

Intrahepatic Cholestasis of Pregnancy in Women With a Multiple Pregnancy: An Analysis of Risks and Pregnancy Outcomes

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Abstract

Objective: This study was conducted to assess the incidence and perinatal outcomes of multiple pregnancies complicated by intrahepatic cholestasis of pregnancy in an urban population.

Methods: We performed a retrospective chart review of all multiple gestation deliveries at our institution between January 2004 and December 2005. Antepartum and delivery data were collected for all patients. Symptoms and treatment were also abstracted for patients in whom intrahepatic cholestasis was diagnosed. We used the Student two-tail *t* test and Fisher exact test to examine the differences between multiple gestation pregnancies with and without cholestasis of pregnancy.

Results: Data were available for 263 multiple pregnancies. The incidence of cholestasis was 4.2% (11/263), with a mean onset at 29.4 weeks. There were no differences in mean gestational age at delivery, preterm delivery rate, meconium histiocytosis, incidence of preeclampsia, or incidence of postpartum hemorrhage between women with and those without cholestasis. There were no intrauterine fetal deaths in the cholestasis group.

Conclusion: Women with multiple gestations complicated by cholestasis of pregnancy do not have increased adverse perinatal outcomes. The absence of unexplained fetal demise may be a result of routine delivery before 40 weeks' gestation in multiple pregnancies.

Résumé

Objectif : Cette étude a été menée pour évaluer l'incidence et les issues périnatales des grossesses multiples compliquées par une cholestase intrahépatique de la grossesse au sein d'une population urbaine.

Méthodes : Nous avons mené une analyse de dossiers rétrospective portant sur tous les accouchements de grossesse multiple s'étant produits au sein de notre établissement entre janvier 2004 et décembre 2005. Des données sur la période antepartum et

l'accouchement ont été recueillies pour toutes les patientes. Les symptômes et la prise en charge ont également fait l'objet d'un résumé pour ce qui est des patientes chez lesquelles une cholestase intrahépatique avait été diagnostiquée. Nous avons utilisé le test de Student bilatéral et la méthode exacte de Fisher pour examiner les différences entre les grossesses multiples présentant une cholestase de la grossesse et celles qui n'en présentaient pas.

Résultats : Des données étaient disponibles pour ce qui est de 263 grossesses multiples. L'incidence de la cholestase était de 4,2 % (11/263); son moment d'apparition moyen était de 29,4 semaines. Aucune différence en matière d'âge gestationnel moyen au moment de l'accouchement, de taux d'accouchement préterme, d'histiocytose associée au méconium, d'incidence de la prééclampsie ou d'incidence de l'hémorragie postpartum n'a été constatée entre les femmes présentant une cholestase et celles qui n'en présentaient pas. Aucun décès foetal intra-utérin n'a été constaté dans le groupe « cholestase ».

Conclusion : Les femmes présentant une grossesse multiple compliquée par une cholestase de la grossesse ne connaissent pas des issues périnatales indésirables accrues. Il est possible que l'absence de décès foetal inexpliqué soit attribuable à la tenue systématique de l'accouchement avant la 40^e semaine de gestation dans le cas des grossesses multiples.

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INTRODUCTION

Intrahepatic cholestasis of pregnancy is the most common liver disease presenting during pregnancy.¹ It is largely a benign maternal condition; however, maternal morbidities include intense pruritus with subsequent sleep deprivation. Serious fetal effects have been reported, including an increased incidence of preterm delivery, meconium staining of amniotic fluid, non-reassuring fetal status requiring delivery, postpartum hemorrhage, and late intrauterine fetal demise.¹⁻⁴

The incidence of intrahepatic cholestasis of pregnancy varies by population. In Canada the incidence of affected

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pregnancies is approximately 0.1%,⁵ and in Europe it ranges from 0.1% to 1.5%.⁶ The highest incidence in the world is in Chile and Bolivia, where the incidence is reported to be as high as 27% in the Arucanean Indian population.⁷ The incidence of intrahepatic cholestasis of pregnancy in multiethnic populations is influenced by risk factors such as ancestry (especially Arucanean Indian), family history, personal history of hepatitis C infection, a previously affected pregnancy, and multiple gestation.⁸

