

Obstetric cholestasis in Hong Kong—local experience with eight consecutive cases

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Obstetric cholestasis is associated with maternal morbidity and adverse foetal outcomes. No information on local incidence is available. We present our experience with eight consecutive cases of obstetric cholestasis diagnosed between January 2003 and December 2005 in a regional hospital in Hong Kong. Three patients presented with pruritus without rash, three with impaired liver function, and two with elevated blood pressure postpartum. Meconium-stained liquor was present in five patients and four had spontaneous preterm delivery (between 34 and 36 weeks). The higher the bile acid level, the more marked the prematurity (correlation coefficient, -0.771 ; $P=0.025$). All those presenting with itchiness delivered preterm. Two patients developed pre-eclampsia. The rates of labour induction and abdominal delivery were both 38%. Heightened awareness among clinicians is required to recognise patients with obstetric cholestasis. Affected pregnancies are associated with meconium passage and prematurity. In our locality, affected women may also have an increased risk of pre-eclampsia. In affected women, the bile acid level is useful in assessing the risk of prematurity.

Introduction

Obstetric cholestasis is also called intrahepatic cholestasis of pregnancy. It is a 'syndrome' specific to pregnancy characterised by deranged liver function tests and generalised itchiness without skin rash, both remitting after delivery. Other causes of pruritus and liver impairment need to be excluded.¹

It was observed that obstetric cholestasis was associated with maternal morbidity and adverse foetal outcomes. In particular, up to 60% of patients may deliver preterm and up to 2% end up with intrauterine death.² Its incidence ranges from 0.02% in most European populations to 28% in the native Araucanian population in Chile.³ No information on local incidence is available. In this paper, our experience with eight consecutive cases is presented. This is the first report on local experience with obstetric cholestasis.

Methods

In January 2003, we diagnosed our first case of obstetric cholestasis. We maintained a registry of all the cases diagnosed subsequently. All cases fulfilled the following criteria: (1) presence of pruritus without skin rash; (2) impaired liver function; (3) alternative diagnoses excluded; and (4) resolution of pruritus and liver biochemistry postpartum.¹ All the pregnancies were dated by early ultrasound examination before 20 weeks' gestation.

For diagnosis of obstetric cholestasis, elevations in any of a wide range of liver function test findings beyond pregnancy-specific limit were considered sufficient.¹ These included serum transaminase, bile salts and/or bilirubin. The upper limit of normal bile acid level in pregnancy was $11 \mu\text{mol/L}$, which was two standard deviations from mean value for later pregnancy.⁴ This cut-off point had also been used in other studies.^{5,6} For transaminase and bilirubin, the upper limit of normal level throughout pregnancy was 20% lower than the range for non-pregnant women.⁷

Standard investigations were undertaken in all cases to rule out alternative diagnoses. These included a viral screen for hepatitis A, B, and C, anti-smooth muscle antibody for chronic active hepatitis, anti-mitochondrial antibody for primary biliary cirrhosis, anti-nuclear antibodies and anti-double-stranded DNA for systemic lupus, and ultrasound for gallstone. Where feasible, opinions from a physician and dermatologist were sought.

Results

A total of eight cases were identified: one in 2003 (case 1), one in 2004 (case 2), and six in

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八個在香港醫院裏治療產科膽汁淤積症病例的經驗

膽汁淤積症與孕婦病患和胎兒不良後果有關。本地有關資料欠奉。我們報告在2003年1月至2005年12月於一所地區醫院診斷患上產科膽汁淤積症的連續個案。3名病人有瘙癢，但無出疹；3人肝功能受損；2人產後血壓上升。5人發現有羊水胎糞，4人在妊娠34至36週自然早產，而膽汁酸水平越高，早產越明顯（相關係數為-0.771； $P=0.025$ ）。最初感到痕癢的患者全部早產。兩人有子癩前症。引產和剖腹產的比率同為38%。醫生須非常警覺才能發現病人患上產科膽汁淤積症。此症對妊娠的影響與胎便排解和早產有關。在本地病例中，患上本症的女性病人比較易出現子癩前症，而量度膽汁酸水平有助評估患者早產的危機。

2005 (Table 1). Six were Chinese, one Indian (case 1), and one Nepalese (case 5). The incidence of obstetric cholestasis was 0.047% overall and 0.056% among Chinese pregnant women (Table 2).

