Intrahepatic Cholestasis of Pregnancy Between 34 Weeks And 40 Weeks- When To Intervene

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ABSTRACT

Objective: To find the appropriate timings for intervention in women with intrahepatic cholestasis of pregnancy.
Study Design: Prospective observational study.
Place and Duration of Study: Gynaecology and Obstetrics Department Combined Military Hospital Okara, from Oct 2019 to Nov 2020.
Methodology: Patients between 34-40 weeks of gestation with intrahepatic cholestasis were included in the study. With clinical and biochemical findings patients were monitored and conventional treatment was given. Intervention by delivery was done when required. Maternal and fetal outcome were followed.
Results: Out of 380 patients with pruritus between 34-40 weeks of gestation, intrahepatic cholestasis was found in 53 patients. Most of the patients 27 (51%) were delivered at 37-completed weeks. At 35-weeks of gestation 6 (11%) patients were delivered, at 36-weeks 8 (15%) patients were delivered, while 2% patients delivered at 39 and 40 weeks of gestation. The number of intrauterine deaths was 1 at 34 weeks of gestation and 2 at 35 weeks of gestation. Transient tachypnea of newborn was observed in 23% neonates. Respiratory Distress Syndrome was observed in 6 (12%) newborns. Neonatal sepsis was observed in 5 and hyperbilirubinaemia was observed in 4 (8%) neonates.
Conclusion: Patients with intrahepatic cholestasis should be preferably delivered between 37 to 38 weeks for a better foetal outcome.

Keywords: Intrahepatic cholestasis, Liver disease, Respiratory distress syndrome.

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INTRODUCTION

The physiological condition of pregnancy simulates those changes that occur in decompensated liver disease. The usual peak is seen in second trimester of pregnancy and the start of disease is symptomatic at the same time. Due to increased estrogens levels there is increased stasis of bile in gall bladder and increased lithogenicity. Similarly the incidence of gall stones formation is increased and contractility of gall bladder is reduced.[1,2]

During a normal pregnancy, there is fall in serum markers level. The levels of alanine aminotransferase, aspartate aminotransferase (AST), ALT, bilirubin and gamma - glutamyl transpeptidase remain normal throughout the course of pregnancy. Only the level of Alkaline Phosphatase increase due to addition from placental secretions.[3,4]

The most common disorder of liver during pregnancy is intrahepatic cholestasis of pregnancy also called as obstetric cholestasis.[4,5] The incidence is 1 in 140 pregnant ladies in United Kingdom. All over the world, the incidence varies geographically with more prevalence in Asia, South America and Chile. The disease is rare in African and Caribbean women.[5,6]

The commonest symptom is pruritus especially of hands and soles and occurs mostly at night. This leads to sleep deprivation. Other symptoms can be skin excoriation if pruritus is severe.[7,8] The onset of ICP is usually in second trimester but it has been seen in patients even at 8 weeks gestation. There is also passage of high colored urine and pale stools.[9,10]

If ICP is suspected, liver functions tests and serum bile salts should be checked. The condition is characterized by raised levels of serum bile salts and serum transaminases. If the disease is severe there can be abnormal coagulation leading to prolonged PT10. Adverse effects on foetus and neonates occur due to raised serum bile acids especially when level goes beyond 40 umol/L. This leads to deposition of lipid soluble unconjugated bilirubin in brain cells mostly at

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basal ganglia leading to kernicterus. This is more common in preterm infants where blood brain barrier is weak.

The rationale of study was to focus on diagnosis, selection, monitoring and medication of pregnant women with intrahepatic cholestasis. The monitoring and medication would decrease the morbidity of patient as well as newborn infants. The study would also be beneficial for postgraduate trainees to learn how to manage high-risk patients.

METHODOLOGY

It was a prospective observational study conducted at CMH Okara for the duration of 14 months from October 2019 to November 2020. Approval from the Institutional Ethical Committee was obtained (IERC/OBS/2020/08). A total of 380 patients were selected through convenient sampling technique. Sample size was calculated using an online sample size calculator.

Inclusion Criteria: Patients between 34-40 weeks of gestation with the intrahepatic cholestasis were included in the study.

Exclusion Criteria: Women with gallstones, viral hepatitis and coagulopathies were excluded from the study. Obstetric cholestasis was diagnosed as exclusion from intrahepatic cholestasis due to gallstones, primary biliary cirrhosis and chronic active hepatitis.