The use of assisted reproductive technologies has increased the incidence of multiple gestations dramatically, and this will likely increase further.⁹ The presence of multiple gestations has been identified as a risk factor for the development of intrahepatic cholestasis of pregnancy,^{3,10-12} with reported rates that range from 9.5%¹² to 20.9%¹¹; however, little is known about the outcomes of these pregnancies. Women with multiple gestations are at increased risk of both maternal and fetal complications such as preterm delivery, fetal growth disorders, IUFD, preeclampsia, and postpartum hemorrhage.¹³ Whether these complications are affected or compounded by the presence of intrahepatic cholestasis of pregnancy is unknown. Like other tertiary care centres, our hospital provides care to a large cohort of multiples through a specialized multiples clinic. The purpose of this study was to determine the incidence of intrahepatic cholestasis of pregnancy in multiple pregnancies in our population. In addition, we sought to determine the antepartum course and pregnancy outcomes in the cases we identified.

MATERIALS AND METHODS

We conducted a chart review of all consecutive patients with multiple gestation who delivered at Sunnybrook Health Sciences Centre, Toronto, Ontario between January 1, 2004, and December 31, 2005. No patients were excluded from the study.

Patients with multiple gestations are referred to the multiples clinic from surrounding hospitals for either consultation or continuing antepartum management and delivery. Only patients who were initially followed or whose care was transferred to our centre were included in this review. Patients with multiple gestations had antepartum care provided by the maternal fetal medicine specialist who directs

the multiples clinic, either alone or in conjunction with another obstetrician working on site. All patients underwent routine ultrasound examinations (beginning at 16 weeks' gestation) every two weeks in the case of monochorionic twins or every four weeks in the case of dichorionic twins. Triplets and monoamniotic twins were scanned more frequently. If any complications occurred during the pregnancy, such as threatened preterm labour or poor fetal growth, the frequency of ultrasound examinations increased according to the judgement of the individual clinician. This included cases in which cholestasis was diagnosed. All patients with a twin pregnancy were delivered by 38 weeks of gestation and those with triplets by 36 weeks of gestation. Monoamniotic twin deliveries were planned by the maternal fetal medicine specialist on a case-by-case basis.

A clinical diagnosis of intrahepatic cholestasis of pregnancy was made if a patient was symptomatic with unrelenting generalized pruritus causing sleep disruption, in the absence of any skin rash or systemic illness. Additional investigations were often performed to confirm the clinical diagnosis, and included measuring total serum bile acids and liver enzymes (aspartate transaminase, alanine transaminase, and ALP). The level of ALP was measured routinely when liver enzyme measurements were performed. No differentiation was made between hepatic and placental sources of ALP. At the discretion of the caregiver, some patients had additional tests, such as hepatitis C screening and an abdominal ultrasound.

The treatment was determined by the attending physician. If a patient developed IHCP, she was managed by the attending obstetrician or maternal fetal medicine specialist, frequently in consultation with an obstetrical medicine specialist (i.e., an internist with a subspecialty interest in obstetrics).

Data collected from the antepartum maternal charts included the development of preeclampsia (defined as blood pressure >140/90 mmHg on two occasions at least six hours apart and at least 1+ proteinuria), HELLP syndrome, fetal growth disorders (i.e., discordant fetal growth or fetal growth restriction <10th centile in either baby), and IUFD. If IHCP was diagnosed, the gestational age at the onset of symptoms, how the diagnosis was made (clinical, biochemical, or both), results of laboratory investigations, and choice of therapy were recorded.

Hospital charts were reviewed to determine the indication for delivery and the gestational age at delivery (preterm delivery was defined as delivery at < 36 weeks of gestation). The development of adverse outcomes associated with IHCP, such as postpartum hemorrhage (defined as estimated blood loss > 500 cc at a vaginal delivery, and

ABBREVIATIONS

ALP	alkaline phosphatase
HELLP	hemolysis, elevated liver enzymes, low platelets
IHCP	intrahepatic cholestasis of pregnancy
IUFD	intrauterine fetal demise

Table 1. Maternal age and gestation at delivery in women with multiple gestation with and without IHCP

Maternal demographics	Patients without IHCP	Patients with IHCP
Number	252	11
Mean maternal age at delivery in years (\pm SD)	33.8 \pm 5.1	36.5 \pm 4.9
Mean Gestational age at delivery (in weeks (\pm SD))	34.1 \pm 4.2	34.7 \pm 1.8

There is no statistically significant difference between these two groups.

