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MATERNAL-FETAL MEDICINE

Usefulness of fetal monitoring in intrahepatic cholestasis of pregnancy: a prospective study

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Abstract
Aim To study the role of fetal surveillance in intrahepatic cholestasis of pregnancy.
Materials and methods A total of 69 women with obstetric cholestasis were included. Fetal surveillance began at 34 weeks or later at diagnosis and included daily maternal record of fetal movements, biophysical profile (i.e., non-stress test, amniotic fluid volume assessment using the four quadrant amniotic fluid index), and Doppler flow velocimetry. Fetal monitoring was done weekly before 36 weeks and biweekly after that.
Results There were no abnormal non-stress test readings and all pregnancies had good biophysical profile. One hundred and sixty Doppler measurements [Systolic–Diastolic (S/D ratio) and Pourcelot index (PR)] were taken from 67 patients at scheduled intervals during the study period. Findings were compared to gestation matched reference values of Doppler flow velocities of umbilical artery of normal pregnant population. Fifty-six out of 160 PR indices and 33 out of 162 S/D ratio readings were above 2 SD and these results were found to be statistically significant. However, there was no significant correlation with the serum levels of alanine transaminase ($r = -0.071$) or with aspartate transaminase ($r = 0.058$). Further, there was no correlation of Doppler with rates of preterm delivery or meconium-stained liquor.
Conclusion Doppler investigation of the umbilical artery might be of some value in recognition of the specific risk of fetal compromise in pregnancies complicated by intrahepatic cholestasis.

Keywords Intrahepatic cholestasis of pregnancy · Doppler flow velocimetry · Antepartum fetal surveillance · Fetal monitoring

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Introduction

Intrahepatic cholestasis of pregnancy (ICP) is a liver disease of as yet undefined etiology and pathogenesis. From the maternal viewpoint, it is essentially benign. In contrast, ICP is a condition with possible lethal outcome for the unborn child if not handled with care [1].

At present, it is not possible to predict which pregnancies are at the risk of fetal complications due to obstetric cholestasis. Cardiotocograph monitoring is not always helpful and intrauterine fetal deaths (IUFD) have been reported in pregnancies with normal cardiotocograms in the preceding 24 h [2]. Results of a study using the fetal biophysical profile were not conclusive, mainly because of the absence of fetal mortality and morbidity in that series [3].

Doppler flow analysis is a useful clinical tool for antepartum fetal surveillance of pregnancies at risk of fetal compromise. When the fetus is distressed one may also find pathological waveforms. The risk of fetal death in ICP is related to the elevated maternal serum concentration of bile

acids. As there is no exact knowledge of mechanism of toxicity, one might speculate whether the serum level of bile acids has an influence on umbilical circulation and whether the severity of maternal disease correlates with the Doppler flow velocity waveform. This study was undertaken to evaluate different fetal surveillance techniques for monitoring in such pregnancies.

