

Intrahepatic Cholestasis Of Pregnancy: Perinatal Outcome And Its Relations With Maternal Bile Acid Levels.

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Abstract

Introduction: Intrahepatic cholestasis of pregnancy (IHCP) is characterised by unexplained pruritus in pregnancy associated with abnormal liver function tests (LFTs), along with or without raised bile acids, which resolves soon after delivery. Overall prevalence of intrahepatic cholestasis is around 0.1-2%. It mainly affects patients in second and third trimester. Maternal morbidities related to obstetrics cholestasis are mainly intense pruritus, but in case of perinatal outcome, it has significant adverse effects like preterm birth, meconium stained amniotic fluid, respiratory distress syndrome, increased admission to neonatal intensive care unit (NICU) and stillbirth. **Aims and objectives:** The aim of this study was to evaluate different perinatal outcome in patients of intrahepatic cholestasis of pregnancy and co-relate it with the maternal bile acids levels. **Material and methods:** This was an observational study. All the pregnant patients with history of pruritus and abnormal liver function test, with bile acid levels > 10 micromol/litre, who fits into definition of obstetric cholestasis were included in this study, as per inclusion and exclusion criteria. **Results:** During the study period, 54 patients were selected for the study and were divided into two groups. 33 patients in group 1 with bile acid levels <40 micromol/litre and 21 patients in group 2 with bile acid levels > 40 micromol/litre. More fetal complications were seen in group 2 when compared to group 1. There was 2 intrauterine death (IUD) and one still birth in group 2 and none in group 1. In group 2 there was 8 low birth weight babies whereas there was one baby in group 1. There were 6 babies in group 2 with respiratory distress syndrome (RDS) and required intubation whereas in group 1, 3 babies had RDS and 4 required intubation. In group 2, 10 babies required neonatal intensive care unit (NICU) admission whereas in group 1, 4 babies required NICU care. **Conclusion:** Increased bile acid levels are related to adverse perinatal outcome and can be used for monitoring the progress of the IHCP. However, timely decision of termination of pregnancy as opposed to in utero continuation of pregnancy comparing the risks over benefits plays very important role in favourable outcome of pregnancy.

Keywords: *IHCP, LFTs, NICU, RDS, IUD*

Introduction:

Intrahepatic cholestasis of pregnancy (IHCP) also called as obstetric cholestasis, is characterised by unexplained pruritus in pregnancy associated with abnormal liver function tests (LFTs), along with or without raised bile acids, which resolves soon after delivery¹. Pruritus is one of the common complaint in pregnancy, seen in around 23% of patients², but obstetric cholestasis is seen in very few cases. Overall prevalence of intrahepatic cholestasis is around 0.1-2%³, whereas in Asian Indian population it is around 1.2-1.5%^{1,4}. It mainly affects patients in second and third trimester. Pruritus in obstetric cholestasis is worse at night, and mainly involve palms of hands and soles of feet. In this condition, levels of bilirubin are raised infrequently but the levels of transaminases, gamma-glutamyl transferase and/or bile salts are raised¹. However, for defining abnormality in LFTs and bile salts, the upper limit of pregnancy-specific ranges should be applied. Maternal morbidities related to obstetric cholestasis are mainly intense pruritus, sleep deprivation due to pruritus and sometimes skin trauma (dermatographia artefacta) due to intense skin scratching¹. But in case of perinatal outcome, it has significant adverse effects like preterm birth (either spontaneously or iatrogenic), meconium stained amniotic fluid, respiratory distress syndrome, increased admission to neonatal intensive care unit (NICU) and stillbirth. About 0.5% prevalence is seen for in utero and perinatal mortality. Higher bile acids levels are associated with increased fetal complications⁵⁻⁹. The mechanism of cholestasis leading to still birth is uncertain and no studies has given bile acid levels threshold above which is associated with fetal death. Till date, management of obstetric cholestasis mainly ranges from maternal and fetal surveillance, medical management including ursodeoxycholic acid for pruritus and abnormal liver function test and sometimes iatrogenic delivery to prevent risk of fetal death^{1,10}.

