Original Article

Association of Intrahepatic Cholestasis of Pregnancy with Adverse Fetal Outcome

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ABSTRACT

Objective: To determine association of intrahepatic cholestasis of pregnancy with adverse fetal outcome.
Study Design: Cohort Study
Place and Duration of Study: This study was conducted at the Department of Gynecology and Obstetrics of PAEC General Hospital Islamabad from August 2015 to Feb 2016.
Materials and Methods: 110 patients were included in the study during second trimester according to inclusive criteria. Two groups with 55 patients each were made. Group A was assigned to the patients with deranged LFTs while Group B was assigned to the patients with normal LFTs. Patients were followed during third trimester. Adverse outcomes like preterm labor and meconium stained liquor were the parameters observed in both groups and these were compared between groups.
Results: Total 110 patients were included in study. Mean age was 27.89 $\pm$ 4.51 years. Out of all 110 patients included in study 27 (24.5%) were prim gravida, 33 (30%) had one pregnancy earlier and 50 (45.5%) had 2 or more pregnancies. In group A 14 patients were prim gravida, 14 had one pregnancy earlier and 27 and more than two pregnancies. In group B 13 patients were prim gravida, 19 had one pregnancy earlier and 23 had two or more pregnancies earlier. In group A mean ALT was 132.75 U/L, AST was 132.04 U/L, ALP was 1049.96 U/L and Bilirubin was 2.34mg/ dL. While in Group B, mean ALT was 28.71 U/L, AST was 28.51 U/L, ALP was 622.69 U/L and Bilirubin was 0.931 mg/dL. In Group A, 35 patients (63.63 %) had meconium stained liquor while in Group B, only 07 patients (12.72%) had meconium stained liquor. In Group A, 32 patients (58.18 %) had Preterm Labor while in Group B, only 07 patients (12.72%) had Preterm Labor.
Conclusion: ICP is a condition that can affect the fetal outcomes and can cause preterm labor and meconium staining as compared to normal pregnancy. Adverse fetal outcomes are not associated with age and parity.
Key Words: Intrahepatic Cholestasis in pregnancy, Liquor, Liver Function Tests, Meconium, Preterm labor.

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INTRODUCTION

Intrahepatic cholestasis of pregnancy (ICP) is characterized by intense itching and is associated with deranged liver function tests (raised serum bile acids or/and raised serum transaminases) in prior normal pregnant woman. It starts during the second or third trimester of pregnancy and symptoms get better within 2 to 3 weeks after delivery.**Error! Bookmark not defined.** Liver function test changes are temporary and their timely interpretation can lead to early treatment and will decrease complications in both mother and fetus.[2]

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Geographic location and ethnicity effect prevalence of intrahepatic cholestasis of pregnancy with 2% in Pakistan and increases to 10% in South American population. While Europe and United states of America have occurrence of 0.1 -1.5% only.[3]

Environmental, genetic and hormonal factors play a role in intrahepatic cholestasis of pregnancy. Increased sex hormone production and their altered metabolism in liver leads to bile acid elevation in mother and fetus blood.[4] Raised bile acids appear to the responsible for severe itching and fetal adverse effects. Most women have benign course but can have increased risk of preterm delivery, meconium staining of amniotic fluid, fetal demise.[5,6,7,8] According to Geenes et al, there is strong association of intrahepatic cholestasis of pregnancy with a number of complications such as preterm deliveries (25%) as compared to 6.5% in controls and meconium stained liquor in 40.4% as compared to 18.6% to control.[9] Shobaili et al concluded expectant management to 40 weeks in patients with intrahepatic cholestasis of pregnancy has fetal outcomes comparable to normal pregnancy.[10]

Different geographic and ethnic population, timing of delivery and lack of diagnostic criteria of previous studies make their findings variable and cannot be applied to our population. This study will help to establish association of adverse fetal outcomes with intrahepatic cholestasis of pregnancy, so that adverse fetal outcomes can be anticipated before labor and associated fetal complication can be avoided.

MATERIALS AND METHODS

This cohort study was conducted at department of Gynecology and Obstetrics of PAEC General Hospital Islamabad from August 2015 to Feb 2016 after approval of ethical committee. Sample size calculations was done with confidence level 95% and P1=40.4% P2=18.6 % and Power of test=80%. Samples were collected through non probability consecutive sampling. 55 patients with singleton pregnancy with deranged LFTS from 24th week of pregnancy were included through non probability consecutive sampling and assigned as group A. Patients with other causes of deranged LFTs like hepatitis A, B, C, E, gallstones, HELLP syndrome and acute fatty liver of pregnancy were excluded from the study. 55 patients with singleton pregnancy with normal LFTS from 24th week of gestation were taken as control and assigned as group B. Informed consent was taken by the patients. Samples were collected from both indoor and outdoor patients.