> 1000 cc at a Caesarean section) and meconium staining of amniotic fluid were also recorded. Meconium staining of amniotic fluid was considered significant if there was evidence of meconium histiocytosis on histologic examination of the placenta, because this indicates that meconium was present for at least three hours.¹⁴

Comparisons between means were made using the Student two-tail *t* test for unpaired data. To test differences between proportions, the Fisher exact test was used. Statistical significance was accepted at the 5% level.

The study was approved by the Research Ethics Board of Sunnybrook Health Sciences Centre.

RESULTS

Within the two-year study period, 272 consecutive multiple pregnancies were identified. Complete data were available for 263/272 pregnancies (96.7%); of these, there were 18 triplet pregnancies, four monochorionic monoamniotic twin pregnancies, 37 monochorionic diamniotic twin pregnancies, and 204 dichorionic diamniotic twin pregnancies.

Maternal demographic data are presented in Table 1. There was no difference in the mean maternal age or mean gestational age at delivery between patients with pregnancy cholestasis (34.7 \pm 1.8 weeks) and those without pregnancy cholestasis (34.1 \pm 4.2, *P* = 0.63). Ethnicity was recorded for only 45% of patients; hence subgroup analysis on the incidence of pregnancy cholestasis within different ethnic groups was not possible.

Eleven patients were given a diagnosis of pregnancy cholestasis. Their antepartum course and pregnancy outcomes are shown in Table 2. In nine patients, the diagnosis was made on the basis of symptomatic pruritus and elevated serum bile acids (defined as > 8.2 μ mol/L), and in two patients the diagnosis was based on symptoms alone. The resulting incidence of pregnancy cholestasis in our cohort was 4.2% (11/263; 95% CI 2.4–7.4). The mean gestational age at which the diagnosis of pregnancy cholestasis was made was 29.4 \pm 4.6 weeks (range 20–34 weeks).

All patients were hepatitis B surface antigen negative. Three patients were tested for the presence of hepatitis C

antibodies, and all tests were negative. Seven patients had an abdominal ultrasound; six of these showed normal results, and the seventh showed non-obstructive cholelithiasis. The use of additional testing reflects the variability in management of pregnancies complicated by cholestasis. Eight patients were treated with medications (Table 2). Five patients initially received antihistamines (either hydroxyzine, diphenhydramine, or both), and ursodeoxycholic acid was added later in one patient. The remaining three patients were immediately given ursodeoxycholic acid, some in addition to antihistamines. The reasons for the choice of medication were not specifically recorded in the charts. A total of five patients received ursodeoxycholic acid. Three out of five patients with serial measurements of bile acids in serum while on ursodeoxycholic acid had an increase in the level of bile acids. In pregnancies affected by cholestasis, the indication for delivery was preterm labour (3 patients), preeclampsia (1 patient), discordant growth (1 patient), symptomatic cholestasis (2 patients), or being at term (4 patients).

Placental pathology was available in all cases. There was no pathologic diagnosis in eight cases. One case showed acute vasculitis and acute chorioamnionitis, one case showed an intervillous infarct, and in only one case was there evidence of meconium histiocytosis in the membranes (a dichorionic diamniotic twin pregnancy in a patient with serum bile acids of 90.6 μ mol/L one week prior to delivery).

The chief maternal and fetal complications are presented in Table 3. There were no significant differences in the incidence of complications between women with and without IHCP. In the two patients with IHCP who had a postpartum hemorrhage, one had a triplet pregnancy and the other had a dichorionic diamniotic twin pregnancy; both were delivered by Caesarean section. Of note, estimated blood loss was not recorded in 32 of the 263 patients (12%).

