

CASE REPORTS

Fetal mortality associated with cholestasis of pregnancy and the potential benefit of therapy with ursodeoxycholic acid

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Abstract

Cholestasis of pregnancy is associated with increased fetal morbidity and mortality and should be treated actively. The significance attached to pruritus in pregnancy is often minimal, but it is a cardinal symptom of cholestasis of pregnancy, which may have no other clinical features. Eight women with previous cholestasis of pregnancy were referred to The Liver Unit within a 12 month period for advice concerning future pregnancies. Thirteen pregnancies had been affected by cholestasis of pregnancy and 12 had been treated expectantly with resultant perinatal morbidity or mortality in 11 (one normal delivery), including; eight stillbirths, two premature deliveries with fetal distress (one died in perinatal period), and an emergency caesarean section for fetal distress. The other pregnancy was treated actively and delivery was uncomplicated. Subsequently, three of these cases with recurrent cholestasis of pregnancy were referred while pregnant. In each, cholestasis developed with severe pruritus, gross increase of serum bile acids, and deranged liver tests. Each was treated with the choleric agent ursodeoxycholic acid, with rapid clinical improvement and resolution of deranged biochemistry. In conclusion, cholestasis of pregnancy continues to be treated expectantly despite its association with increased morbidity and mortality and evidence suggesting improved prognosis with active treatment and the potential of reducing the associated perinatal mortality. In an uncontrolled series of three patients with cholestasis of pregnancy, ursodeoxycholic acid seemed to provide safe and effective therapy.

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Keywords: cholestasis of pregnancy, fetal mortality, prognosis, treatment, ursodeoxycholic acid.

Cholestasis of pregnancy is a disease of unknown aetiology, which may cause severe and intractable pruritus. The maternal prognosis is excellent, with symptoms and biochemical derangements resolving rapidly post

partum, but cholestasis of pregnancy is associated with significant fetal morbidity and mortality.¹⁻⁹ Cholestasis of pregnancy typically develops during the third trimester of pregnancy, but occasionally presents before 20 weeks. By definition, dermatological disease should be absent, if a diagnosis is made on clinical criteria alone,⁹ but this is not necessary if biochemical evidence of cholestasis is obtained. Most patients are not jaundiced and many have normal standard liver function tests. Serum alanine transaminase (ALT) is the most sensitive of the conventional liver function tests,¹⁰⁻¹² although serum bile acids are invariably increased.^{10 11 13} Symptoms vary from mild pruritus to intractable pruritus, associated with gastrointestinal upset and icterus. Symptoms almost invariably resolve within one week of delivery.

Treatment of cholestasis of pregnancy varies widely. Despite evidence to the contrary, some obstetricians still perceive cholestasis of pregnancy as a benign condition and adopt an expectant policy. We report eight cases with a history of cholestasis of pregnancy whose pregnancies had mostly been treated conservatively. Three of these cases were pregnant at the time of referral and treated with the choleric ursodeoxycholic acid.

Case reports and previous obstetric histories (Table)

Case 1: 34 year old white woman

First pregnancy, 1986 – pruritus from 28 weeks gestation. She was reassured. Spontaneous onset of labour at 37/40. Stillborn female. Pruritus settled within two days.

Second pregnancy 1988 – pruritus from 27/40. Induction of labour at 38/40, because of previous intra-uterine death. No meconium staining. Male baby, alive and well. Pruritus settled within four days.

Third pregnancy – pruritus from 26 weeks, without jaundice. Fetal movements were normal and she was reassured. Liver functions tests became abnormal, with increased serum aspartate transaminase (AST) (135). Spontaneous onset of labour at 39/40, with stillborn female. Pruritus settled almost immediately.

