

Outcome of Pregnancy Complicated by Obstetric Cholestasis

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ABSTRACT

BACKGROUND

Pruritus is the primary clinical symptom of ICP. It may considerably impair the patient's quality of life causing sleep deprivation, psychological suffering and even suicidal thoughts. Pruritus is most severe in the evening, with a predilection for the palms of the hands and soles of the feet, and is not associated with any specific skin lesions. The main biochemical alterations are elevations of serum bile acids and aminotransferase activities. We wanted to study the outcome of pregnancy complicated by obstetric cholestasis in terms of maternal and foetal outcome.

METHODS

This is a prospective study done over a period of 18 months in 80 booked antenatal patients who complained of pruritus during their pregnancy. They were followed, and maternal and perinatal outcomes recorded. Appropriate statistical analysis was used for result.

RESULTS

Incidence of obstetric cholestasis in our hospital was 5%. Majority of the patients were primigravida (60%) and presented at gestational age between 32-36 weeks. Maternal morbidities are due to sleep disturbance (68.75%), dyslipidaemia (48.75%), deranged coagulation profile (22.5%), PPH (8.75%), increased operative interference (57.5%) and PROM (23.75%). Perinatal outcomes were MSL (23.75%), prematurity (25%), stillbirth (2.5%), NICU admission (18.75%), foetal distress (20%) and LBW (18.75%). Maximum number of patients were delivered between 37-38 weeks.

CONCLUSIONS

Active and timely intervention is needed to avoid unnecessary and early intervention and prevent the risk of prematurity.

KEY WORDS

Obstetric Cholestasis, Intrahepatic Cholestasis of Pregnancy, Foetal Distress, Ursodeoxycholic Acid, Pruritus in Pregnancy, Sleep Disturbance in Pregnancy

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BACKGROUND

Intrahepatic cholestasis of pregnancy (ICP) or obstetric cholestasis (OC), is the most common liver disorder during pregnancy. It normally presents in the second half of pregnancy,¹ typically to recur in subsequent pregnancies and is associated with significantly high adverse maternal and foetal outcome.² The aetiology is complex and appears to be heterogenous³ possibly with hormonal, genetic, environmental and dietary influences. It usually presents in the third trimester, after 30 weeks of gestation, but rare cases developing as early as 6 to 10 weeks⁴ have been described. The prevalence varies according to geographic location² and ethnicity. The incidence of obstetric cholestasis among Indian women has been reported to be about 1%.^{5,6}

Pruritus is the primary clinical symptom of ICP. It may considerably impair the patient's quality of life causing sleep deprivation, psychological suffering and even suicidal thoughts. Pruritus is most severe in the evening, with a predilection for the palms of the hands and soles of the feet, and is not associated with any specific skin lesions. The main biochemical alterations are elevations of serum bile acids and aminotransferase activities. Serum total bile acid level may increase 10–100 times above the normal range and higher foetal complications rates were observed with maternal fasting bile acid level exceeding 40 μmol/L.⁷ Obstetric cholestasis is a stressful condition for mothers and is associated with significant maternal morbidities. They have an increased risk for postpartum haemorrhage. There is also increased risk for preterm labour and operative interference.

Intrahepatic Cholestasis of pregnancy can have devastating consequences for the foetus. Adverse foetal outcomes associated with the condition include preterm labour, preterm prelabour rupture of membrane, foetal distress, abnormal CTG, meconium staining, spontaneous intrauterine death.^{4,8} Ursodeoxycholic Acid is the drug mainly used for relief of pruritus and improvement of the liver dysfunction, and is very effective in treating this condition.

There is considerable debate on extent of maternal and foetal risks in different studies done on outcome of pregnancies complicated by OC and in our hospital no studies has been done to study the demographic variation and effect of obstetric cholestasis on maternal and foetal outcome hence this study is chosen.

