A Study of Obstetric Intrahepatic Cholestasis and Its Maternal and Perinatal Outcome at a Tertiary Care Hospital in Nagpur

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ABSTRACT

BACKGROUND

Intrahepatic cholestasis of pregnancy (ICP) is a multifactorial pregnancy specific liver disorder which is also known as obstetric cholestasis. The purpose of this study was to establish the value of maternal serum bile acid in diagnosis of ICP, evaluate the treatment of ICP with UDCA (ursodeoxycholic acid) and its influence on maternal and neonatal outcome.

METHODS

It was a cross-sectional study. 90 women diagnosed with ICP were studied for a period of 2 years and 3 months at tertiary care government hospital. Statistical analysis was performed using chi square test. 'P' value of < 0.05 was considered as statistically significant in this observational study.

RESULTS

The present study evaluates that ICP is more common in multigravida and in age group of 26 years – 30 years. It recurs in subsequent pregnancies significantly. Itching, most common symptom is commenced at 34 weeks ± 2.85 weeks. Transaminases were normal with elevated serum bile acid levels in 32.33 % cases. The mean gestational age at delivery ranged between 35 to 39 weeks. Most common mode of delivery is lower segment caesarean section (LSCS) with commonest indication as meconium-stained amniotic fluid (MSAF) and 31 babies required neonatal intensive care unit (NICU).

CONCLUSIONS

Precise diagnosis, follow up, target medication and active management is required. Although maternal outcome for patients is good and without any long-term sequelae, fetal outcome can be devastating. Active management with close antenatal surveillance of the fetus is usually recommended for better perinatal outcome.

KEYWORDS

Intrahepatic Cholestasis of Pregnancy (ICP), Ursodeoxycholic Acid (UDCA), Neonatal Intensive Care Unit (NICU), Lower Segment Caesarean Section (LSCS)

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DOI: 10.18410/jebmh/2021/603

How to Cite This Article:
Vaidya PJ, Kumbhalwar SA, Vaidya MJ. A study of obstetric intrahepatic cholestasis and its maternal and perinatal outcome at a tertiary care hospital in Nagpur. J Evid Based Med Healthc 2021;8(37):3323-3327. DOI: 10.18410/jebmh/2021/603

Submission 26-12-2020,
Peer Review 03-01-2021,
Acceptance 20-08-2021,
Published 13-09-2021.

BACKGROUND

ICP is a pregnancy-specific liver disorder affecting approximately 1 % of pregnancies in India[1,2] characterized by maternal pruritus and elevated serum bile acid and/or elevated serum liver enzymes. It typically arises in the late second and early third trimester of pregnancy and disappears spontaneously after delivery.

It is characterized by generalized itching often commencing with pruritus of palms and soles of feet with no other skin manifestations. Usually, symptoms disappear in the early postpartum period although often return in subsequent pregnancies or after oral contraceptive pills.

It has multifactorial aetiology with environmental, hormonal, and genetic contributions. The diagnosis is made on the basis of symptoms of persistent generalized pruritus, elevated serum bile acid and abnormal biochemical serum liver markers with absent viral markers (hepatitis E, hepatitis A, hepatitis C and hepatitis B).

Increased maternal blood levels of serum bile acids (BAs) are the most sensitive and specific biochemical marker of ICP[3] and are widely used as a diagnostic tool. ICP poses a risk for the foetus and is thus associated with an increased risk for adverse perinatal outcome, including foetal distress, spontaneous preterm labour and even intrauterine foetal death (IUFD).

Women with ICP have an increased rate of unexplained IUFD at term, mostly between 37 and 39 gestational weeks and usually higher when the total BA value is ≥ 40 μmol/L.[4] Ursodeoxycholic acid is the most promising medical treatment.

The proper and timely diagnosis with active management, including foetal antenatal monitoring and labour induction, is usually recommended. However, individually tailored management of ICP affected pregnancies is recommended rather than following a routine active management protocol.[5,6]

Objectives

1. To determine serum bile acids levels in obstetric cholestasis.
2. To determine maternal and perinatal outcomes in obstetric cholestasis.

METHODS

It is a cross sectional study. The total number of 90 patients were evaluated after ethics committee clearance (IEC NO - 150). Attrition due to labour induction or dropouts due to transfer to other facilities were considered during data analysis.

It is an observational study of patients presenting with intrahepatic cholestasis of pregnancy. Study was conducted in the Department of Obstetrics and Gynaecology, tertiary care Hospital for period of two years and three months from July 2014 to October 2016.