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Case reports

Case	Pregnancy	Onset	UDCA RX	Icterus	A/N clinic	Onset labour	Gestation	Mode of delivery	AST	Meconium staining	Outcome	Cessation of pruritus
1	1st	28/40	No	No	Yes	SPONT	37/40	Vaginal	243	Yes	Stillbirth	2 Days
	2nd	27/40	No	No	Yes	Induced	38/40	Vaginal	129	No	Normal	4 Days
	3rd	26/40	No	No	Yes	SPONT	Term	Vaginal	135	Yes	Stillbirth	1 Day
	4th	25/40	Yes	No	Yes	C/s	35/40	ELEC C/s	213	No	Normal	2 Days
2	1st	35/40	No	No	Yes	SPONT	38/40	EMERG C/s	N/D	Yes	Fetal distress	3 Days
	2nd	35/40	No	No	Yes	SPONT	Term	Vaginal	82	Yes	Stillbirth	1 Day
	3rd	28/40	Yes	No	Yes	C/s	35/40	ELEC C/s	42	No	Normal	0 Days
3	1st	28/40	No	No	Yes	SPONT	36/40	Vaginal	N/D	N/K	Perinatal death	7 Days
	2nd	None	No	No	Yes	SPONT	Term	Vaginal	N/D	No	Normal	N/A
	3rd	32/40	No	No	Yes	SPONT	37/40	Vaginal	N/D	No	Normal	7 Days
	4th	30/40	Yes	No	Yes	Induced	38/40	Vaginal	205	No	Normal	2 Days
4	1st	None	No	N/A	Yes	SPONT	Term	Vaginal	N/D	No	Normal	N/A
	2nd	30/40	No	No	Yes	SPONT	36/40	Vaginal	N/D	?	Fetal distress	1 Week
	3rd	31/40	No	No	Yes	SPONT	Term	Vaginal	N/D	Yes	Stillbirth	2 Days
5	1st	None	No	N/A	Yes	SPONT	35/40	Vaginal	N/D	Yes	PREM+NIL	N/A*
	2nd	None	No	N/A	Yes	SPONT	Term	Vaginal	N/D	No	Normal	N/A
	3rd	25/40	No	No	Yes	SPONT	32/40	Vaginal	N/D	Yes	Stillbirth	1 Day
6	1st	31/40	No	No	Yes	SPONT	Term	Vaginal	N/D	Yes	Stillbirth	7 Days
7	1st	28/40	No	No	Yes	SPONT	37/40	Vaginal	N/D	Yes	Stillbirth	7 Days
8	1st	32/40	No	No	Yes	SPONT	37/40	Vaginal	172	Yes	Stillbirth	1 Day

A summary of details of all pregnancies of eight females referred subsequently to The Liver Unit. A total of 13 pregnancies were affected by cholestasis of pregnancy, resulting in two normal deliveries, two premature deliveries with fetal distress (1 perinatal death), one emergency caesarean section at 38 weeks for fetal distress, and eight stillbirths occurred. *First baby of case 5 was born premature, but with no other complications. UDCA RX=ursodeoxycholic acid therapy; N/D=liver function tests not done before delivery; A/N CLINIC=antenatal clinic; N/A=not applicable; N/K=not known; SPONT=spontaneous; EMERG/ELEC C/s=emergency or elective caesarean section.

Case 2: 29 year old white woman

First pregnancy – pruritus from 35/40. Spontaneous onset of labour, at 38⁺ weeks gestation. Emergency caesarean section for fetal distress. Baby discharged alive and well. Pruritus settled within three days.

Second pregnancy – pruritus from 35/40, without jaundice. Fetal movements were normal, she was reassured, and the pregnancy was treated routinely. Serum AST was increased at 82 IU/l. Spontaneous onset of labour at term, with a stillborn baby delivered vaginally. Pruritus settled within one day.

Case 3: 30 year old white woman

First pregnancy – pruritus from 28 weeks. Spontaneous labour at 36/40, with fetal distress. The baby was transferred to special care baby unit (SCBU). The baby was discharged home, but readmitted with recurrent convulsions and died in the perinatal period.

Second pregnancy – normal.

Third pregnancy – pruritus from 32/40. Spontaneous onset of labour at 37/40, with delivery of healthy baby.

Case 4: 30 year old white woman

First pregnancy – normal.

Second pregnancy – pruritus from 30 weeks gestation. Early labour, at 36/40, with fetal distress. Baby discharged alive and well.

Third pregnancy – pruritus from 31 weeks gestation, without jaundice. The pregnancy was treated routinely. Liver function tests were not monitored and she was reassured. Spontaneous onset of labour at term, with stillborn baby. Pruritus settled within two days.

Case 5: 28 year old white woman

First pregnancy – normal pregnancy. Spontaneous labour 35/40, meconium stained liquor, baby discharged fit and well.

Second pregnancy – normal.

Third pregnancy – pruritus from 25 weeks gestation, without jaundice and liver function tests were not monitored. Fetal movements were normal and she was reassured. Onset of labour was spontaneous at 32 weeks, with a stillborn baby delivered vaginally. Pruritus settled within one day.

