Operative delivery rates following induction of labour for obstetric cholestasis

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Summary: The aim of this study was to determine whether women induced for obstetric cholestasis (OC) have increased rates of operative delivery compared with women without OC who are induced. This retrospective case-control study included 64 women with OC (singleton pregnancies), who had labour induced compared with two control groups (matched for parity and gestational week at delivery). The majority of women were induced at 37 weeks. We found no significant increase in the rate of operative or assisted delivery in OC cases compared with either control group. Women with OC who are induced between 36 and 40 weeks gestation do not have increased rates of assisted or operative delivery compared with induced controls.

Keywords: maternal–fetal medicine, physiology, gastroenterology, high-risk pregnancy

INTRODUCTION

Obstetric cholestasis (OC), also known as intrahepatic cholestasis of pregnancy, is a disorder of pregnancy characterized by maternal pruritus, raised serum bile acids and impaired liver function tests. It affects 0.7% of pregnant women in the UK.¹ For the mother the disease is usually transient and resolves rapidly following delivery, but the condition is associated with spontaneous preterm labour, meconium-stained amniotic fluid and fetal asphyxial events,^{1–6} all of which have been reported to occur more commonly in pregnancies where the maternal fasting serum bile acid levels are greater than 40 µmol/L.^{4,5,7} Unexplained intrauterine fetal death is thought to occur more commonly at later gestational weeks^{1,8,9} and as a consequence many obstetricians deliver women with OC between 37 and 38 weeks gestation.¹⁰ However, concerns over such 'active management' include the risk of failed induction and slow progress in the first or second stage of labour requiring operative delivery by caesarean section or instrumental assistance. Increased respiratory morbidity in infants delivered at 37 or 38 weeks gestation has also been reported.^{11,12} Uncertainty exists as to the clinical implications and disadvantages of a policy of 'active management' as no detailed data exist describing outcomes of induction of labour in this group.

The aims of this study were to evaluate whether women with OC, who undergo induction of labour, have different rates of assisted and operative delivery compared with women induced for other reasons.

MATERIALS AND METHODS

A retrospective case-control study was undertaken to identify women with OC and compare those who were induced with two control groups: (1) women matched for parity induced at any gestation (most commonly post-dates) and (2) women matched for gestation and parity induced for a medical complication.

Identification of OC cases

All women diagnosed as having OC with a singleton pregnancy delivered at Queen Charlotte's and Chelsea Hospital (QCCH) between 1 January 1996 and 31 May 2004 were identified using three parallel methods for triangulation: a database maintained in the obstetric medicine clinic, laboratory databases for bile acid assays and the labour ward database of all deliveries at QCCH.

Women were diagnosed as having OC if they fulfilled the criteria of a history of pruritus that resolved in the postnatal period in conjunction with raised serum bile acids. In women in whom serum bile acids were not measured (e.g. due to late gestation), women were diagnosed as having OC if they had symptomatic pruritus in association with liver transaminases above the pregnancy-specific normal reference range. Details of the first pregnancy affected by OC for each woman were

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recorded and subsequent pregnancies were excluded, along with any women concurrently suffering other disorders of pregnancy (e.g. preeclampsia). In accordance with the hospital guidelines in use during the duration of the study period, women with OC were offered active management including induction of labour at 37 weeks gestation.

Babies were defined as small for gestational age if their weight was below the 10th centile for gestation. Abnormalities in the cardiotocography (CTG) were defined as reduced variability <5 bpm, late decelerations and bradycardia (less than 100 bpm) or tachycardia (above 180 bpm). Postpartum haemorrhage was defined as >500 mL blood loss in the first 24 hours.

Identification of controls

As women with uncomplicated pregnancies are not induced at 37 weeks gestation, two alternative control groups were used as comparators. Each induced OC pregnancy was matched with two controls. The first control group comprised the next woman to deliver at QCCH, matched for parity (nulliparous or multiparous) and mode of onset of labour (i.e. induced). Controls were excluded if they had any known disorder of pregnancy (e.g. preeclampsia, gestational diabetes). They were identified using the labour ward database from which clinical information was obtained. Induction before 40 weeks is unusual where there is no medical disorder and hence this group of controls included women who had been induced for other reasons, such as pregnancy continuing after 40 weeks, advanced maternal age and spontaneous prelabour rupture of membranes.

The second control group comprised the next woman to deliver at QCCH who underwent induction of labour and who was matched for gestational week at delivery. As a consequence women in this group had been induced for medical complications such as preeclampsia, pregnancy induced hypertension and gestational diabetes.

Statistics

All data were analysed with the Mann-Whitney *U* test, χ^2 and Fisher's exact tests using SPSS for Windows, version 18 (SPSS Inc, Chicago, IL, USA). A two-tailed test has been used throughout, with a 5% significance level. The median is given with the interquartile range.