Baseline characteristics

All were singleton pregnancies. The maternal age ranged from 25 to 36 years, with a mean of 32 years. Cases 2, 4, and 7 were primiparous. The others were nulliparous. While cases 2 and 4 had no evidence of obstetric cholestasis in their previous pregnancy, case 7 recalled generalised itchiness without apparent rash in her last pregnancy. The latter patient was not investigated at that time and the itchiness subsided after delivery.

Presentations and diagnosis

All eight patients had generalised skin itchiness without rash. In two, it started over the abdomen and in one over the extremities. In six of eight patients, the onset of itchiness was in the third trimester (Table 1); the earliest onset being 20 weeks (case 1). The gestational onset of itchiness was not associated with the level of bile acids (correlation coefficient, -0.519; $P=0.233$, Spearman's rank correlation).

Serum bile acid and alanine aminotransferase (ALT) levels were elevated in all eight cases. While bile acid level at diagnosis varied between 13 and 77.2 $\mu\text{mol/L}$, peak ALT level ranged between 68 and 394 IU/L (Table 1). Half of the patients also had mildly elevated serum bilirubin levels (up to 30 $\mu\text{mol/L}$).

Three patients (cases 2, 6, and 8) first presented with characteristic pruritus. Three were incidentally found to have impaired liver function for unrelated complaints before the onset of pruritus (cases 1, 5, and 7). Case 1 had liver function checked in India at 14 weeks for unknown reasons. Case 5 had liver function checked at 32 weeks for non-specific abdominal pain, and case 7 at 28 weeks for flu. The remaining two patients (cases 3 and 4) had no complaint; both were noted to have elevated blood pressure postpartum. Subsequent work-up uncovered impaired liver function and characteristic pruritus was noted only on retrospective questioning.

After delivery, pruritus resolved in all patients, as did the ALT except in case 8 who was a hepatitis B carrier. Six weeks postpartum, her ALT improved to 43 IU/L and the serum bile acid level to 13 $\mu\text{mol/L}$.

TABLE 1. Outline of the eight cases of obstetric cholestasis*

Case No.	Gestation at onset of itchiness (weeks)	Bile acid at diagnosis ($\mu\text{mol/L}$) [reference level, <11 $\mu\text{mol/L}$ †]	Peak ALT (IU/L) [reference level, <25 IU/L†]	Maturity at delivery (weeks)	Mode of delivery	Birth weight (kg)	Complications	Treatment
1	20	72	394	36	NSD	2.36	PPROM Meconium	Emollient Vitamin K
2	28	42	147	34	NSD	2.06	Preterm labour	-
3	38	16.6	212	40	Abdominal	4.04	Pre-eclampsia PPH Meconium	MgSO ₄ Vitamin K FFP
4	Not mentioned	21.7	68	39	NSD	3.58	PIH Meconium	-
5	34	22	183	37	Abdominal	3.13	-	-
6	33	45	230	35	NSD	2.50	Preterm labour NICU	Emollient
7	33	13	110	39	Abdominal	3.47	Meconium	-
8	33	77.2	123	35	NSD	2.54	Preterm labour Pre-eclampsia Meconium	MgSO ₄

* ALT denotes alanine aminotransferase, FFP fresh frozen plasma, MgSO₄ magnesium sulphate, NICU neonatal intensive care unit, NSD normal spontaneous delivery, PIH pregnancy-induced hypertension, PPH postpartum haemorrhage, and PPRM preterm prelabour rupture of membranes

† Reference level during pregnancy

TABLE 2. Incidence of obstetric cholestasis

	2003	2004	2005	Average, 2003-2005	Chinese, 2004-2005
No. of cases	1	1	6	8	6
Total No. of deliveries	5765	5179	5969	16 911	10 794
Incidence (%)	0.017	0.019	0.10	0.047	0.056

Resolution of itchiness and improvement in liver function after delivery were consistent with obstetric cholestasis. Case 5 was found to have gallstone. Nevertheless, there was no evidence of biliary obstruction on ultrasound. Co-existing pathology was not identified in the other six cases.

The diagnosis of obstetric cholestasis for two of the patients may have been possible earlier. Thus, case 2 complained of characteristic itchiness without rash for 2 weeks at 30 weeks, but obstetric cholestasis was only suspected (and confirmed by liver function tests) at 34 weeks. Case 7 was noted to have impaired liver function at 28 weeks; her 36-week routine checkup reported itchiness for the past 3 weeks and at 39 weeks, the diagnosis of obstetric cholestasis was finally realised.