Materials and methods

This prospective study was conducted in the Departments of Obstetrics and Gynecology, Hepatology and Biochemistry, Postgraduate Institute of Medical Education and Research, Chandigarh. Over a 15-month period (Jan 2007–March 2008) a total of 69 women with obstetric cholestasis were included. Verbal and written consent were taken from all women before participating in the research. Ethical committee approval was obtained. Diagnosis was based on generalized persistent pruritus in association with abnormal liver function tests in pregnant women during the third trimester (32–36 weeks). A medical history including pruritus in previous pregnancy, outcome of prior pregnancies, skin disorders, liver/gall-bladder disorders, and use of oral contraceptives was taken. The clinical diagnosis was confirmed by raised transaminases [alanine transaminase (ALT)/aspartate transaminase (AST)] [4, 5]. The upper end of the normal range for transaminases was taken as 40 IU/L and any values above this were considered abnormal. On detection of abnormal liver function, viral markers were done and a liver ultrasound was performed. Obstetric cholestasis was excluded on findings of gallstones or biliary obstruction on liver ultrasound and evidence of acute infection with hepatitis A, B, C or E on serology. Once identified, women were consecutively enrolled in the study. Multiple pregnancies were excluded to eliminate confounding factors. All women with preeclampsia were excluded because a hypertensive disorder is likely to have a greater influence on the course of pregnancy than the pregnancy associated liver disorder. Fetal surveillance began at 34 weeks or later at diagnosis and included daily maternal record of fetal movements, biophysical profile [i.e., non-stress test (NST), amniotic fluid volume assessment using the four quadrant amniotic fluid index (AFI)], and Doppler flow velocimetry to monitor fetal well-being. Fetal monitoring was conducted weekly before 36 weeks and twice a week after that. Participants who did not attend the scheduled visits or who did not return for delivery at the stipulated time were considered as 'lost to follow-up'. These women were excluded from analysis of outcome of present pregnancy; however, data regarding patient's history was used for statistical calculations. A combined real time pulsed wave Doppler ultrasound machine (ATL HDI 1500) with a 3.5 MHz convex sector transducer was used. Biophysical profile was calculated using Manning score. Doppler flow analysis was conducted by a single operator (senior gynecologist) with substantial experience of ultrasonography. For Doppler, all patients were examined in a semi-recumbent position. Umbilical artery velocity waveforms were obtained transabdominally. Real time ultrasonography was performed first to ascertain that the fetus is in a resting- and non-breathing-state and to identify the umbilical artery. Under real time control, peak systolic (A) and end diastolic (B) velocities of 2–3 cardiac cycles were measured by electronic calipers and the Pourcelot index (PR) [$PR = (A-B)/A$] was calculated [6]. The procedure was carried out at two different locations along the umbilical cord but avoiding the cord near the placenta and near the abdominal wall. The mean value of the two readings was used for analysis.

All patients in our study received treatment with ursodeoxycholic acid (300 mg twice daily). In patients with severe symptoms, the dose was further increased to 900 mg to a maximum of 1,500 mg/day.

Statistical analysis

Data were analyzed using the statistical package SPSS for Windows 16.0 (SPSS, Chicago, IL, USA). Correlation between Doppler measurements [PR index and Systolic–Diastolic (S/D ratio)] and a number of biochemical measurements was analyzed using linear regression. Student's two-tailed *t* test was used for comparison of two means.

Results

A total of 69 women, were recruited for this study. Of these, 67 completed the study and 2 were lost to follow-up. Table 1 shows the demographic characteristics of the study population. The mean age of the women was 27.55 ± 4.317 years (range 20–37 years).

Majority of the women under study were nulliparous (43/69) while 26/69 were multiparous. Recurrent cholestasis was observed in 17/26 patients (65.38 %) while 6/26 women gave history of a previous preterm delivery. The median gestation at the onset of pruritus as recalled by women at their first interviews was 31 weeks (range 18–36 weeks) while the median gestation at diagnosis of obstetric cholestasis was 35 weeks (range 23–36 weeks). The mean serum AST level at diagnosis was 145.90 ± 102.66 IU/L (range 32–518 IU/L); serum ALT was 165.64 ± 116.4 IU/L (range 36–511 IU/L). Only two patients out of 67 reported decreased fetal movements. Both these patients presented with meconium-stained liquor at delivery.

Table 1 Demographic characteristics

Parameter	Mean ± SD	Minimum	Maximum
Age (years)	27.55 ± 4.317	20	37
Gestation at pruritus (weeks)	31	18	36
Gestation at diagnosis (weeks)	35	23	36
ALT (IU/L)	165.64 ± 116.4	36	511
AST (IU/L)	145.90 ± 102.66	32	518
TSB (mg/dL)	0.7[a]	0.4	3.4
		$n = 69$	

SD standard deviation

[a] Median

CTG surveillance of the fetuses was performed at scheduled checkups on 325 occasions. No CTG abnormalities requiring immediate operative delivery were observed. Biophysical profile done for fetal surveillance was good and did not show any abnormal results. Oligohydramnios defined as AFI <5 cm was noticed in 3/67 patients. However, this decrease in liquor did not lead to fetal asphyxia or poor biophysical profile and thus, did not correlate to fetal outcome. Table 2 represents comparative analysis of different surveillance techniques in relation to meconium-stained liquor.