Case 6: a 35 year old white woman

First pregnancy – pruritus from 31 weeks, without jaundice. Fetal movements normal and the pregnancy was treated routinely. Liver function tests were not monitored. Spontaneous onset of labour at term, with a stillborn baby delivered vaginally. Pruritus settled within seven days.

Case 7: a 28 year old white woman

First pregnancy – pruritus from 28 weeks gestation, without jaundice. Liver function tests were not monitored and pregnancy was treated routinely. Spontaneous onset of labour at 37/40, with a stillborn baby delivered vaginally. Pruritus settled within seven days.

Case 8: a 27 year old white woman

First pregnancy – pruritus from 32 weeks, without jaundice. Serum AST increased at 172 IU/l, but fetal movements were normal and she was reassured. Spontaneous labour at 37 weeks gestation, with a stillborn baby delivered vaginally. Relief of pruritus occurred immediately post partum.

Cases treated with ursodeoxycholic acid

Cases 1 to 3 were each referred during pregnancy. The clinical course, effect of ursodeoxycholic acid (UDCA) therapy, and outcome of these three pregnancies is described. Because UDCA is not licensed for use in cholestasis of pregnancy fully informed patient consent was obtained before this treatment. In case 1, S-adenosyl-L-methionine was started before the

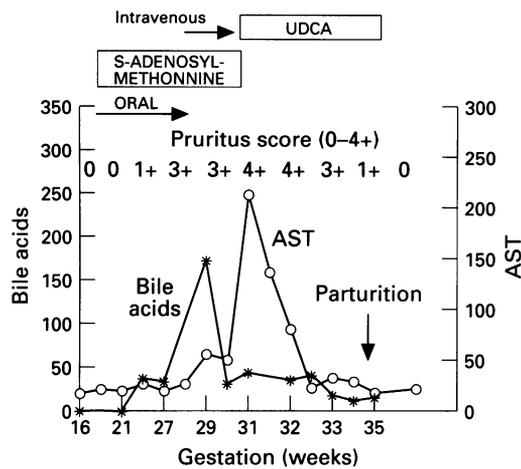


Figure 1: Clinical and biochemical parameters: case 1.

onset of symptoms in an effort to prevent cholestasis developing.

All three patients were booked to antenatal clinics at 10 weeks, while asymptomatic. Ultrasound scans at 16 weeks were normal in each.

Each received standard antenatal care. When symptoms of cholestasis developed inpatient observation was offered. Cardiotocography and Doppler ultrasound examinations of fetus and placenta were carried out weekly. In cases 1 and 2, amniocentesis was performed at 35 weeks gestation to examine the lecithin: sphingomyelin ratio, to determine evidence of fetal lung maturity, and proceed to delivery by caesarean section, if appropriate. Labour was induced in case 3 at 38/40.

Each patient kept her own record of 'pruritus score' between 0 and 4+. 0 indicated no pruritus; 1+ indicated occasional pruritus; 2+ indicated more prolonged episodes; 3+ indicated pruritus present more than absent; 4+ represented almost constant pruritus, present by day and night.

Liver function tests were measured by the hospital clinical chemistry department. Samples for serum bile acids were stored at -20°C and analysed using a commercial total serum bile acid kit, assaying 3α -hydroxy bile acids (Sigma, UK).

Case 1 received S-adenosyl-L-methionine (Ademetionine), provided in oral and intravenous formulations by Knoll Ltd (BASF group).

Cases 1 and 2 received UDCA 750 mg daily

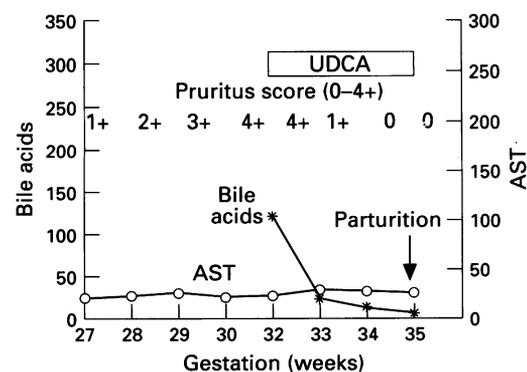


Figure 2: Clinical and biochemical parameters: case 2.

('Ursofalk', Thames Laboratories, UK). Case 3 received 1000 mg daily.

Progress

Case 1

Figure 1 is a diagrammatic representation of serum AST, pruritus score, and serum bile acids.