Dermatologists were consulted for two of the patients because of pruritus without rash, and were diagnosed to have eczema (case 2) and polymorphic eruption of pregnancy (case 7). Physicians were consulted for six patients, but could not arrive at any conclusion for cases 3, 5, and 7. One patient was correctly diagnosed with obstetric cholestasis (case 6). One was diagnosed with chronic hepatitis (case 2) and another was labelled pregnancy-related deranged liver function (case 1).

Maternal outcomes

Two (25%) patients developed pre-eclampsia (Table 1); both received magnesium sulphate to prevent eclampsia. One (case 3) had a postpartum haemorrhage and wound haematoma associated with deranged clotting (international normalised ratio, 2.2; prothrombin time, 25 seconds). The haemoglobin dropped from 141 g/L intrapartum to 86 g/L after delivery. She was treated with vitamin K and fresh frozen plasma. Only case 1 received vitamin K for prophylaxis against the theoretical risk of bleeding associated with obstetric cholestasis. As in the other six patients not receiving prophylaxis, no abnormal bleeding was observed. Two patients were treated with topical emollients for symptomatic relief of itchiness. No patient received ursodeoxycholic acid (UDCA), dexamethasone, or S adenosyl methionine.

Three of the patients had labour induced—for preterm prelabour rupture of membranes and obstetric cholestasis (case 1), obstetric cholestasis (case 5), and deranged liver function (case 7). Three

patients underwent emergency abdominal delivery; for non-reassuring foetal status intrapartum (cases 3 and 7) and failed induction (case 5).

Neonatal outcomes

Four (50%) cases had preterm labour and delivered between 34 and 36 weeks. Higher bile acid levels at diagnosis were associated with earlier gestational spontaneous prematurity (correlation coefficient, -0.771; $P=0.025$, Spearman's rank correlation). Neither the extent of ALT level elevation nor the onset of itchiness were associated with preterm births (correlation coefficient, -0.205; $P=0.627$ and correlation coefficient, 0.636; $P=0.125$, respectively). Patients presenting first with itchiness (cases 2, 6, and 8) delivered earlier (all being preterm). In contrast, only one in three cases initially presenting with deranged liver function delivered preterm. Both patients presenting with elevated blood pressure postpartum delivered at term (cases 3 and 4).

The birth weights of the eight babies ranged between 2.06 and 4.04 kg, with a mean of 2.96 kg. Of the eight babies, the lowest Apgar score at five minutes of life was 9, the lowest cord blood pH was 7.15, and meconium was passed in five (63%) cases. Only the baby of case 6 (born at 35 weeks) stayed in the neonatal intensive care unit (for 2 days) because of apnoea of prematurity. There was no stillbirth.

Discussion

The prevalence of obstetric cholestasis varies between populations. It is influenced by genetic and environmental factors. Data for Chinese population are still preliminary. Reports from Sichuan, China showed that in the 10 years from 1991 to 2000, the incidence was 5.2%.⁸ This slightly increased to 6% in the 5 years from 1999 to 2003.⁹ Our report shows that the incidence in a major local obstetric unit is 0.047% overall and 0.056% among Chinese pregnant women (Table 2). Compared with those reported in Sichuan, China, it is likely that our incidence is underestimated.

Underestimation may be a reason for the low incidence reported elsewhere.³ In England, for example, growing awareness has increased the incidence from 0.1% two decades ago to 0.7% today.³ Obstetric cholestasis remains widely disregarded as

an important clinical problem. Many obstetricians still consider its main symptom, pruritus, a natural association of pregnancy.² In 25% of our cases, recognition of the characteristic pruritus by obstetricians is delayed. The increase in number of cases diagnosed in 2005 may, at least in part, be due to heightened awareness among obstetricians. It also appears that diagnosis of obstetric cholestasis poses a challenge to dermatology and physician colleagues.

Obstetric cholestasis is a pregnancy-specific syndrome consisting of both clinical disturbance (pruritus without rash) and biochemical (liver functional) impairment. Pruritus is the mode of presentation in 97% of patients and abnormal liver function tests in 3%.⁸ In our series, three (38%) women had abnormal liver function, which was recognised before pruritus. The early recognition of impaired liver may be due to liberal inclusion of liver function tests for unrelated complaints.