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RESULTS

Ninety-six women fulfilling the diagnostic criteria were identified. Of these, nine women had two pregnancies in the time period studied and hence for all analysis the second of these pregnancies was not included. Data on 87 women were thus available.

Obstetric cholestasis cases (*n* = 87)

The median week of onset of pruritus was 33 weeks gestation (interquartile range [IQR] 30–35 weeks). However, the earliest

case was diagnosed at 11 weeks gestation and in four pregnancies women did not develop pruritus until after 37 weeks gestation. Ursodeoxycholic acid (UDCA) was used to treat 57 (66%) women; three (3%) received dexamethasone and six (7%) women took cholestyramine. Antenatal vitamin K was given to 62 women (71%). The median highest reported level of serum bile acids, alanine aminotransferase (ALT) and aspartate aminotransferase (AST) were 36 $\mu\text{mol/L}$ (IQR 25–76 $\mu\text{mol/L}$), 155 IU/L (IQR 78–267 IU/L) and 100 IU/L (IQR 47–152 IU/L) respectively. Five women had normal AST and ALT despite raised serum bile acid levels. Of the 40 multiparous women, 21 (52%) had OC in a previous pregnancy. Four women (5%) had a history of intrauterine death; there were no stillbirths in the time period studied.

Delivery

Of 87 women with OC, 12 women underwent a prelabour caesarean section. In one case an emergency caesarean section was performed at 35 weeks gestation following an abnormal CTG noted on routine monitoring. In all other cases, there were obstetric reasons to avoid induction of labour (e.g. previous caesarean section). Eleven went into spontaneous labour (two before 36 weeks gestation).

Sixty-four women undergoing induction of labour (35 nulliparous and 29 multiparous) were matched with two controls each. Of these 64 women with OC, five were delivered at 39 weeks due to late presentation or because the bile acids did not rise until very late in the pregnancy. One woman was delivered at 40 weeks due to a late diagnosis. Indications for induction in the control groups are shown in Table 1.

After subgrouping by parity, there were no significant differences in the lengths of stage one, stage two or total length of labour, the rates of instrumental delivery or caesarean section, Apgar score at five minutes or the number of women having regional anaesthesia between OC cases and controls. The gestational week at delivery was significantly later in control group 1 ($P < 0.001$) compared with women with OC, as would be expected as this group was not matched for gestational week at delivery (in contrast to control group 2).

The birthweight of infants born to OC mothers was significantly lower compared with control group 1 (for nulliparous women $P = 0.017$ and for multiparous women $P < 0.001$) and higher than those in control group 2 for multiparous women ($P = 0.037$). There was also a trend for birthweight to be higher in the offspring of nulliparous women with OC compared with control group 2 ($P = 0.056$).

CTG abnormalities were seen more frequently in nulliparous OC cases compared with nulliparous women in control groups 1 and 2 ($P < 0.001$ and $P = 0.008$, respectively) but there was no difference in multiparous women with OC compared with controls. There was a significantly higher incidence of meconium staining ($P = 0.027$) and lower incidence of postpartum haemorrhage ($P = 0.014$) in nulliparous OC women compared with nulliparous women in control group 2 (see Table 1).

Multiparous women in control group 2 had an increased incidence of delivery of small for gestational age infants ($P = 0.003$), in keeping with a proportion of this group being induced for preeclampsia (27%) and suspected fetal growth restriction (22%). No other significant differences were seen.

Table 1 Clinical features of OC and control cases that were managed with induction of labour

	Obstetric cholestasis		Control one (matched for parity)		Control two (matched for gestation)	
	Nulliparous	Multiparous	Nulliparous	Multiparous	Nulliparous	Multiparous
Number	35	29	35	29	35	29
Gestational age at delivery (weeks)	37 (37–37)	37 (37–38)	41 (39–41)	40 (39–41)	37 (37–38)	37 (37–38)
Indication for induction	Obstetric cholestasis		Post dates (50%); prelabour ROM (23%); other* (27%)		GH (30%); preeclampsia (27%); FGR (22%); other† (21%)	
Length of 1st stage (minutes)	375 (249–540)	347 (180–585)	368 (285–540)	255 (180–440)	320 (240–540)	270 (124–429)
Length of 2nd stage (minutes)	80 (37–111)	24 (10–38)	108 (57–155)	30 (15–70)	50 (26–105)	29 (10–72)
Regional anaesthesia	31 (89%)	21 (72%)	30 (85%)	21 (72%)	35 (100%)	18 (62%)
CTG abnormality	21 (60%)	7 (24%)	4 (11%)	3 (10%)	10 (29%)	3 (10%)
Meconium staining	5 (14%)	1 (3%)	4 (11%)	2 (7%)	0 (0%)	0 (0%)
Apgar at 5 minutes	10 (9–10)	10 (9–10)	10 (9–10)	10 (9–10)	10 (9–10)	10 (9–10)
Cord arterial pH	7.26 (7.17–7.30)	7.30 (7.23–7.35)	7.24 (7.20–7.28)	7.30 (7.24–7.35)	7.29 (7.23–7.31)	7.25 (7.22–7.29)
Delivery mode						
SVD	17 (49%)	26 (90%)	16 (46%)	22 (76%)	16 (46%)	23 (80%)
AVD	12 (34%)	1 (3%)	9 (26%)	4 (14%)	7 (20%)	1 (3%)
Emergency CS	6 (17%)	2 (7%)	10 (29%)	3 (10%)	12 (34%)	5 (17%)
Birth weight (grams)	3080 (2788–3292)	3120 (2763–3383)	3350 (2960–3690)	3620 (3338–3990)	2740 (2500–3200)	2840 (2195–3215)
SGA	4 (12%)	1 (3%)	3 (9%)	0 (0%)	8 (23%)	9 (31%)