In the patients who had IUFD, only one of the fetuses died in each twin pair; three occurred in monochorionic diamniotic twins, and five occurred in dichorionic diamniotic twins. None of the patients with IHCP experienced a fetal demise.

Table 2. Antepartum course and pregnancy outcome of women with intrahepatic cholestasis of pregnancy

Patient	Gestational age at diagnosis (weeks)	Bile acids at diagnosis ($\mu\text{mol/L}$)	Maximum serum bile acid level ($\mu\text{mol/L}$)	Medication and gestational age at start of therapy	Gestational age at delivery (weeks)	Indication for delivery	Postpartum hemorrhage
Patient no. 1 DC/DA	20	25.4	25.4	Diphenhydramine @ 20 weeks Ursodeoxycholic acid @ 24 weeks	34	Preterm labour	No
Patient no. 2 DC/DA	33	58.7	58.7	Hydroxizine @ 33 weeks	33+4	Preterm labour	No
Patient no. 3 DC/DA	31	69.8	69.8	Hydroxizine post-partum	36+1	Term twins	2500 mL
Patient no. 4 MC/DA	34	33	33	None	34+5	Discordant growth	1200 mL
Patient no. 5 DC/DA	25	29.8	90.62 @ 33 weeks	Diphenhydramine @ 25 weeks Hydroxizine @ 27 weeks Ursodeoxycholic acid @ 30 weeks	34+1	IHCP	No
Patient no. 6 DC/DA	33+2	41.6	41.6	None	34+2	Preeclampsia	No
Patient no. 7 Triplets	30	12.4	15.4 @ 31 weeks	Ursodeoxycholic acid @ 31 weeks	35+4	Term triplets	3000 mL
Patient no. 8 DC/DA	34	Not done		None	37+4	Term twins	No
Patient no. 9 DC/DA	28	67.5	67.5	Ursodeoxycholic acid @ 28 weeks	34+5	IHCP	No
Patient no. 10 DC/DA	32	Not done		Hydroxizine @ 34 weeks	36+3	Term twins	No
Patient no. 11 DC/DA	25	13.6	53.6 @ 28 weeks	Ursodeoxycholic acid and Hydroxizine @ 25 weeks	30+5	PPROM/ preterm labour	No

Laboratory results normal range: bile acids < 8.2 $\mu\text{mol/L}$

DC/DA: dichorionic diamniotic twins; MC/DA: monchorionic diamniotic twins; PPROM: preterm premature rupture of membranes.

DISCUSSION

Although the number of patients is relatively small, our study is one of the largest recent studies assessing the incidence of IHCP specifically in a cohort of pregnant women with multiple gestations. Our findings are consistent with recently published data in which the incidence of pregnancy cholestasis in multiple gestations is reported to be 3.2%.³ In our study, there were no differences in maternal and fetal outcomes between patients with IHCP and those without.

The diagnosis of IHCP is usually based on clinical symptoms, as well as on elevated serum bile acids. The likely mechanism of bile acid elevation relates to hepatic dysfunction that results in an alteration of the metabolism of bile acids, leading to elevated serum levels.^{6,15} This is probably a result of a combination of hormonal factors (elevated levels of estrogen and progesterone due to pregnancy) interacting

with genetic and environmental factors.^{6,8,16} Bile acids may cause pruritus by depositing on nerve endings in the skin, or by accumulating in the hepatocyte, causing the release of some pruritogenic material.^{15,17,18} It is also possible that the elevation in bile acids is simply a marker of hepatic dysfunction, resulting in abnormal clearance of other toxic substrates.¹⁹ It has recently been reported that adverse perinatal outcomes, such as preterm labour and meconium staining, are related to bile acid levels, especially if greater than 40 $\mu\text{mol/L}$.¹⁰

In our study population, six out of nine patients who had serum bile acids measured had levels that were > 40 $\mu\text{mol/L}$. In accordance with Glantz et al.,¹⁰ we chose this level of bile acids to define severe cholestasis of pregnancy. Most patients in whom bile acids were measured had an adverse perinatal outcome. One patient with elevated bile acids was