Bile acid levels in serum were elevated in all our patients. Bile acid is a sensitive, but not specific marker for obstetric cholestasis.³ Normal bile acid levels do not exclude obstetric cholestasis,¹ nor do elevated levels equate to the diagnosis. Asymptomatic hypercholanaemia of pregnancy is a benign biochemical variant in some pregnant women with no clinical significance.⁵ Although we obtained serum bile acid levels in all cases, the assay is expensive and the result is not immediately available. In routine practice, it is reasonable only to request the level if pruritus occurs with normal liver function test results.¹

The aetiology of obstetric cholestasis is multifactorial, with contributions from genetic, environmental, and hormonal factors. Evidence suggests that obstetric cholestasis manifests clinically when the secretory capacity of mildly malfunctioning canalicular transporters are overwhelmed by the high levels of sex hormones in pregnancy, though there are no problems outside pregnancy.³ Specifically, there is an increased gamma glutamyl transferase level associated with dysfunction in a bile canalicular transporter called multidrug resistance protein 3 due to mutation.¹⁰

After extensive review of the available evidence, the Royal College of Obstetricians and Gynaecologists (RCOG) has concluded that obstetric cholestasis increases the risk of spontaneous prematurity.¹ Half of our patients delivered preterm. The gestation at preterm birth was correlated with the level of bile acid at diagnosis. It seems that the higher the bile acid level, the higher is the risk of prematurity and the earlier is the gestation at delivery. We also observed that while itchiness as the first presenting symptom was associated with prematurity, the gestation at onset of itchiness was not related to the gestation of prematurity. Further study is required to verify this.

All our patients with prematurity were beyond 34 weeks, which was consistent with a recent report that the majority of spontaneous preterm births in obstetric cholestasis were after 32 weeks.¹¹ Although good neonatal outcome is usually expected for near-term babies, they are not completely free from the complications of prematurity; in our series, a 35-weeker required neonatal intensive care unit admission because of apnoea of prematurity.

Whether obstetric cholestasis is associated with higher rates of meconium passage is still debated.¹ In the literature, meconium passage in up to 45% of cases has been reported.³ Meconium was passed in 63% of our patients. Nevertheless, this does not seem to affect the neonatal outcomes. Moreover, according to a recent report, in obstetric cholestasis the stillbirth rate is not increased.¹

In this study, 25% of patients had pre-eclampsia. Over the same period of time (2003-2005), the incidence of pre-eclampsia in our unit was 0.79% (134 of 16 913 cases). While epidemiological studies failed to demonstrate whether obstetric cholestasis is associated with pre-eclampsia,^{12,13} molecular studies in Finns showed there may be a common risk locus associated with both conditions in the vicinity of the 2p13-p12 region.¹⁴ Maternal serum bile acid level was not elevated in pre-eclamptic toxemia (PET).¹⁵ However, in women with PET and impaired liver function, the median bile acid level was greater than in normal pregnant controls and 8% had markedly elevated bile acid levels though none reported pruritus.¹⁶ Therefore, characteristic pruritus in cases 3 and 8 substantiated the diagnosis of obstetric cholestasis, despite the potential effect of PET on liver function and bile acid levels.

The management of obstetric cholestasis is controversial. No specific foetal monitoring modality is recommended.¹ Labour was induced for case 7 because of deteriorating liver function. This practice is not supported by RCOG as evidence is not robust.¹ Labour was also induced for case 5 at 37 weeks for obstetric cholestasis. This is a widely adopted practice to reduce later stillbirth. Again, it is not evidence-based.¹ Topical emollients were used for symptomatic relief; although safe, but their efficacy is unknown.¹ Vitamin K was used in some of our cases. It is used for physiological reasons, although evidence is sparse. In the United Kingdom, UDCA has been widely used for obstetric cholestasis for years. Small trials suggested it might help relieve pruritus and improve liver biochemistry.^{3,17,18} However, a review of the available evidence did not support such use outside research settings,¹ nor was it used by us. Likewise, evidence for dexamethasone and S adenosyl methionine is inconclusive.¹ Obstetric cholestasis was associated with preterm birth. However, it has not been proved that treatment reduces the rate of spontaneous

prematurity.¹¹ The management of obstetric cholestasis therefore has to be individualised.

Conclusion

The incidence of obstetric cholestasis in a major local obstetric unit was around 0.05%, which was likely an underestimate; local clinicians need to increase

awareness of this entity. Obstetric cholestasis is associated with prematurity and passage of meconium. Determination of bile acid level is potentially useful for risk assessment of prematurity in affected women. The possibility that itchiness as an initial presentation is associated with prematurity and the relatively high incidence of pre-eclampsia among local women with obstetric cholestasis requires further investigation.

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