One hundred and sixty Doppler readings were taken from 67 patients at scheduled intervals during the study period. Results of Doppler flow analysis in patients with obstetric cholestasis are shown in Figs. 1 and 2. In Fig. 1 the PR indices of the umbilical artery velocity waveforms are plotted. Table 3 demonstrates the frequency of abnormal PR index values at different weeks of gestation. Ten out of 31 readings taken at 35 weeks were above the 95th centile for that gestation. Similarly, 42.1 % of readings taken at 35–36 weeks and 39.5 % of values taken at 36–37 weeks were above the reference range [7].

The S/D ratio at different weeks of gestation is plotted in Fig. 2. The highest value was 6.8 and the lowest value was 1.3. Absent end diastolic flow was seen in 2/67 of patients. There was no significant correlation with the serum levels of ALT, AST or ALP. In three pregnancies affected by intrahepatic cholestasis, umbilical venous pulsations were noticed. These pregnancies were induced prior to their scheduled time of delivery. Table 4 demonstrates the frequency of abnormal systolic–diastolic ratios at different weeks of gestation. Seven out of 34 readings taken at 35 weeks were above the 95th centile for that gestation. Similarly, 27 % of the readings taken at 35–36 weeks and 22.7 % of values taken at 36–37 weeks were above the reference range [8]. These findings of abnormal Doppler were statistically significant. There was neither significant correlation with the serum levels of ALT ($r = -0.071$) nor with AST ($r = 0.058$) as demonstrated by Fig. 3, where 'r' is the correlation coefficient. Further, there was no correlation of Doppler with rates of spontaneous preterm delivery or meconium-stained liquor.

Table 2 Comparative analysis of different surveillance techniques

Method	No. of abnormal results (%)	MSL
Fetal movement	2 (2.9 %)	2 (100 %)
Non-stress test	0	0
Oligohydramnios (<5 cm)	3 (4.5 %)	0
Biophysical profile	0	0
Venous pulsations	3 (4.5 %)	0
AEDF	2 (2.9 %)	0
	$n = 67$	

Fetal complication rates

No episode of fetal asphyxia or bradycardia was observed. The overall rate of meconium passage was 7.46 % (5/67). There was no case of meconium aspiration syndrome. The median Apgar score was 8 at 1 min and 9 at 5 min. None of the newborns had Apgar score less than 7 at 5 min.

Discussion

Obstetric cholestasis or intrahepatic cholestasis of pregnancy is a reversible form of cholestasis that appears during the second half of pregnancy and persists until delivery. Maternal prognosis is excellent and the symptoms i.e., intractable pruritus and serum abnormalities resolve rapidly postpartum [1]. However, it entails an increased risk to the fetus. Various strategies have been proposed to improve obstetric outcome. Nevertheless, in several studies, the investigators have concluded that fetal death in ICP may not be predictable by traditional antepartum surveillance, and that delivery after establishment of fetal lung maturity may reduce fetal mortality rate [9]. Obstetric management consists of weighing the risk of premature delivery against the risk of sudden death in utero. To allow term delivery (≥37 weeks) in patients with ICP, it appears essential to ascertain early prognostic markers for poor fetal outcome. This study was designed to determine whether the adverse outcome previously reported in patients with cholestasis of pregnancy could be predicted by antenatal fetal surveillance.

