Original research article

Maternal and Perinatal Outcome in Intrahepatic Cholestasis of Pregnancy

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Abstract

Background : Intrahepatic cholestasis of pregnancy (ICP) is a multifactorial condition of pregnancy characterised by pruritis in the absence of a skin rash ,with , raised bile acids, and/or abnormal liver function tests neither of which has an alternative cause and both of which resolve after delivery. We in the current study tried to evaluate maternal and perinatal outcomes in cases and controls in obstetrics department presenting at our hospital .

Methods: Antenatal patients complaining of unexplained pruritis without rash, with raised bile acids and/or abnormal LFTs were included in our prospective one year case-control study. There were 60 cases of ICP in our study and 60 controls . Maternal and perinatal outcomes were compared in both groups and statistical analysis was performed using chi-square test and fisher exact test . 'p' value < 0.05 was considered as statistically significant in this observational study .

Results : Sleep disturbance due to pruritis was present in 93.3% of the cases. Abnormalities in ALT and AST levels were seen in 98.3% and 100% cases respectively. Total bile acid levels were assessed for all the cases. 88.4 % of cases with ICP had mildly elevated bile acids (10-40 micromol/L) whereas severe derangement (>40 micromol/L) was seen in 11.7% of the cases. Mean POG at delivery was lower in cases (36.78 weeks with SD 1.76) than controls (38.09 weeks with SD 0.83 weeks).Significantly high Cesarean rates were seen among cases (65%) compared to the control group (40%). Meconium stained liquor was present in 47.3% of the total live births in cases compared to 5% in the control group.. Out of 60 cases diagnosed with ICP, 57 (95%) were live births whereas 3 (5%) were IUFDs . LFTs were in the normal range in 100% of cases 6 weeks postpartum . . 98.2% of total live born neonates were alive and healthy.

Conclusion : Our study was a prospective case control study with 60 cases diagnosed as ICP and same number of age and parity matched controls with Raised bile acids were found to be associated with fetal and neonatal outcomes like IUD, neonatal death, prematurity, need for assisted ventilation and NICU care, small for gestational age babies.

Maternal outcomes like higher LSCS deliveries, troublesome symptoms as pruritis and sleep disturbance have been studied.
Keywords : Intrahepatic cholestasis of pregnancy [ICP] , Serum total bile acids, pruritis, preterm labor, meconium stained liquor.

Introduction

Intrahepatic cholestasis of pregnancy (ICP) is a multifactorial condition of pregnancy characterised by pruritis in the absence of a skin rash ,with raised serum bile acids , and/or abnormal liver function tests neither of which has an alternative cause and both of which resolve after delivery. It is also known as recurrent jaundice of pregnancy, cholestatic hepatosis, and icterus gravidarum.[1,22]

The LFTs are elevated beyond pregnancy specific limits. The clinical importance of obstetric cholestasis lie in the potential fetal risks and the associated maternal morbidities, which include intense pruritis and consequent sleep deprivation.[2] Pruritis is a common complaint in pregnancy, incidence being 23% of total pregnancies and only a small proportion of these will have obstetric cholestasis.[3] The pruritis of obstetric cholestasis is typically worse at night, is often widespread and may involve the palms of hands and/or soles of the feet. [2]

There is a significant genetic influence, so the incidence of obstetric cholestasis varies in different populations. In Indian studies, the incidence reported is 1-1.5%.[4,5] Seasonal variations have also been studied in obstetric cholestasis. It occurs more commonly in the winter months.[6] It is more common in multiple gestations versus singleton pregnancies.[1,2] It has a recently recognised association with gestational diabetes, may reoccur in subsequent pregnancies, women with gallstones, and women who are seropositive for hepatitis C.[7,8,9,10,11,12]

Current research focuses on the numerous mutations in genes that control hepatocellular transport systems. Examples include mutations of the ABCB4 gene which encodes multidrug resistance protein 3 (MDR3) associated with progressive familial intrahepatic cholestasis and errors of the ABCB11 gene which encodes a bile-salt export pump.[13,14]The diagnosis of obstetric cholestasis is one of exclusion. If the LFTs are abnormal then other causes of abnormal LFTs should be excluded. Skin disorders should be ruled out as a cause of pruritis. BP should be checked carefully to rule out HDP. Acute viral hepatitis can be distinguished by low serum transaminases seen in cholestasis.

Materials and Methods :

It was a prospective one year case control study in the department of Obstetrics and Gynaecology at Sri Guru Ram Das University of Health Sciences, Sri Amritsar. Study period was from 1st Aug 2020 to 31st July 2021. Clearance from Ethical Committee was taken before start of the study. All patients meeting the inclusion criteria were enrolled for study after taking consent. Similar number of patients matched with age, parity and normal LFTs . Post natal resolution of pruritis and abnormal LFTs was confirmed for cases at 2 to 6 weeks with no other obstetric complication, who delivered at our institute were taken as controls.