History was taken and physical examination was done to confirm patient age, gestational age and to rule out history of hypertension, dark colored urine, pale stools and jaundice. Ultrasound Abdomen was performed in radiology department of hospital to rule out any other cause of liver disease. Blood samples were taken to perform the liver function tests, viral serology for hepatitis A, B, C and E. Biweekly follow up in 2nd trimester and weekly follow up in 3rd trimester was done in obstetrics department. Both the groups were compared for fetal outcomes by time of delivery and meconium staining of amniotic fluid.

Data was analyzed on SPSS version 21. Age, parity, Gestational age, Liver Function Tests were Quantitative Variable, Mean SD will be calculated. Preterm delivery, Meconium stained liquor were Qualitative variables. Frequency and percentage will be calculated. Effect modifier like age, gestational age was controlled by stratification, fetal outcome measured post-stratification. Chi square test will be used to compare frequency of fetal outcomes between two groups.

RESULTS

Total number of patients included in the study was 110. Group A and B both included 55 patients each. Mean age in Group A was 28.25 $\pm$ 4.904 years while in Group B mean age was 27.53$\pm$4.104 years as shown in Figure 1.

In group A, 14 patients were prim gravida, 14 had one pregnancy earlier and 27 had more than two pregnancies. In group B, 13 patients were prim gravida, 19 had one pregnancy earlier and 23 had two or more pregnancies earlier as shown in Table 1.

In Group A mean ALT,AST,ALP and bilirubin at time of diagnosis was 132.75 $\pm$ 62.25 U/L, 132.04 $\pm$ 60.98 U/L, 1049.96 $\pm$ 162.44 U/L and 2.34 $\pm$ 0.39 mg/dL respectively. In Group B mean ALT,AST,ALP and bilirubin was at the time of diagnosis 28.71 $\pm$ 6.42 U/L, 28.51 $\pm$ 5.77 U/L, 622.69 $\pm$ 84.31 U/L and 0.93 $\pm$ 0.078 mg/L respectively as shown in Table 2.

In Group A, mean ALT,AST,ALP and bilirubin at time of delivery was 54.07$\pm$ 27.498 U/L, 62.78$\pm$ 31.309 U/L, 678.02 $\pm$ 100.260 U/L and 1.5064 $\pm$ 0.251 mg/dL respectively. In Group B mean, ALT,AST,ALP and bilirubin was 38.18 $\pm$ 21.852 U/L, 29.58 $\pm$ 5.315 U/L, 575.40 $\pm$ 124.393 U/L, 0.80 $\pm$ 0.085 mg/dL respectively as shown in Table 2.

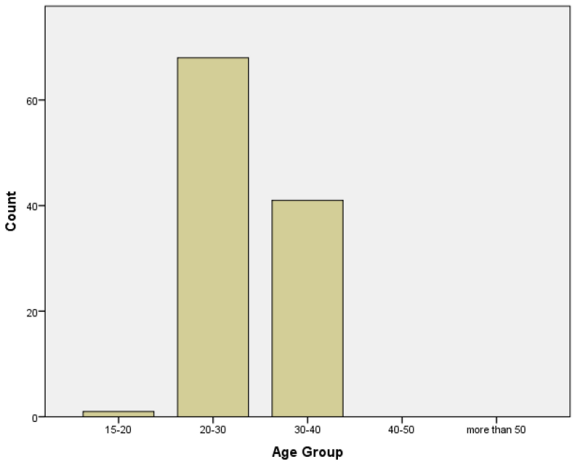

Figure No.1: Age Group Distribution

Table 1: Parity Distribution of Groups (N=110)

Parity		Group A	Group B
Valid	0	14	13
	1	14	19
	2-10	27	23
	Total	55	55

Table No.2: Mean of Liver Function Test of the patient at the time of diagnosis and delivery (N=110)

		ALT	AST	ALP	Bilirubin
At the time of Diagnosis	Group A	132.75	132.04	1049.96	2.3455
	Group B	28.71	28.51	622.69	.9316
At the time of Delivery	Group A	54.07	62.78	678.02	1.5064
	Group B	38.18	29.58	575.40	.8058

In Group A, 35 patients (63.63 %) had meconium stained liquor while in Group B, only 07 patients (12.72%) had meconium stained liquor. When we compared both groups for statistical difference p value was 0.000. This shows that there was a significant

difference in both groups in term of meconium stained Liquor. (p Value <0.05) as shown in Table 3.