Clinical examination was carried out and relevant investigations were made. Patients were monitored with signs and symptoms, cardiotocography, ultra-sound scan and biochemically. Liver function tests were carried out regularly and raised bilirubin and alanine transferase (ALT) were noted. Symptoms of itching, dark coloured stools, steotorrhoea and malaise were noted on every visit. Combined clinical and biochemical findings revealed intrahepatic cholestasis in 53 patients. Treatment with antihistamines, topical creams, ursodeoxycholic acid and vitamin K were given. Steroid injections for foetal lung maturity were given as per protocol. These patients were either admitted to Obstetrics Ward or were followed regularly on weekly OPD visits, where they were inquired about intensity of itching, skin rash, high colored urine or stool. Foetal movements record, cardiotocography and ultrasound for foetal wellbeing, amniotic fluid index and umbilical artery doppler were carried regularly. Any change in general and obstetric conditions was noted. If derangement of any parameter was observed, the intervention either by the induction of labour or lower segment caesarean section was done. Delivery was carried out according to Bishop score and history. Indication of delivery was the decrease or absent foetal movements along with persistent non-reactive cardiotocography. Another indication of delivery was decreased amniotic fluid index and less foetal movements with non-reactive cardiotocography. Some women were delivered due to raised or reverse umbilical artery doppler flow indices. Meconium staining of liquor was noted. The newborns were shifted to NICU as per the hospital protocol. The infants born to all the high-risk women were shifted to NICU for observation, monitoring, treatment and follow up. Patients were monitored in post-delivery/post-operative suites later on. All the 53 patients were stable with regular follow up during puerperium.

Statistical Package for Social Sciences (SPSS) version 21 was used for the data analysis. Mean and percentages were calculated for qualitative variables like foetal movements, non- reactive CTG.

RESULTS

Out of 380 patients with pruritus between 34-40 weeks of gestation, intrahepatic cholestasis was found in 53 patients. Most of the patients 27 (51%) were delivered at 37 completed weeks; however some had to be delivered earlier due to foetal compromise. At 34-weeks of gestation, 5 (9%) women were delivered. At 35-weeks of gestation 6 patients and at 36-weeks 8 (15%) patients were delivered. 2% patients delivered at 39 and 40 weeks of gestation (Table-I). The number of intrauterine deaths was 1 at 34 weeks of gestation and 1 at 35 weeks of gestation (Table-II).

Table-I: Distribution of patients according to gestational age at delivery (n=53).

Gestational Age	No of Patients	Percentage
34 ± weeks	5	9
35 ± weeks	6	11
36 ± weeks	8	15
37 ± weeks	27	51
38 ±weeks	5	9
39 ±weeks	1	2
40 ± weeks	1	2

Table -II: Intrauterine Deaths according to gestational age (n=53).

Gestational Age	No of Patients	Intrauterine Deaths	Percentage
34 ± weeks	5	1	20
35 ± weeks	6	1	17
36 ± weeks	8	0	0
37 ± weeks	27	0	0
38 ± weeks	5	0	0
39 ± weeks	1	0	0
40 ±weeks	1	0	0

Intervention for delivery due to raised LFT's was carried out in 20 (39%) patients. Delivery due to persistent non-reactive cardiotocography or decrease or absent foetal movements was carried out in 8 (16%) women. Patients have raised LFT's and non-reassuring CTG were.[9] Women with reduced AFI and deranged umbilical artery indices were 7 (14%) and those with all the deranged parameters were 9 (Table-III).

Table-III: Deranged parameters followed by intervention (n=51, two Intrauterine deaths).

Deranged Parameters	No. of Patients	Percentage
Raised liver function tests	20	39
Persistent Non- reactive cardiotocographs	8	16
Raised liver function tests ± Non-reactive cardiotocographs	9	18
Decreased amniotic fluid index/Deranged Umbilical Artery Doppler Ultrasound	7	14
Raised liver function tests ± Non-reactive cardiotocographs ± Raised Doppler blood flow	9	18

Only one woman delivered at 34 weeks of gestation with meconium stained liquor. At 35 weeks of gestation, meconium stained liquor was seen in 1 patient. At 37 weeks of gestation the meconium stained liquor was seen in 6 (22%) patients (Table-IV).