Table 3. Maternal and fetal complications in patients with and without IHCP

Complications	Patients without IHCP	Patients with IHCP
Maternal Complications		
Preeclampsia/HELLP	17	1
Postpartum hemorrhage	29	3
Fetal Complications		
Preterm labour (< 36 weeks)	98/252 (39%)	3/11 (27%)
IUFD	8	0
Histologic evidence of meconium staining	2	1

delivered at 34 weeks' gestation and was found to have meconium histiocytosis on placental pathology. It is well known that multiple pregnancies are also at increased risk of preterm labour, preeclampsia and postpartum hemorrhage.²⁰ Whether the additional diagnosis of cholestasis in these pregnancies increases the risk of those events is the important question. Unfortunately, this will be difficult to elucidate because of the small absolute number of reported multiples with cholestasis.

The most serious risk reported with pregnancy cholestasis is IUFD. Suggested mechanisms of IUFD include direct fetal toxicity of bile acids through altered colonic motility²¹ and adverse effects on cardiac contractility, resulting in fetal demise.²² Recent guidelines published by the Royal College of Obstetricians and Gynaecologists suggest that the risk of fetal demise is comparable to that of the general population.²³

Although it is impossible to draw significant conclusions with such a rare outcome, our data show no difference in the incidence of fetal demise between those with cholestasis and those without. In addition, there were no cases of fetal demise in the group with cholestasis. The design of larger studies to further investigate this outcome should take into consideration the fact that, in general, multiple pregnancies are routinely delivered by 38 weeks' gestation because of the increase in morbidity and mortality after this gestation.^{13,24} If cholestasis contributes to the risk of IUFD at gestational ages > 38 weeks, then this outcome will rarely be observed since patients will have been delivered by that time regardless of the additional diagnosis of cholestasis.

Other issues regarding antepartum management in patients with pregnancy cholestasis in singleton pregnancies include fetal surveillance, induction of labour at 37–38 weeks, and treatment with ursodeoxycholic acid. There is no consensus on what, if any, increase in fetal surveillance there should be in singleton pregnancies affected with cholestasis. Increasing surveillance because of the diagnosis of pregnancy cholestasis alone has never been proven to improve

outcome in singletons.²³ In multiple pregnancies, there is an increase in fetal surveillance because of the maternal and fetal risks inherent to the condition of multiple gestation. What, if any, additional antenatal testing should be instituted due to a diagnosis of cholestasis is yet to be determined. Finally, delivery planning for singleton pregnancies with pregnancy cholestasis often includes induction of labour at 37–38 weeks.^{1,2} In women with multiple pregnancies who are routinely managed in this way, the additional diagnosis of pregnancy cholestasis may be an indication for earlier intervention, but this has yet to be investigated.

We initiated treatment for pregnancy cholestasis in our patients who were severely symptomatic. Ursodeoxycholic acid is commonly prescribed to decrease symptomatic pruritus.²⁵ This medication is used in order to bring down the serum level of bile acids and alleviate symptoms, as well as to possibly decrease the risk of adverse obstetrical events.²⁶ In our cohort, we found that symptomatic relief was obtained, but ursodeoxycholic acid had a minimal effect on the levels of bile acids or liver enzymes. It is conceivable that a larger dose is required for patients carrying multiple pregnancies, as the volume of distribution is greater, but more study is needed. Whether the use of ursodeoxycholic acid decreases the risk of adverse obstetric events requires further study in a much larger population.

CONCLUSION

The incidence of IHCP in patients with multiple gestations in our cohort was 4.2 %. This is 42 times higher than the reported incidence in Canadian women with a singleton pregnancy. We cannot accurately determine the risk of adverse fetal events among these patients, although the risk is likely low. Clinicians who manage multiple pregnancies should be aware of the increased incidence of IHCP in this population. Our study did not show any difference in adverse maternal and fetal outcomes in those with or without pregnancy cholestasis but is consistent with reports that

patients with elevated bile acids > 40 $\mu\text{mol/L}$ experience adverse outcomes. Since the adverse outcomes are common to both multiple pregnancies and reported outcomes in cholestasis-affected singleton pregnancies, it is impossible to determine whether the adverse outcome is due to pregnancy cholestasis, multiple gestation, or their combination. Clearly, additional study into this area is necessary to answer these questions.

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