The first trimester was normal. S-adenosyl-L-methionine 1600 mg daily, was started orally at 16 weeks as prophylaxis, even though liver function tests and serum bile acids were normal. Dyspepsia and diarrhoea developed, so the dose was reduced to 1200 mg daily. Despite S-adenosyl-L-methionine, pruritus developed at 25 weeks gestation. Liver function tests remained normal, but serum bile acid concentrations were increased. At 29 weeks, pruritus became increasingly severe and serum AST became abnormal. Intravenous S-adenosyl-L-methionine, 1200 mg daily, was started, but AST continued to rise -213 IU/l ($<30\text{ IU/l}$) and pruritus became more troublesome. She was admitted to hospital for close monitoring. At 31 weeks, S-adenosyl-L-methionine was stopped and UDCA was started at 750 mg daily, by mouth. Symptomatic improvement occurred within days and serum AST and serum bile acids fell to normal values within two weeks of starting treatment. Fetal monitoring by cardiotocography and Doppler ultrasound was satisfactory throughout this period.

Amniocentesis confirmed fetal lung maturity at 35 weeks gestation. Delivery of a live-born male (35/40 gestation) was performed by caesarean section. The baby was nursed on SCBU for nine days. He required oxygen therapy, but not mechanical ventilation. He was discharged home at 18 days.

Case 2

Figure 2 is a diagrammatic representation of liver function tests, pruritus score, and serum bile acids.

Liver function tests were initially normal. Pruritus developed at 28 weeks gestation and became severe. She was referred as an outpatient to The Liver Unit at 33 weeks gestation. Liver function tests were only mildly deranged, but serum bile acids were greatly increased. UDCA was started orally at 750 mg daily. Pruritus completely resolved within five days of starting treatment, with return of serum bile acids to normal concentrations.

Amniocentesis was performed at 35 weeks to assess fetal lung maturity. The following day a liveborn female was delivered by caesarean section. She was nursed on SCBU for five days, requiring oxygen therapy, but not requiring assisted ventilation. She was discharged home at 10 days.

Case 3

Figure 3 is a diagrammatic representation of ALT, pruritus score, and serum bile acids.

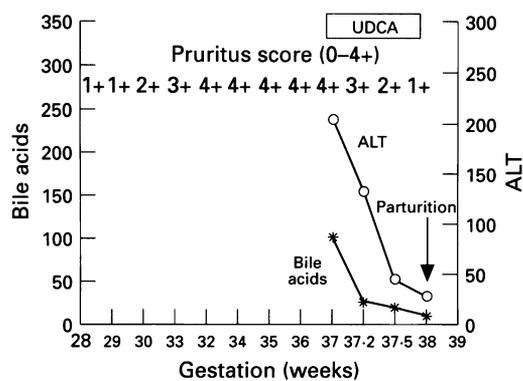


Figure 3: Clinical and biochemical parameters: case 3.

The first and second trimesters were normal. Pruritus developed at 30 weeks gestation. She was referred as an outpatient to The Liver Unit when liver function tests and serum bile acids were noted to be abnormal at 37 weeks. Treatment with UDCA was started orally at 1000 mg daily. Serum ALT rapidly returned to normal from a peak of 205 IU/l (<30 IU/l). Serum bile acids rapidly declined from a peak of 102 U/l (<8.1 U/l) and pruritus, which had been intractable for several weeks had almost disappeared by the time she was induced at 38/40. Serum bile acids responded rapidly.

A healthy female baby was delivered vaginally.

Discussion

Treatment of cholestasis of pregnancy varies widely. Despite evidence to the contrary,^{2-9 12} some obstetricians still perceive cholestasis of pregnancy as a benign condition and adopt an expectant treatment policy. We have reported eight cases who had experienced at least one previous episode of cholestasis of pregnancy and were referred to The Liver Unit within a 12 month period. All pregnancies, except one, had been treated conservatively receiving standard antenatal care, without additional fetal or maternal monitoring. All women were reassured that pruritus occurs within the spectrum of normal pregnancy and is 'nothing to worry about'. Each had experienced a stillbirth or perinatal death in association with cholestasis of pregnancy. One patient had suffered a second stillbirth and two had pregnancies complicated by fetal distress requiring immediate delivery. These were all associated with cholestasis of pregnancy.