Inclusion Criteria

All consenting pregnant patients presenting with obstetric cholestasis. Obstetric cholestasis fulfils following criteria:

1. Clinical pruritus.
2. Biochemical - Serum bile acids > 10 μmol/litre

Exclusion Criteria

1. Surgical cholestasis.
2. Acute fulminant liver disease.
3. Viral hepatitis.
4. Autoimmune liver disease.
5. Pre-existing skin disorder.
6. Drug induced hepatitis.
7. Pancreatitis with pregnancy.
8. Any other pre-existing liver disorder.
9. Patients who deliver outside or who have irregular follow up.

Statistical Analysis

Statistics was analysed by using chi-square test. P - value of < 0.05 was considered as statistically significant.

RESULTS

In the present study, 53 % women between age group of 26 – 30 years were affected (Table 1). The mean age of these women was 27.4 ± 3.18 (21 - 36) years. Only 3.3 % of elderly women were affected with ICP. The recurrence rate among multigravida was 38.18 % (Table 1). 21 (23.33 %) patients had past history of ICP. Of which, 11 (12.23 %) presented with ICP earlier than that in previous pregnancy and 2 (2.23 %) had family history of ICP.

Mean gestational age at commencement of itching was 34.64 +/- 2.85 weeks i.e. between 23 - 38 weeks (Table 2). In only 1 out of 90 patients, the symptom started before 20 weeks. In addition to itching, patients also experienced nausea and vomiting, dysuria, high coloured urine and right hypochondriac pain.

Using pregnancy specific ranges for the liver function tests (LFTs), it was found that increase in alanine aminotransaminase (ALT) was slightly higher than aspartate aminotransferase (AST) which was expected (Table 4). In 29 cases (32.33 %), transaminases were normal with elevated bile acid levels. Mild hyperbilirubinemia was present in 2.2 % of the women (Table 4). The highest bilirubin level noted was 2.2 mg %.

In the study, 90 % of the total cases had mild grade of ICP. 9 (10 %) patients presented with severe grade of ICP; of which 7 (78 %) underwent LSCS and 1 (11 %) full term normal delivery (FTND) and 1 (11 %) instrumental delivery (Table 5).

The mean gestational age at delivery ranged between 35 - 39 weeks with most of the women delivering at 37 - 39 weeks (Table 3). In the present study, it was noticed that rate of caesarean section was higher than other modes of deliveries such as full-term vaginal delivery and instrumental

deliveries. 69 (76 %) ICP patients had LSCS with 7 (10 %) LSCS carried out electively and 62 (89 %) were done on emergency basis (Table 5). LSCS was indicated most commonly for meconium stained amniotic fluid followed by non-progress of labour, fetal distress, abnormal colour Doppler, non-reassuring cardiotocography, previous LSCS, twins & breech.

Perinatal outcome was good with only 31 (34.4 %) babies requiring NICU admission (Table 6). Most common indication for NICU stay was found to be MSAF followed by prolonged leaking, abnormal colour Doppler, tachypnoea, respiratory distress syndrome (RDS), delayed cry, grunting, and prematurity (Table 6). 74 (82.23 %) out of 90 patients had APGAR (appearance, pulse, grimace, activity and respiration) score 9/10 at 1 minute and 89 (98.8 %) out of 90 had APGAR score of 9/10 at 5 minutes (Table 6).

	Variables	Number of Cases (n)	Percentage (%)
Age-group in years (n = 90)	21 – 25	26	28.9
	26 - 30	48	53.0
	31 - 35	13	14.4
	> 35	3	3.3
Gravida status (n = 90)	Primigravida	35	38.9
	Multigravida	55	61.1
Previous history of ICP in multigravida (n = 55)	Yes	21	38.18
	No	34	61.81

Table 1. General Profile, Obstetric Scores and Previous History of ICP among the Patients

Gestational Age	Onset of Itching n (%)	Frequency of Cases at the Time of Diagnosis in Relation to Gestational Age n (%)
< 24 weeks	1 (1.1 %)	0 (0.0 %)
24 to 27.6 weeks	2 (2.2 %)	1 (1.1 %)
28 to 31.6 weeks	5 (5.6 %)	4 (4.4 %)
32 to 35.6 weeks	58 (64.4 %)	38 (44.5 %)
> 36 weeks	24 (26.7 %)	47 (50 %)

Table 2. Gestational Age and Onset of Symptom (Itching)

Gestational Age at the Time of Delivery (weeks)	No. of Cases with Percentage
35 to 35.6	5 (5.6 %)
36 to 36.6	8 (8.9 %)
37 to 37.6	33 (36.7 %)
38 to 38.6	36 (40 %)
39 to 40	8 (8.9 %)

Table 3. Gestational Age at the Time of Delivery

Liver Function Test Values	Number of Cases (n = 90)
Increased SGOT	35 (38.9 %)
Increased SGPT	26 (28.89 %)
Increased serum bilirubin	2 (2.2 %)
Normal SGOT SGPT & serum bilirubin	27 (30 %)
Serum bile acid levels	
Mild (10 - 40)	81 (90 %)
Severe (> 40)	09 (10 %)