In our hospital, we actively manage cases of obstetric cholestasis by weekly monitoring the patients clinically, by laboratory investigations and ultrasonography and biophysical profile and inducing the patients at 37⁺⁰ to 37⁺⁶ weeks of gestation. In this study, we tried to establish a relationship between bile acid levels and perinatal outcome, so that we can improve our obstetric outcome without jeopardising the fetal outcome.

Aims and objectives:

The aim of this study was to evaluate different perinatal outcome in patients of intrahepatic cholestasis of pregnancy and co-relate it with the maternal bile acids levels.

Material and methods:

This was an observational study, conducted in the obs-gynae department of Shalinitai Meghe hospital and research centre and Datta Meghe Medical College, Hingana, Nagpur from 1st November 2019 to 31st July 2020. All the pregnant patients with history of pruritus and abnormal liver function test, with bile acid levels > 10 micromol/litre, who fits into category of obstetric cholestasis were included in this study, as per inclusion and exclusion criteria.

Inclusion criteria:

1. Primigravida
2. Singleton pregnancy.
 3. Gestational age of pregnancy between 30 and 40 weeks
 4. Pruritus with elevated liver enzymes (alanine aminotransferase >41 U/l and/or aspartate aminotransferase >40 U/l)

Exclusion criteria:

1. acute fatty liver of pregnancy (AFLP)
2. Chronic liver disease (hepatitis B, hepatitis C, primary biliary cirrhosis, primary sclerosing cholangitis, symptomatic cholelithiasis, cholecystitis and others)
3. Human immunodeficiency virus infection
4. Smoking, alcohol, and drug addiction
5. Dermatological diseases with itching and rash
6. Gestational hypertension or preeclampsia or HELLP syndrome
7. Multiple pregnancy

8. Intrauterine growth restriction, oligohydramnios, and anemia.

Detailed history and proper examination was done of all patients, all necessary antenatal investigations were sent, including liver function test and bile acid levels. Ultrasonography was done for fetal well being. All patients were given symptomatic treatment along with tablet ursodeoxycholic acid. Weekly or twice weekly monitoring of these patients done as per the severity of cholestasis. Patients were monitored till 37-38 weeks of pregnancy and then induction of labour done, as per institutional protocol. All the intrapartum and postpartum complications and perinatal outcome were noted. These patients were divided in two groups as per the bile acid levels < 40 micromol/L (group 1) and >40 micromol/L (group 2)

Results

During the study period, total number of deliveries were 878, out of which, 54 patients were selected for the study which fits into the definition of intrahepatic cholestasis of pregnancy and were as per the inclusion and exclusion criteria. 33 (61.1%) patients were in group 1 where bile acid levels were < 40 micromol/L and 21 (38.9%) were in group 2 where bile acid levels were > 40 micromol/L. (Table 1)

Table 1: shows bile acid level in both groups

Total IHCP patients	Bile acid level	
	Group 1 (< 40 mmol/l)	Group 2 (>40 mmol/l)
54	33(61.1%)	21(38.9%)

Table 2: Method and Mode of delivery

Category	Bile acid level	
	≤ 40 (33 pts)	>40 (21 pts)
Preterm delivery	2 (6.06%)	7 (33.33%)
Induction of labour	16 (48.48%)	18 (85.71%)
NVD	21	11
LSCS	12	10

On comparing the obstetrics outcome in both groups (Table 2), it showed, 2 preterm deliveries in group 1 and 7 in group 2. Induction of labour was done in 16 patients in group 1 and in 18 patients in group 2. 12 patients had caesarean section in group 1 and whereas 10 patients in group 2 undergone caesarean section.

Table 3: Perinatal complications

Category	Bile acid level		P value
	≤ 40	>40	
Fetal complications	5(15.15%)	13(61.9%)	<0.05

Table 4: Perinatal complications according to bile acid levels

Category	Bile acid levels		P value
	≤ 40	>	
IUD	0	2	0.17

Low birth weight	1	8	0.0 013
Still birth	0	1	0.3 889
RDS	3	6	0.1 306
Intubation	4	6	0.1 619
NICU admission	4	1 0	0.0 091