GH, gestational hypertension; CTG, cardiotocography; SVD, spontaneous vaginal delivery; AVD, assisted vaginal delivery; CS, caesarean section; SGA, small for gestational age; OC, obstetric cholestasis; ROM, rupture of membranes

All values are median (interquartile range [IQR]) or number (%)

*Other reasons for induction in control group 1 (matched for parity) were advanced maternal age, previous stillbirth, antepartum haemorrhage, social reasons and suspected fetal distress

†Other reasons in control group 2 were diabetes, polyhydramnios and rhesus disease

COMMENT

Comparison of the OC cases with both the parity-matched control group and the gestation-matched control group showed that women with OC undergoing induction of labour had comparable rates of instrumental delivery or caesarean section after induction of labour, despite increased rates of abnormal CTGs and meconium staining during labour. There were no significant differences in the length of first or second stages of labour between the three groups, with comparable rates of regional anaesthesia. Meconium staining, a feature of OC,^{1,2,4,13,14} was seen in a greater proportion of all OC cases (9%) compared with gestation-matched controls (0%) ($P = 0.025$). Notably, five of the six cases of meconium staining in the parity-matched controls were women induced for pregnancy continuing beyond 41 weeks gestation. A significant difference in the rate of CTG abnormality was noted in nulliparous women with OC compared with both control groups, consistent with previous studies.^{1,4,5,15}

The birthweight was significantly higher in the women with OC compared with the gestation-matched controls, reflecting the underlying placental insufficiency syndromes for which many of these control groups were induced. It is notable that the increased proportion of cases with meconium staining and CTG abnormality did not translate into greater operative delivery rate. These results provide encouraging data to reassure clinicians and women with OC that induction is not associated with increased rates of operative delivery compared with gestation or parity matched induced controls, particularly given concerns about the iatrogenic consequences of elective early delivery in OC.^{11,12} The operative delivery rate in this study was comparable to other studies^{13,14} and to the overall rate at QCCH (41% of nulliparous women and 12% of multiparous women induced in 2006 required caesarean section).

It is a strength of the study that considerable effort was made to identify all women with OC who met the eligibility criteria and that two groups of controls were identified. Previous

studies have commonly reported outcomes for OC cases only. We believe that we have chosen control groups that allow comparison of the rates of clinically important endpoints, e.g. duration of labour and mode of delivery, to be evaluated in the context of the gestational week at delivery and the presence of maternal disease.

Previous studies have reported similar rates of meconium staining.^{1,2,4,15–17} The additional use of prelabour amniocentesis² and amnioscopy¹⁵ by some investigators is unlikely to have increased the detection rate as meconium staining becomes apparent at whatever point the membranes rupture prior to birth.

There are currently no data available from adequately powered studies to ascertain whether UDCA treatment decreases the rates of preterm labour, meconium staining or CTG abnormalities. However, a large prospective study showed that maternal fasting serum bile acids of greater than 40 mol/L are associated with these complications.⁴ Given that most women with bile acid levels above 40 μ mol/L respond to UDCA,^{4,18} it is feasible that the rates of fetal complications were lower in women who received this treatment. However, this study was not large enough to establish whether this is the case. A pilot study to address this issue, the PITCH study, is currently underway in the UK.¹⁹

In summary the data presented in this study are encouraging as they show that women with OC who have labour induced before 40 weeks gestation do not have increased rates of instrumental or operative delivery compared with women induced without OC. In addition they do not have higher rates of adverse outcomes related to delivery than controls.

DECLARATIONS

Competing interests: CW, FC, FP are all employees of Imperial College London or of the Imperial College Healthcare NHS Trust (ICHNT). JW was an employee of ICHNT when the manuscript

was submitted. LC is an employee of Kings College London, AB is an employee of Queens Medical Centre, Nottingham and NL is an employee of Northwick Park NHS Trust.

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