Table 4. Liver Function Test in ICP

	Maternal outcomes	Cases	%
Mode of delivery (n = 90)	LSCS	69	76.6
	FTND	10	11.1
	Instrumental	11	12.2
Mode of LSCS (n = 69)	Emergency	62	89.9
	Elective	07	10.1
Indication of LSCS (n = 69)	Meconium-stained amniotic fluid	22	31.9
	Non progress of labour	13	18.8
	Foetal distress	12	17.4
	Others	22	31.9

Table 5. Maternal Outcome

	Perinatal Outcomes	Cases	Percentage
Requirement of NICU (n = 90)	Yes	31	34.44
	No	59	65.55
APGAR score of babies at 1 minute	7 / 10	06	6.66
	8 / 10	10	11.11
	9 / 10	74	82.22
APGAR score of babies at 5 minutes	8 / 10	01	1.1
	9 / 10	89	98.8
indications of NICU stay (n = 31)	MSAF	10	32.25
	Prolonged LEAK	7	22.58
	Abnormal CD	5	16.12
	Tachypnoea	4	12.90
	RDS	2	2.2
	Delayed cry	1	6.4
	Grunting	1	6.4
	Prematurity	1	6.4

Table 6. Perinatal Outcome

DISCUSSION

This study mainly concentrates on role of bile acids in diagnosis of ICP with course of patients in antenatal period and its subsequent maternal and perinatal outcome.

Maximum women between age group of 26 - 30 years were affected and mean age at presentation was 27.4 ± 3.18 (range 21 - 36) years. Heinonen S & P Kirkinen in 1999[7] and Gonzalez et al.[8] in 1989 reported that women of relatively advanced age (> 35 years) are at increased risk of developing ICP. In our study, it was observed that only 3.3 % of elderly women were affected with ICP.

Among 90 studied cases, maximum patients were multigravida and recurrence rate was 38.8 %. Out of 21 patients with past history of ICP, 11 presented earlier than that in previous pregnancy. Heinonen and Kirkinen[7] proposed multiparity increases the occurrence of ICP which is similar to our study. Reyes H[9] in 1992 and Heinonen and Kirkinen[7] observed that ICP tends to recur in subsequent pregnancies in approximately 60 – 70 % of the women.

In our study, 2.2 % of patients had family history of ICP and they also had recurrence. Hay[10] studied that one out of six cases of ICP is familial, and in such cases, it recurs in 92 %. In study by Turunen et al.[11] in 2013 observed an increased risk of ICP among first-degree relatives. In the present study, 4.4 % of twins were affected with ICP. Gonzalez et al.[8] Rioseco et al.[12] Koivurova et al.[13] observed that incidence of ICP is higher in twin pregnancies than singletons (2.7 %).

In our study, generalized pruritus was the cardinal symptom in all and was most pronounced in the palms and soles and mean gestational age at commencement of itching was 34.64 +/- 2.85 weeks i.e., between 23 - 38 weeks. In study by Kenyon AP, Piercy CN, Girling J et al.[1] severe pruritus of the soles of the feet may be particularly suggestive of ICP. Brites et al.[14] in 1998, Kenyon et al.[1] in 2002 and Saleh & Abdo in 2007 suggested approximately 80 % of patients have symptoms after 30 weeks and the condition presents in the late second and third trimester of pregnancy. In our study, 94.4 % women were diagnosed in third trimester. Kenyon AP, Piercy CN, Grilling J et al.[1] in 2002 and Ray A, Tata RJ, Balsara R et al.[2] in 2005 studied ICP diagnosed usually in the third trimester.

ALT and bile acid concentrations have been widely used to diagnose ICP. In our study, bile acid was elevated in all

patients and cut off for bile acid level > 10 µmol/L was the inclusion criteria. 90 % of the total cases had mild (10 - 40 µmol/L) grade of ICP. Nine patients experienced severe (> 40 µmol/L) grade of ICP. Serum bile acid levels are sensitive indicators of hepatobiliary disease. Elevated serum bile acid levels have been used to screen for cholestatic disorders observed by Mushtaq et al.[15] and Haas et al.[16] Lammert F et al.[17] Chen et al.[18] Glantz et al.[19] noticed elevated serum BA levels are the most sensitive indicator of ICP. A bile acid level ≥ 10 µmol/L during pregnancy was the diagnostic criteria for ICP in the study of Glantz et al.[19] The most commonly elevated LFTs have been reported as transaminases[20] and typically the transaminases range from just normal to several hundreds.[21] In the present study, the transaminases were raised in 70 % of the women and it was noticed that increase in ALT was slightly higher than AST which was expected. In 29 cases (32.33 %), transaminases were normal with elevated bile acid levels. Dann AT, AP Kenyon, L Poston et al.[22] in 2004 observed serum ALT levels usually also rise in ICP, while other biochemical features remain normal. Minor elevations of liver enzymes are observed in up to 60 % of ICP patients in study by Tan in 2003.[23] The levels of both AST and ALT in the serum can rise in patients with ICP, but ALT seems to be the more sensitive indicator of the two in study by Bacq Y.[24]