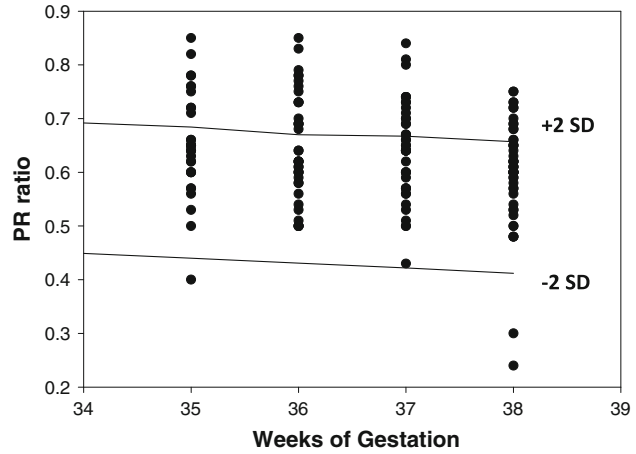

Fig. 1 Umbilical artery PR index against normal distribution

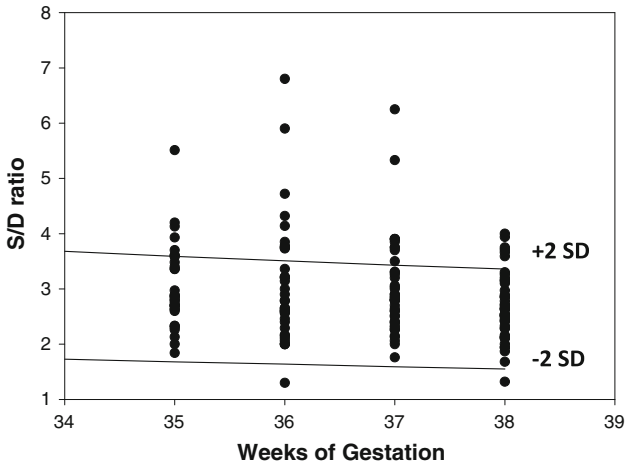

Fig. 2 Umbilical artery S/D ratio against normal distribution

In our study, there were no abnormal non-stress test readings and all pregnancies had good biophysical profile. These results were consistent with the previous studies which reported normal NST even in complicated obstetric cholestasis pregnancies [2, 10, 11]. Even in the series where patients with ICP were hospitalized and underwent daily fetal monitoring, cases of stillbirth with reassuring fetal testing as recently as 7 h before fetal death were reported [2]. Glantz et al. [11] in their large observational study had performed CTG surveillance on 1,479 occasions. All but two cases had normal NSTs at delivery. In the study by Alsulyman et al. [2], six abnormal antepartum test results were seen with two requiring immediate operative delivery. However, in a recent study [12], an immediate cesarean delivery was prompted in three cases by the presence of non-reassuring non-stress tests. It is difficult to comment whether pregnancies with poor perinatal outcome would have shown similar results. Traditional fetal testing, thus, might be considered to have a modest ability to predict some cases of fetal compromise associated with obstetric cholestasis. In only 3/67 pregnancies oligohydramnios was noted. This decrease in liquor was not related to intrauterine growth restriction (IUGR) or poor biophysical profile and thus cannot be related to a chronic disease process. This was similar to the study by Alsulyman et al. [2] where oligohydramnios was noticed in 4/79 pregnancies with obstetric cholestasis.