METHODS

The study was prospective study conducted in department of Obstetrics and Gynaecology, Bokaro General Hospital, a tertiary care centre in Bokaro District of Jharkhand over a period of One and a half year(June 2016 to Dec 2017). 80 Pregnant women with complain of pruritus in late second & third trimester with specific predilection to palms and soles and in night were included with exclusion to other liver disorder.

Sample size was calculated for continuous outcome and means by the statistical formula as follow;

$$n = \{z^2 p (1-p)\} / d^2$$

N (Total population) = 3609 per year (Approx.)

n=sample size for current study

z = Z is standard normal variate at level of significance (i.e. 1.96 for 95% confidence level)

p= Expected prevalence or proportion = 5.5% = 0.055 (taken from previous year hospital data)

d= Precision = 0.05 (Type 1 error)

Therefore,

$$n = \{z^2 p (1-p)\} / d^2 = \{(1.96)^2 (0.055) (1 - 0.055)\} / (0.05)^2 = 79.87 \approx 80$$

Hence the required sample size is 80.

Patients were informed about the purpose of study and aim of study and after taking informed consent included in study. Through history was elicited and clinical examination is done. Lab investigation was done like Liver Function Test, Prothrombin Time International Normalized Ratio and Lipid Profile to see pre-treatment value. Due to some constrain, Serum bile acid testing was not done in present study and serum transaminases level were used to follow the patients.

LFT was repeated weekly or fortnightly depending on transaminases value. All patients included in study has been given Ursodeoxycholic acid 300-1200 mg/day in divided doses for the rest of antenatal period. Labour and delivery events of these women is monitored and recorded properly along with postpartum and perinatal periods. Women are followed at 6 weeks of post-partum period for resolution of symptoms as well as for normal or altered LFT. The Frequency of obstetric cholestasis in the hospital, the Period of Gestation at which it appears, and the Relationship of Obstetric Cholestasis with Maternal Age and Parity were studied.

Maternal Outcomes were studied in reference to Sleep Disturbance due to severe pruritus, dyslipidaemia⁹, Deranged Coagulation Profile (increased PT), PROM, Mode Of Delivery - vaginal delivery, forceps application, elective and emergency caesarean section, Postpartum Haemorrhage. Foetal Outcome were studied in reference to Foetal Distress (defined as either foetal bradycardia <100 bpm or foetal tachycardia >160 bpm), Meconium Stained Liquor, Preterm Birth (delivery before 37 weeks of gestation), Low Birth Weight (birth weight <2.5 Kg), NICU admission rate and Perinatal Death (IUFD/Still born). Postpartum resolution was studied in reference to improvement of pruritus and abnormal Liver Function Tests after 6 weeks of delivery.

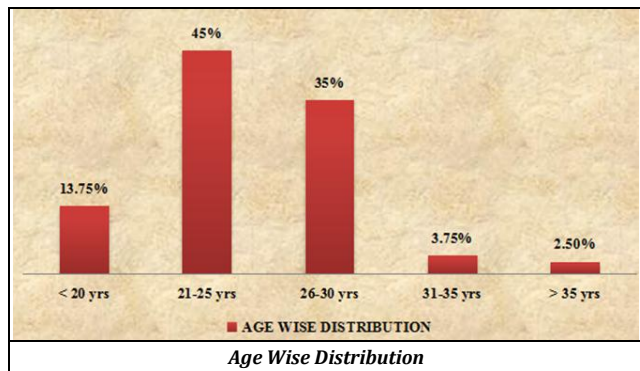
Statistical Analysis

Statistical analysis was carried out in present study by using SPSS version and Microsoft Excel 2010 for graphical representation. The data are presented as Mean ±SD, 95% confidence interval or as percentage where appropriate. A "p-value" should be considered to be no significant if > 0.05 and significant if <0.05. Mean, standard deviation and variance was calculated by Chi square test and proportion test.