Table 3 Preterm Labor and Different LFTs at time of Diagnosis (N=110)

Preterm		ALT (at time of Diagnosis)	AST (at time of Diagnosis)	ALP (at time of Diagnosis)	Bilirubin (at time of Diagnosis)mg/dL
Yes	Mean	140.00	139.38	1014.21	2.1610
	N	39	39	39	39
	Std. Deviation	79.296	77.693	272.007	.67487
	Minimum	15	17	320	.90
	Maximum	300	295	1500	3.00
No	Mean	48.17	47.80	738.62	1.3515
	N	71	71	71	71
	Std. Deviation	28.772	28.501	173.449	.65276
	Minimum	15	17	350	.75
	Maximum	110	110	1100	3.00
Total	Mean	80.73	80.27	836.33	1.6385
	N	110	110	110	110
	Std. Deviation	68.347	67.550	250.308	.76404
	Minimum	15	17	320	.75
	Maximum	300	295	1500	3.00

Table No.4: Meconium Liquor and Different LFTs at time of Diagnosis (N=110)

Meconium liquor		ALT (at time of Diagnosis)	AST (at time of Diagnosis)	ALP (at time of Diagnosis)	Bilirubin (at time of Diagnosis)mg/dL
Yes	Mean	122.24	122.52	984.62	2.1019
	N	42	42	42	42
	Std. Deviation	74.723	73.709	231.918	.64208
	Minimum	20	21	350	.85
	Maximum	300	295	1400	3.00
No	Mean	55.09	54.18	744.74	1.3524
	N	68	68	68	68
	Std. Deviation	49.349	47.838	216.139	.69259
	Minimum	15	17	320	.75
	Maximum	240	225	1500	3.00
Total	Mean	80.73	80.27	836.33	1.6385
	N	110	110	110	110
	Std. Deviation	68.347	67.550	250.308	.76404
	Minimum	15	17	320	.75
	Maximum	300	295	1500	3.00

We found that Preterm labor occurred in Patients having mean ALT of 140 ± 79.296 U/L, AST of 139.38 ±77.693 U/L, ALP of 1014.21 ± 272.007 U/L and Bilirubin of 2.161± 0.674 mg/dL. There was statistically significant difference in both groups in terms of ALT, AST, ALP and bilirubin (p Value = 0.00) Preterm labor occurred in patients having mean ALT of 122.24±74.723U/L, AST of 122.52 ±73.709 U/L, ALP of 984.62 ±231.918U/L and bilirubin of 2.10 ± 0.64 mg/dL. There was statistically significant difference in both groups in terms of ALT, AST, ALP and bilirubin (p Value = 0.00) as shown in Table 4.

DISCUSSION

Intrahepatic cholestasis of pregnancy like other disorders arising pregnancy such as HELLP, acute fatty liver of pregnancy and hemolysis leads to elevated liver enzymes and serious complication in mother and fetus. Early diagnosis and prompt management can lessen these complications. **Error! Bookmark not defined.,Error! Bookmark not defined.,Error! Bookmark not defined.,**[11]

In our study it was observed that cholestasis during pregnancy can have a detrimental effect on proceeding of pregnancy. Cholestasis can be easily diagnosed by an elevation in LFTs. ALT, AST, Bilirubin and ALP was measured in our study. We have observed that elevated levels of Liver function tests in second trimester influence the fetal outcomes. Meconium stained Liquor and preterm Labor were two of these outcomes observed in our study. Preterm Labor was observed in 58% of the patients with elevated LFTs during second trimester while it was seen in 13% in normal pregnancies. Meconium stained liquor is another serious complication observed in patients with ICP. In our study we observed that Meconium staining was found in 63%. It was further observed that Preterm Labor was associated with meconium staining in both groups. There was statistically significant difference (p value <0.05) in both groups.

A prospective population-based cohort study was carried out over 12 months (June 2010 to May 2011) by Victoria G et al .[9] Cases of severe ICP were identified through the UK Obstetric Surveillance System (UKOSS). In this cohort they have observed meconium staining in patients with ICP at 35 week preterm Labor at 40%. Preterm Labor was observed in 25 % of the cases with ICP. There was positive correlation observed between ICP and complications like preterm delivery and meconium stained liquor. Similar observations were noted in our study.

Age is considered as one of the risk factor for development of ICP. This was identified by Glantz

et al, that age has a correlation with development of ICP and may cause adverse fetal outcome.[4] In our study we couldn't find any correlation between age and development of ICP. There was no significant difference in both groups in terms of age. (p value >0.05).

Parity is another factor thought to influence development of ICP. Increasing parity is considered to influence on adverse fetal outcome in patients having ICP.[9] Al Shobaili et al found some correlation between multiple gestations and adverse fetal outcomes but that was not significant. Our study couldn't find any correlation among multiparous women or prim gravida either in term of development of ICP or adverse fetal outcomes.[8]

CONCLUSION

ICP is a condition that can affect the fetal outcomes and can cause preterm labor and meconium staining as compared to normal pregnancy. Adverse fetal outcomes are not associated with age and parity.

Author's Contribution:

Concept & Design of Study:	Aisha Aslam
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Conflict of Interest: The study has no conflict of interest to declare by any author.

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