Inclusion criteria

1.Antenatal patients complaining of unexplained pruritis without rash , with raised bile acids and/or abnormal LFTs .

Exclusion criteria

1.Patients having pruritis associated with rash and other dermatological conditions
2.Hypertensive disorders of pregnancy
3. Patients with serum bilirubin>5mg/dl, AST/ALT>500u/l, or viral hepatitis or chronic carriers of HbsAg, HCV or having gallstones or liver cirrhosis on USG were excluded from study.

In patients having unexplained pruritis with normal bile acids and normal LFTs, LFTs and bile acids were repeated after 1 to 2 weeks.. Pregnancy specific range of LFTs was taken as reference range.[1]Tests done were Complete blood count, PTI, total serum bilirubin, direct serum bilirubin, indirect serum bilirubin, AST (SGOT), ALT(SGPT),
Alkaline phosphatase, GGT, serum total proteins, fasting serum total bile acids, HBsAg, HCV, USG Abdomen. Pruritis was graded on Visual analogue scale. Details were entered in a proforma. Cases were followed up till 6 weeks of delivery. Maternal outcomes were defined by severity of pruritis,sleep disturbance ,period of gestation [POG] at delivery , preterm labor, mode of delivery, postpartum haemorrhage[PPH]. Perinatal outcomes were defines as meconium stained liquor, APGAR score , neonatal intensive care unit [NICU] stay .

Statistical analysis

Data collected was statistically analysed using SPSS version 20 [IBM SPSS statistics Inc. Chicago ,Illinois , USA] Windows software program . Descriptive statistics included computation of percentages , means and standard deviations. The analysis of variance [ANOVA] for quantitative data within three groups was used for quantitative data comparison of all clinical indicators . Chi-square test and fisher exact test were used for qualitative data whenever two or more than two groups were used to compare . Level of significance was set at p</= 0.05 .

Results

Median age of cases and controls being the same of 26.90 +/- 3.79 thus both the groups are comparable . 65% of cases and 70% controls were qualified upto matric . And 61.8 % cases while 58.3% controls belonged to middle class with most of cases (85%) and controls (88.3%) from rural background .[Table 1]

Table 1 [Demographic profile]

Factors		Cases[n=60]		Controls[n=60]	
		N	%	N	%
Age [years]	<20	1	1.7	1	1,7
	20-25	21	35	21	35
	25-30	28	46.7	28	46.7
	>30	10	16.7	10	16.7
Socioeconomic Status	Upper	21	34.9	25	41.6
	Middle	37	61.8	35	58.3
	Lower	2	3.3	0	0
Education	Upto 10^{TH}	39	65	42	70
	10^{TH} -12^{TH}	19	31.7	17	28.3
	Graduate and above	2	3.4	1	1,7
Background	Rural	51	85	53	88.3
	Urban	9	15	7	11.7

Table 2:

Obstetric history		Cases N=60 n	%	Controls N=60 n	%
Gravidity	Primigravida	36	60	36	60
	Multigravida	24	40	24	40
Past history of obstetric cholestatsis	Present	14	58.3	0	0
	Absent	10	41.7	100	100
POG at delivery	<28 weeks	1	1.7	0	0
	28-32 weeks	0	0	0	0
	32-24 weeks	1	1.7	0	0
	34-37 weeks	31	51.7	6	10
	>37 weeks	27	45	54	90
Cause of prematurity	Spontaneous labor	32	96.96	6	10
	Induced labor	1	3.04	0	0

Of the cases maximum were primigravidae [60 %] with parity matched with control . Among multigravidae 58.3 % had previous history of obstetric cholestasis in cases . Mean POG at delivery was lower in cases (36.78±1.76 weeks) as compared to controls (38.09±0.83 weeks).[Table 2]

Table 3 [Biochemical profile in cases

		Frequency	Percent
Serum Bilirubin [mg/dl]	0.1-1.1 [normal]	53	88.3
	>1.1 [abnormal]	7	11.7
AST [IU/L]	<35	0	0
	35-100	23	38.3
	100-200	21	35.0
	200-400	13	21.7
	400-499	3	5.0
ALT [IU/L]	<35	1	1.7
	35-100	18	30.0
	100-200	22	36.7
	200-400	17	28.3
	400-499	2	3.3
S.Bile acid [umol/L]	10-40	53	88.3
	>40	7	11.7

88.3 % patients had normal serum bilirubin . Serum aminotransferances [AST and ALT] were elevated 2-20 folds above the normal range in majority . 88.3 % patients had mildly elevated S. bile acids . [Table 3]

Table 4 [maternal outcomes]