RESULTS

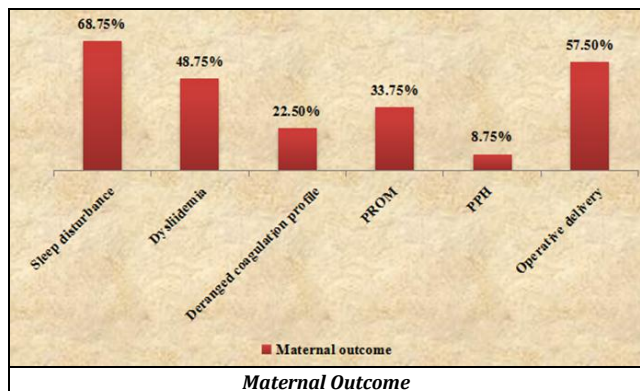
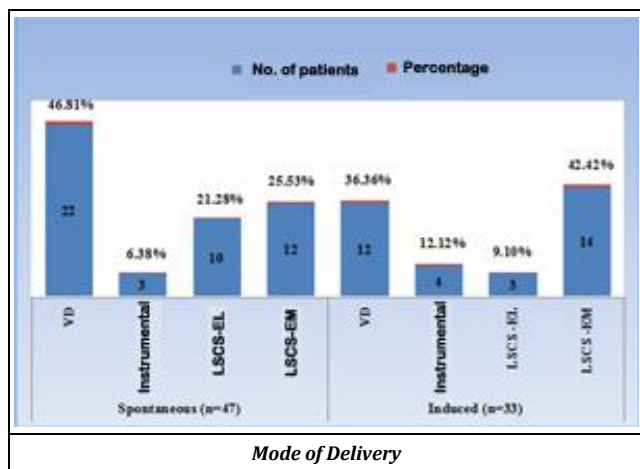
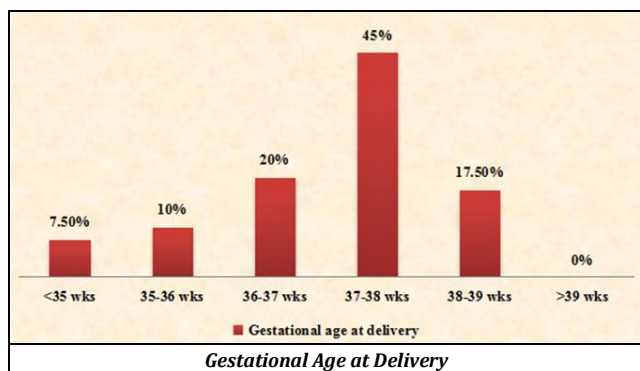
Parameter	No. of Patients (n)	Percentage
with obstetric cholestasis	183	5.07 ≈ 5%
without obstetric cholestasis	3426	94.93 ≈ 95%
Total deliveries	3609	100%

Incidence of OBS Cholestasis in Our Hospitals



Gestational Age (in Weeks)	No. of Patients	Percentage
<28 weeks	3	3.75%
28-32wks	13	16.25%
32-36 wks	54	67.5%
>36 wks	10	12.5%
Total	80	100%

Gestational Age at Diagnosis



Post-Partum Resolution	No. of Patients	Percentage
YES	78	97.5%
NO	2	2.5%

Post-Partum Resolution of LFT (after 6 Wks. of Delivery)

Foetal Outcome	Number	Percentage
MSL	19	23.75%
Foetal distress	16	20%
Preterm birth	20	25%
LBW	15	18.75%
NICU admission	15	18.75%
IUFD/stillborn	2	2.5%

Distribution of Foetal Outcome

The total number of deliveries during study period was 3609, among them 183 patients had Obstetric Cholestasis according to inclusion and exclusion criteria. So, the incidence is 5%.

The mean age (mean ± S.D.) of the patients was 24.95 ± 3.68 years with range 18 – 44 years. Most of the patients (45%) were at age between 21-25 years which was significantly higher than other age groups, like between 26-30 years and <20 years (p<0.0001). Only 3.75% of the patients were at age between 31-35 years and 2.5% were at age >35 years.