When cholestasis of pregnancy was recognised as a clinical entity, it was considered benign.¹⁴⁻¹⁸ Subsequent reports showed a consistent pattern of increased fetal morbidity and mortality.^{2-9 12} Fifty six cases from Sydney had a perinatal death rate of 11%, spontaneous premature labour in 36%, and heavily meconium stained liquor in 27%.² A later study from the same centre showed improved results,³ after an elective policy was instituted. Despite careful fetal monitoring, the authors were unable to predict a poor outcome in those babies who died. All stillbirths were associated with meconium staining. Amniocentesis for the presence/absence of meconium was the most sensitive predictor of fetal well being.³

A study of 18 patients from Vancouver¹ recorded fetal distress in 33.3% and meconium staining in 58%. These authors,¹ and others^{3 19} recommended delivery when evidence of lung maturity has been established, although early delivery is not without morbidity. Shaw reported 59% morbidity in their intervention group.¹

Some authors report fetal prognosis to correlate with disease severity.^{2 8 20} In a prospective study of 117 patients with cholestasis of pregnancy, Laatikainen⁸ reported concentrations of serum bile acids to be a more sensitive predictor of fetal distress than standard liver function tests, so that women with highest serum bile acid concentrations should be subjected to more intensive monitoring. Even in mild or moderate cases, however, fetal risk was still noted.⁸ Biochemical markers of fetoplacental function, oestriol, and human placental lactogen, have proved ineffective at predicting fetal distress.^{21 22}

Development of the optimal treatment policy in cholestasis of pregnancy is hindered by difficulty predicting fetal outcome. The stillborn babies in the cases we report showed no evidence of dysmaturity, suggesting that chronic nutritional deficiency was not present and all but one of the fetal deaths occurred at, or beyond, 37 weeks gestation. These findings are in accordance with previous reports, in which most stillbirths occurred late in pregnancy.^{2 6 22-24} This provides a rationale for early delivery in cholestasis of pregnancy. Invasive means of monitoring may assist prognostication.³ Non-invasive measures should include regular cardiotocographs, yet these may remain normal until a very late stage, even in cases of stillbirth.⁸

Despite uncertainty as to the mechanism of cholestasis, treatment with choleric agents has been shown to be of benefit in uncontrolled and controlled trials, including S-adenosyl-L-methionine, which has been used with variable benefit,²⁵⁻²⁸ although a double blind placebo controlled study showed no benefit.²⁹ Other agents used with apparent benefit include epomediol,³⁰ dexamethasone,³¹ and UDCA.^{19 32}

We have presented the progress of three women treated with UDCA, all of whom had previous stillbirths or perinatal deaths associated with cholestasis of pregnancy. Our cases suggest UDCA provides well tolerated and effective treatment. In each case there was rapid symptomatic relief and biochemical improvement. The mechanism of action of UDCA is unknown, but its effects probably result from modification of the bile acid pool, choleresis, and a reduction of serum bile acids. While there are concerns over prescribing novel drugs during pregnancy, the start of treatment is usually delayed until the third trimester, which minimises the risk of teratogenicity. There are no reports of adverse effects upon the fetus as yet.

Because the mechanism of fetal toxicity is unknown, it cannot be assumed that resolution of clinical and biochemical derangements associated with cholestasis of pregnancy will necessarily reduce fetal morbidity, though this seems a likely further benefit.

UDCA has been of benefit in the treatment of cholestasis of pregnancy in other small series,^{19 32} but to date there are no results from controlled trials. Palma¹⁹ reported improvement of serum bile acid concentrations and pruritus in response to 1000 mg UDCA daily in eight patients. In three of eight patients, withdrawal of treatment was associated with relapse of symptoms and biochemical derangement, which settled when UDCA was reinstated. UDCA also reduces biochemical parameters of cholestasis in other cholestatic liver diseases.^{33 34}

We have reported on eight women with cholestasis of pregnancy associated with eight stillbirths, a perinatal death, and two potential 'near misses'. We suggest there is a causal relation between cholestasis of pregnancy and the stillbirths, although this cannot be proved. Cholestasis of pregnancy causes distressing symptoms and is associated with significant increases in fetal morbidity and mortality. The aim of this report is to highlight the condition, which we consider to be commonly under recognised and inappropriately treated.

Its recognition is essential if early diagnosis is to permit timely fetal surveillance and intervention. Most stillbirths occur at or just before term. Elective delivery when fetal lung maturity is established could prevent the vast majority of such fetal loss. Appropriate obstetric treatment in cholestasis of pregnancy therefore represents a potential means by which perinatal mortality can be reduced.

UDCA, in a small, uncontrolled series seems effective at improving biochemical abnormalities and symptoms. Whether this would influence morbidity and mortality associated with the condition is unknown. These biochemical and clinical end points should be measured in controlled trials.

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