	Cases [N=60] n	%	Controls [N= 60] n	%
Pruritis [VAS>5]	60	100	0	0
Sleep disturbance	56	93.3	0	0
PPH	0	0	0	0
LSCS	39	65	24	40
Preterm labor	33	55	6	10

There were various maternal complications such as preterm labor [55%] , and LSCS [65%] more in cases [table 4]

Table 5 [perinatal outcomes]

		Cases[N=60] n	%	Controls [N=60] n	%
Prematurity		33	55	12	20
Colour of liquor	Clear	30	52.6	57	95
	Meconium stained	14	24.56	3	5
	Thick meconium	13	22.8	0	0
	Meconium total cases	27	45	3	5
Fetal distress		10	16.6	1	1.7
Alive		57	95	60	100
Still births'		0	0	0	0
IUD		3	5	0	0
SGA[small for gestational age]		22	36.6	16	26.6
APGAR	<7	4	7.9	1	1.7
	7-10	53	92.1	59	98.3
NICU admission	No	44	77.20	54	90
	Yes	13	22.8	6	10

Perinatal outcomes revelaed preterm birth[55%] intrauterine death[5%], neonates required NICU stay [22.8] and more fetal distress[16.6%] in cases as compared to controls . [table 5]

DISCUSSION

There was a history of cholestasis in previous pregnancy in 58.3% of multiparous patients in our study whereas various studies found recurrence rate in subsequent pregnancies as high as 60-70%.[4,5,15]

In our study, pruritis was a distressing symptoms in all the cases100% cases had pruritis . Sleep disturbance due to pruritis was present in 93.3% of the cases. Medda S et al reported 60% incidence of sleep disturbance in their study.[15]

Total bilirubin levels were normal in 88.3% of the cases diagnosed with ICP. The mean value was 0.69 mg/dl with a standard deviation of 0.708 mg/dl. Various other studies report hyperbilirubinemia rarely exceeding 4-5 mg/dl.[2,15]

Abnormalities in ALT and AST levels were seen in 98.3% and 100% cases respectively. Most of the cases had ALT levels in the range of 100-200 U/L which is about 3 times the normal range for pregnancy (<35 U/L). Only one case had normal ALT levels.

AST levels were raised in 100% of the cases and the mean value was 178.98 with a standard deviation of 144.24. These results were similar to various other studies.[4,15,16,17] In cholestasis, serum transaminases (AST and ALT) rarely exceed 1000 U/L, even though their levels can rise 2-10 fold above the normal range.[i,ii] Similar results were obtained by Alkananda et al.[18] In our study we had taken the range of ALT and AST upto 500 U/L in the inclusion criteria for cases of ICP.

Total bile acid levels were assessed for all the cases. 88.3 % of cases with ICP had mildly elevated serum bile acids whereas severe derangement (>40 micromol/L) was seen in 11.7% of the cases in our study. Mei Y et al reported 37 (10.6%) cases with mild ICP (TBA 10-39 micromol/L) and 21 (6%) cases with severe ICP (>= 40 micromol/L) in their study of 350 cases of twin pregnancies with ICP.[19]

Mean POG at delivery was lower in cases (36.78 weeks with SD 1.76) than controls (38.09 weeks with SD 0.83 weeks). 51.7% of cases delivered at 34-37 weeks (late preterm) whereas incidence of early preterm (32-34 weeks) and extremely preterm (< 28 weeks) was 1.7% each. Incidence of preterm labor in cases was 55.2% compared to 10% in the controls with a significant p value (0.001). Only 1 case was induced before term. Thus iatrogenic prematurity was 3.03% among cases of ICP in our study and the rest were spontaneous preterm deliveries came in spontaneous labor . Browers and coworkers (2015) reported spontaneous preterm birth rate of 19% in patients with severely deranged bile acids as compared to 96.97% rate as seen in our study.[20,21] Various other studies reporr preterm birth rates as high as 44%,38% and 22%.[4,11,15]

Conclusion

Our study was a prospective case control study with 60 cases diagnosed as ICP and same number of age and parity matched controls with Raised bile acids were found to be associated with fetal and neonatal outcomes like IUD, neonatal death, prematurity, need for assisted ventilation and NICU care, small for gestational age babies.

Maternal outcomes like higher LSCS deliveries, troublesome symptoms as pruritis and sleep disturbance have been studied.Antenatal patients with pruritis should be never ignored , so that we can early diagnose the disease and prevent the grave prognosis to fetus and mother .

Strength of our study lies in its evaluation of serum total bile acid levels in the clinical assessment of the various fetal and maternal risks. Appropriate management of ICP can prevent grave fetal complications such as IUD and stillbirth. But we look forward to larger studies in this field, so that the true magnitude of ICP can be reflected.

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