in 2007[6]. The Royal College of Obstetricians and Gynaecologists has concluded that the incidence of premature birth is increased in obstetric cholestasis[1], and other studies of obstetric cholestasis have similar findings[4,12,13]. In one study[4], obstetric cholestasis was stratified into mild and severe using bile acid level of 40 μmol/L as cut-off, which may help to reduce intervention and thus save medical costs. The bile acids cut-off at 40 μmol/L established in a Swedish population[4] was confirmed to be applicable locally in a predominantly Chinese population. In this case series, the bile acid level of ≥40 μmol/L was associated with prematurity <37 weeks. Nevertheless, prematurity <34 weeks remained rare. The earlier gestation at delivery and lower birth weight in patients with obstetric cholestasis compared with the non–obstetric cholestasis group were clinically trivial. Although a higher proportion of such babies required treatment in the SCBU, the neonatal outcomes were generally good. This suggests that obstetric cholestasis in this population may be clinically more benign and require less active intervention than in other populations, especially when the bile acid

level is <40 μmol/L. This result is in contrast to the more adverse outcomes, including a 2% intrauterine death rate reported elsewhere[2,3]. However, this finding could also be due to the small sample size in this study, in which no adverse outcomes, including intrauterine death, were found.

The recurrence rate has been reported to be as high as 45-90%[13]. Although it was not possible to calculate a recurrence rate from this small cohort, two of 13 patients had recurrences. For these two patients, the clinical manifestations, including symptom intensity, biochemistry derangement, and neonatal and maternal outcomes, were similar in subsequent pregnancies. Thus, it is important to offer follow-up for appropriate counselling and to discuss possible recurrence of the condition in subsequent pregnancies.

This is the first study to present data on the sensitivity of clinical suspicion of obstetric cholestasis. In this cohort, 15 cases of obstetric cholestasis were diagnosed out of 41 suspected cases, for a sensitivity of 36%. The women's demographic and biophysical parameters were not helpful for diagnosis of suspected obstetric cholestasis. Whether it is possible to improve clinical judgement by considering symptomatology will require further study. The serum bile acid levels could be checked by a specialist, but not necessarily restricted to MFM subspecialists. It is not clear whether the diagnostic accuracy could be improved with the input of MFM subspecialists for all suspicious cases.

The present study is limited by its retrospective design and small sample size of only 15 cases of obstetric cholestasis. The sample size is small despite inclusion of cases from an earlier study[6] and associated heightened awareness of the condition in the department. This attests to the rarity of the condition. Departmental statistics is a useful control mechanism. However, only a limited number of items is available for reference in the annual departmental statistics, which restricts the scope of the study. Given the apparently low prevalence of obstetric cholestasis and the even rarer adverse fetal outcomes, a multi-centre study with a large sample size may be the way forward to further elucidate this obstetric condition.

Conclusions

The prevalence of obstetric cholestasis is low in this locality. Strict criteria for diagnosis should be adopted. Obstetric cholestasis was associated with a high risk of prematurity and possibly pre-eclampsia. However, obstetric cholestasis seems to run a more benign course in patients in this locality than in other regions, and management should be individualised. Conservative management can be considered, especially if the bile acid level is <40 μmol/L. Future study of a larger sample size or a territory-wide audit is needed to confirm these findings.

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