In the present study, Mild hyperbilirubinemia was present in 2.2 % of the women and the highest bilirubin level noted was 2.2 mg which is similar to other studies. No case of clinical jaundice was observed. In study by Oztas E, K Erkenekli, S Ozler et al.[25] in 2015 observed the levels of serum bilirubin are elevated in the most severe form of ICP and total bilirubin levels are also increased but usually the values are less than 5 mg/dL. Kenyon AP, Girling J Chave reported that elevated levels of bilirubin have been noted in approximately 22 – 56 % patients respectively but clinical jaundice is rare.[20]

In our study, UDCA was prescribed in all of the women and there was complete relief of pruritus in all studied patients, hence bile acid levels were not repeated. Several studies demonstrate that in addition to providing safe and effective relief of pruritus and improving LFTs, UDCA may improve the perinatal outcome.[26,27] Hence, UDCA is considered as most promising treatment for ICP. The severity of pruritus was reduced statistically, significantly better with UDCA than with placebo or no drugs in study by Bacq et al. in 2012. Chappell et al.[28] and Grand'Maison et al.[29] also suggested UDCA-treatment reduces pruritus and improves the biochemical features of patients with ICP. According to our results, low-dose UDCA treatment (300 mg/d) was effective in mild ICP patients. The dose of UDCA has varied between different randomized controlled trials. In most trials, the dose of UDCA has been between 600 and 900 mg/day. In the studies of Palma et al.[30] and Glantz et al.[3] the UDCA dose was quite high, 1000 mg/day. Floreani et al and associates used the 450 mg/day. Diaferia et al.[31] reported that pruritus abated and biochemical parameters improved in ICP when the dose of UDCA was 600 mg/day.

In the present study, it was noticed that rate of caesarean section was higher than other modes of deliveries. Rate of caesarean section was 76.6 %. Among 90 ICP patients, 69 had LSCS, out of which ,7 LSCS were carried out electively and 62 were done on emergency basis. Kremer AE, R Bolier, R van Dijk et al.[5] In 2014 it was noticed that apart from significant morbidity due to intense pruritus, ICP does not seem to have serious health consequences for the mother. There is an increased risk of delivery by LSCS (25.9 – 36 %).

In present study, we observed 32.2 % MSAF, 6.4 % prematurity, 2.2 % RDS. But perinatal outcome was good with only 31 babies requiring NICU admission. In the present study, a significant increase in the incidence of meconium staining of amniotic fluid (32.2 %) was noticed. Most common indication for NICU stay was found to be MSAF followed by prolonged leaking, abnormal colour Doppler, RDS, delayed cry, grunting, and prematurity.

82.23 % babies had APGAR score of 9/10 at 1 minute and 98.8 % babies had it at 5 minutes. Various studies observed that ICP increases the risk of preterm birth (12 – 44 %), fetal distress during labor (10 – 44 %) and intrauterine fetal death (1 – 3 %). Few studies suggested that the disease has been related to a high incidence of perinatal complications including an increase in perinatal mortality rate (35/1000), a high incidence of meconium-stained amniotic fluid (up to 45 %), preterm labour (up to 44 %), and fetal distress (up to 22 %).

CONCLUSIONS

In this study of obstetric intrahepatic cholestasis of pregnancy and its maternal and perinatal outcome, we sought information on course of the disease and role of bile acids in diagnosis. The consequences of ICP primarily affect the mother in mostly third trimester of pregnancy, with discomfort from pruritus, occasional mild jaundice, and nausea and it recurs in subsequent pregnancies. Increased maternal blood levels of serum bile acids are the most sensitive and specific biochemical marker of ICP and are widely used as a diagnostic tool. In view of the risks for the fetus, ICP is still severe gestational disorder that requires attention in health care and it is advisable that patients of ICP should be evaluated and monitored for fetal effects.

Its precise diagnosis, follow up, target medication and care for at risk cases would reduce perinatal and maternal complications.

Data sharing statement provided by the authors is available with the full text of this article at jebmh.com.
Financial or other competing interests: None.
Disclosure forms provided by the authors are available with the full text of this article at jebmh.com.

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