Doppler velocimetry of the umbilical artery in normal pregnancies has revealed that there is considerable variation in values of PR index and S/D ratio at different weeks of gestation. It has been shown that the S/D ratio and the PR index decrease with advancing gestation [7]. Upper limit of normal (95th centile) of the Doppler values at a particular gestation were, therefore, used as reference values [7, 8]. In our study, the mean PR index was 0.65 at

Table 3 PR indices at different weeks of gestation

Pourcelot ratio at (weeks)	Mean ± SD	95th centile	Abnormal value (no. of readings)	*p* value
34–35	0.654 ± 0.09	0.684	10/31 (32.3 %)	0.005
35^{+1}–36	0.646 ± 0.09	0.675	16/38 (42.1 %)	0.168
36^{+1}–37	0.643 ± 0.08	0.667	17/43 (39.5 %)	0.05
37^{+1}–38	0.599 ± 0.10	0.657	13/48 (27.1 %)	0.001
			$n = 160$	

Table 4 S/D ratio at different weeks of gestation

Systolic–diastolic ratio (weeks)	Mean ± SD	95th centile	Abnormal value (no. of readings)	*p* value
34–35	3.02 ± 0.74	3.59	7/34 (20.65 %)	0.001
35^{+1}–36	3.07 ± 1.1	3.51	10/37 (27 %)	0.001
36^{+1}–37	2.99 ± 0.84	3.43	10/44 (22.7 %)	0.001
37^{+1}–38	2.67 ± 0.59	3.36	6/47 (12.8 %)	0.001
			$n = 162$	

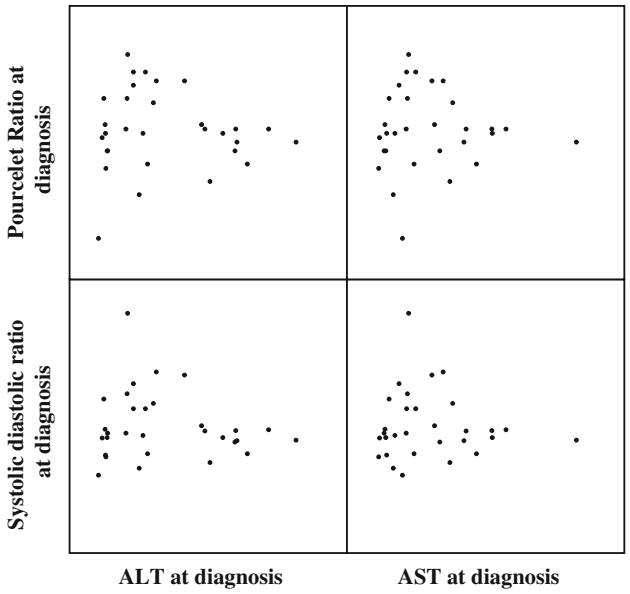

Fig. 3 Scatter matrix plot of Doppler values versus liver function tests

35 weeks of gestation and 0.599 at term. The highest value was 0.85 and the lowest 0.24. When based on the upper level of 2 SD, a PR index of greater than 0.657 at 38 weeks of gestation was regarded as pathological. The Doppler velocity waveform indices measured in pregnancies complicated by intrahepatic cholestasis were above the normal range in most cases. Of the PR indices, 56 values (35 %) were measured to be abnormal. In addition, when the S/D ratio was measured, 33 values (20.37 %) were beyond the range of normality. The highest value was 6.88 and the lowest value 1.3. There were no other abnormalities in these pregnancies which would serve to explain the pathological Doppler findings.

These results are in contrast to the previous study by Guerra et al. [13] which concluded that there were no significant changes in any of the blood flow velocity indices determined by Doppler blood flow analysis in patients with cholestasis. Zimmermann et al. [6] determined Pourcelot ratio in affected pregnancies with obstetric cholestasis and found Doppler to be of little value in studying the disease specific risk of fetal compromise. That study did not demonstrate any effect on umbilical circulation even in severe cases with high levels of ALT.

Our study did not demonstrate any correlation of Doppler flow with the severity of cholestasis. No correlation was found between Doppler flow indices and severity of pruritus on visual analog scale. These findings were in line with the study by Zimmerman et al. [6], where only 2 of the 29 PR indices were measured to be above upper limit of normal in a patient who had moderate intrahepatic cholestasis (ALT 139 IU/L and bile acids 24 μmol/L). The two patients who had absent end diastolic flow on Doppler analysis did not show greatly raised liver transaminases. One patient, however, had a comorbid factor in the form of IUGR.