In 54 pregnancies, fetal complications were seen in group 2 when compared to group 1 and this difference is highly significant (Table 3). When perinatal complications were compared in both groups (Table 4), there was 2 intrauterine death (IUD) in group 2 and no IUD in group 1, however no significant difference was seen in both groups. There was one still birth in group 2 and none in group 1. In group 2 there was 8 babies with low birth weight whereas there was one low birth weight baby in group 1, which shows significant difference (p value < 0.05). There were 6 babies in group 2 with respiratory distress syndrome (RDS) and required intubation whereas in group 1, 3 babies had RDS and 4 required intubation. In group 2, 10 babies required neonatal intensive care unit (NICU) admission whereas in group 1, 4 babies required NICU admission, which showed statistically significant difference in both groups (p value < 0.05)

Discussion

Although intrahepatic cholestasis of pregnancy have different prevalence according to different ethnicity and geographical background and it causes lesser maternal effects compared to other gestational complications, but it has significant impact on the fetal outcomes. In our study, we selected 54 patients of IHCP and were divided according to bile acid levels in two groups. On comparing the two groups, fetal complications were significantly more when value of bile acids was more than 40 micromol/litre (p value < 0.05). Similar findings were in the studies of Arthuis C et al⁵, Zecca E et al⁷, C Ovadia et al⁹ and Posh S et al¹¹. In all these studies, fetal complications were more when bile acid levels increases above 40 micromole/litre. These complications included still birth, meconium stained liquor, respiratory distress, NICU admission. In our study, preterm deliveries were more in group 2 compared to group 1, which showed statistically significant difference (p < 0.05). Similar higher incidence of preterm deliveries were seen in the study of Posh S et al¹¹, Glantz A et al¹², and in the study of Kawakita T et al¹³. These preterm deliveries were either spontaneous or induced for fetal well being due to increasing bile acid levels. In our study, incidences of intrauterine death (IUD) and still birth were more in group 2 but there was no statistically significant difference. The risk of respiratory distress syndrome and need for intubation were more in the group 2 but there was no significant difference in two groups. Whereas in the study of Arthuis C et al⁵ and Posh S et al¹¹ showed greater risk of respiratory distress in the babies of IHCP patients of raised bile acid levels. It is said that increasing levels of bile acids inhibits the role of surfactant in lung maturations^{5,11}. Our study showed that, group 2 had more low birth weight babies compared to group 1, which was statistically significant (p value < 0.05). Similar findings were seen in the studies of Posh S et al¹¹ and Li L et al¹⁴. Exact cause of low birth can not be commented but iatrogenic induction of labour to prevent fetal complications could be one of the reason for low birth weight.

In our study, we had higher rate of NICU admission in group 2 compared to group 1 and which showed significant difference (p value < 0.05). This could be attributed to various factors like low birth weight, prematurity, respiratory distress, meconium staining of amniotic fluid in the group of raised bile acid levels. Similar higher incidence of NICU admission was seen in the meta-analysis of C Ovadia et al¹⁰. Many articles from GBD Study are reported on similar aspects¹⁵⁻¹⁸. Few articles on ectopic pregnancy were also reported^{19,20,21}. Mishra and Inamdar reported a case of Deep Venous Thrombosis in Pregnancy²². Nakade et. al. reported on Status of Vitamins and Minerals in Pregnancy²³. Yadav et. al. conducted a study on Comparative Study of Serum Lipid Profile of Women with Preeclampsia and Normotensive Pregnancy^{24,25,26,27,28}.

CONCLUSIONS

Intrahepatic cholestasis of pregnancy is one of the known complications of pregnancy with no definitive cause or predictive markers but it definitely converts the normal pregnancy into high risk one. Early diagnosis and prompt maternal and fetal surveillance can reduce the complications caused by it. Increased bile acid levels can be used for monitoring the progress of the disease and use of ursodeoxycholic acid can help in relieving the maternal symptoms but timely decision of termination of pregnancy as opposed to in utero continuation of pregnancy comparing the risks over benefits plays a very important role in favourable outcome of pregnancy. In our study, we studied the 54 patients of IHCP, and raised bile acid levels was the most important factor for fetal complications. Low birth weight and increased NICU stay were important fetal complications of our study. Since we had a less sample size to give a definitive comment on the relationship between bile acid levels and perinatal outcome, further research is required on a larger scale.

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