Table-IV: Meconium stained liquor according to gestational age (n=51).

Gestational Age	No. of Patients	Meconium stained liquor	Percentage
34 ± weeks	5	1	20
35 ± weeks	6	1	16
36 ± weeks	8	1	12
37 ± weeks	27	6	22
38 ± weeks	5	2	40
39 ± weeks	1	1	100
40 ± weeks	1	1	100

Transient tachypnea of newborn was observed in 23% neonates. Respiratory distress syndrome was observed in 6 (12%) newborns. Neonatal sepsis was observed in 5 (10%) neonates while hypoglycaemiawas seen in 3 (6%) neonates. Meconium aspiration was seen in 4 (8%) newborns and there was no neonatal death (Table-V).

Table-V: Neonatal complications (n=51).

Neonatal Complications	No. of Newborns	%
Transient tachypnea	12	23
Respiratory distress syndrome	6	12
Neonatal Sepsis	5	10
Hypoglycemia	3	6
Hyperbilirubinemia	4	8
Meconium aspiration syndrome	4	8
Neonatal Deaths	-	-

DISCUSSION

Cholestasis of pregnancy needs early detection, regular monitoring and should be managed properly to get good foetal outcome.[11,12] In our study majority of women were delivered at 37 weeks of gestation. There were preterm deliveries as well but this was due to derangement in any of parameters indicating for an early delivery. Those who were delivered at 38, 39 weeks were the ones who were booked, got treatment but refused the admission. They came either in labour or with complaints of decrease foetal movements. The study conducted by Chappel *et al,* published in British Medical Journal also showed that patient should be monitored to term as compared to preterm birth.[6]

In our study, there was no intrauterine death after 36 weeks due to close monitoring. Although we had one at 34 and 35 weeks but these fetuses had severe FGR due to aberrant intrauterine fetal hypoxia. This was compared to study conducted by Mohan *et al,* in their review, they showed that there was no significance difference of stillbirths in ICP or other obstetric population. Although the risk of prematurity was higher due to foetal compromise.[7]

The study conducted by Kalsoom *et al*, showed the diagnosis and management of ICP. The results showed high frequency of maternal and foetal morbidity with ICP as compared to our study.[8] Similar study by Hafeez *et al*, showed frequency of ICP in Punjab Pakistan. They reported that labour was induced in 64% of women due to high LFT's as in our study. In their study meconium aspiration was 48% which was much higher than our study.[9]

In our study population, indication for delivery was raised liver function tests (39%). On the other hand, decrease or absent foetal movements and non-reactive cardiotocography was also one of the indication for delivery (16%). Raised umbilical artery Doppler values and reduced amniotic fluid index was observed in 14% of women. Similar studies conducted by Wood *et al*, and Cui *et al*, described management of ICP. Their reviews showed diagnosis and management of ICP population same way as in our study.[12,13]

Foetal outcome was better in term deliveries as compared to pre-term although meconium staining was increased with gestational age. It was 20% at 34 weeks gestation and was 100% at 39 and 40 weeks. There was no neonatal death in our study. Our results were comparable to the data published by Singh and Kenyon *et al*. They published meta-analysis of nine published articles from 2000 to 2015 with focus on ICP.

The main perinatal outcomes were preterm birth, meconium stained liquor, asphyxia and respiratory distress syndrome. They found that with raised serum bile acids there was increased risk of adverse foetal outcome specially asphyxia and RDS.[14,15]

Managing these patients is of paramount importance to reduce the foeto-maternal morbidity and mortality. They are delivered either by induction or by caesarean section between 37 and 38 weeks as per current recommendation.[16-18] To reduce maternal and foetal morbidity early detection and management is required. Our results were profound with the help of multidisciplinary teamwork.

LIMITATIONS OF STUDY

Non-availability of bile acids was the major limitation of our study but we adopted a pragmatic approach towards diagnosing ICP.

CONCLUSION

Patients with intrahepatic cholestasis should be preferably delivered between 37-38 weeks for a better foetal outcome.

Conflict of Interest: None.

Authors' Contribution

TY: Conception manusecript writing, AI: Design, NA: Data analysis, FZ: Supervision, SM: Manusecript editing, UY: Intellectual.

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