There are limited data reporting association between Doppler and abnormal fetal outcome. The abnormal Doppler values in our study did not correlate with any of the fetal complications such as IUGR, meconium-stained liquor, and preterm labor. However, all the pregnancies examined ended with a favorable fetal outcome. We, thus, have no knowledge of how the Doppler flow velocity waveform of umbilical artery would have been affected if intrahepatic cholestasis had resulted in the death of the fetus. We hypothesize that these changes in Doppler were probably early and treatment possibly modified the course of the disease.

Conclusion

We feel that it is probably because of intensive surveillance, closer follow-up, and intervention by induction of labor that we found good perinatal outcome despite abnormal Doppler values. On the basis of our cases, however, we are persuaded to argue that Doppler investigation of the umbilical artery might be of some value in recognition of the specific risk of fetal compromise in pregnancies complicated by intrahepatic cholestasis.

Conflict of interest We declare that we have no conflict of interest in relation to the article.

References

1. Lammert F, Marschall HU, Glantz A, Matern S (2000) Intrahepatic cholestasis of pregnancy: molecular pathogenesis, diagnosis and management. J Hepatol 33:1012–1021
2. Alsulyman OM, Ouzounian JG, Ames-Castro M, Goodwin TM (1996) Intrahepatic cholestasis of pregnancy: perinatal outcome associated with expectant management. Am J Obstet Gynecol 175:957–960
3. Martinez E, Rodriguez N, Lisoni M, Cruzat L, Glasinovic J, Marinovic I (1987) Usefulness of biophysical profile in intrahepatic cholestasis of pregnancy. Rev Chil Obstet Ginecol 52:137–141
4. Bacq Y, Sapey T, Brechot MC, Pierre F, Fignon A, Dubios F (1997) Intrahepatic cholestasis of pregnancy: a French prospective study. Hepatology 26:358–364
5. Heikkinen J, Maentausta O, Ylostalo P, Janne O (1981) Changes in serum bileacid concentrations during normal pregnancy, in patients with intrahepatic cholestasis of pregnancy and in pregnant women with itching. Br J Obstet Gynaecol 88:240–245
6. Zimmermann P, Koskinen J, Vaalamo P, Ranata T (1991) Doppler umbilical artery velocimetry in pregnancies complicated by intrahepatic cholestasis. J Perinat Med 19:351–355
7. Acharya G, Wilsgaard T, Bernsten GKR et al (2005) Reference ranges for serial measurements of umbilical artery Doppler indices in the second half of pregnancy. Am J Obstet Gynecol 192:937

8. Merz E (ed) (2005) Ultrasonography in obstetrics and gynecology, vol I. Thieme, Stuttgart
9. Shaw D, Frohlich J, Wittmann BA, Willms M (1982) A prospective study of 18 patients with cholestasis of pregnancy. Am J Obstet Gynecol 142:621–625
10. Rioseco AJ, Ivankovic MB, Manjur A, Hamed F, Kato SR, Parer JT et al (1994) Intrahepatic cholestasis of pregnancy: a retrospective case control study of perinatal outcome. Am J Obstet Gynecol 170:890–895
11. Glantz A, Marshall HU, Mattsson LA (2004) Intrahepatic cholestasis of pregnancy: relationships between bile acid levels and fetal complication rates. Hepatology 40:467–474
12. Roncaglia N, Arreghini A, Locatelli A, Bellini P, Andreotti C, Ghidini A (2002) Obstetric cholestasis: outcome with active management. Eur J Obstet Gynecol Reprod Biol 100:167–170
13. Guerra F, Guzman S, Campos G (1994) Evaluation of maternal and fetal blood flow indices in intrahepatic cholestasis of pregnancy. Rev Chil Obstet Ginecol 59:17–21