In 80 patients, 48 (60%) were primigravida and 32 (40%) were multigravida. So the occurrence was seen more in primigravida than in multigravida (p<0.05). Most of the patients (67.50%) diagnosed between 32-36 weeks followed by 28-32 weeks (16.25%) which was significant [p – value {p < 0.0001}]. 3.75% and 12.5% patients were diagnosed at <28 weeks and >36 weeks of gestation respectively.

68.75% of the patients had sleep disturbance which was significant (p<0.0001). 22.5% of the patients had deranged coagulation profile (p<0.0001). Mostly they had increased PT INR. PROM was found in 23.75% of cases in our study (p<0.0001). The mean gestational age of delivery (mean ± S.D.) of the patients was 37 weeks ± 1 day with range 33 – 40 weeks. Most of the patients (45%) were delivered between 37-38 weeks (p<0.0001); followed by 36-37 weeks and 38-39 weeks, in which 20.0% and 17.50% patients delivered, respectively. Only 7.5% patients delivered before 35 weeks of gestation. In present study spontaneous onset of labour is seen in 47 (58.75%) patients whereas induction is done in 33 (41.25%) patients. In spontaneous group, most of the patients had VD (46.81%) and LSCS was done in 46.81% of cases out of which 25.53% and 21.28% were elective and emergency respectively, and 6.38% of cases had instrumental delivery.

In the induced group most patient underwent LSCS (51.52%) followed by vaginal delivery (36.36%). Instrumental delivery was seen in 12.12% of cases. Although operative delivery in present study was more than vaginal delivery but the results were not significant (p>0.05).

In our study among 80 cases of obstetric cholestasis, 7 (8.75%) patients had postpartum haemorrhage during delivery and early puerperium while 73 patients did not experience postpartum haemorrhage (91.25%) (p<0.0001).

In most of the cases, postpartum resolution of LFT (97%) was found (p<0.01) after 6 weeks of delivery and no symptoms found (p<0.0001).

In foetal outcome, Meconium Stained Liquor was found in 23.75% of the cases (p<0.0001), foetal distress in 20% (p<0.0001). LBW in 18.75% (p<0.0001). In 18.75% of the cases NICU admission were required due to low birth weight,

foetal distress and meconium aspiration ($p < 0.0001$). IUFD or Still Born was found only in 2% of the cases ($p < 0.0001$).

DISCUSSION

Intrahepatic cholestasis of pregnancy (ICP) is the most common liver disease seen in pregnancy.¹⁰ It is typically a reversible cholestatic disease presenting in the second to third trimester of pregnancy and is characterized by pruritus predominantly of the palms and soles, elevated serum aminotransferases and/or elevated serum bile acid levels ($> \text{or} = 10$ micromol/L) with spontaneous relief of laboratory abnormalities and symptoms promptly after delivery but no later than one month post-partum.

OC has been observed in almost all ethnic groups, but there is relevant geographical variation in its incidence. Incidence of OC in present study is 5%. Padmaja et al¹¹ and Ge et al found highest incidence of 8.2% and 6.5% respectively whereas Hafeez et al,¹² Sohail et al,¹³ Furrer et al¹⁴ and Rook et al¹⁵ found lower incidence of OC that is 3.1%, 2.8%, 2.3% and 1.9% respectively. The cause of so much variation from present study is may be due to geographical variation, ethnicity, environmental factor, different food habits or sample size calculation. More over our hospital is tertiary referral centre and hence incidence may be high due to referral of high risk pregnancies.

In OC, pruritus is intense and has specific predilection to palm and sole and mainly at night and hence pruritus leads to variable degree of sleep disturbances in patients with OC. The main presenting symptom in present study was generalised pruritus with varying degree of severity leading to sleep disturbance. Sleep disturbances in present study was 68.75% which is comparable to studies done by authors as Medda et al¹⁶ (60%) and Alakananda et al¹⁷ (65%). Skin rash and clinical jaundice was not noticed in any patients with OC. Serum bilirubin rarely exceeds more than 2 mg. Serum aminotransferases (ALT and AST) were raised from 2-10 fold but not above 1000 U/L. Serum bile acid testing was not done in present study as it was not readily available to the patient and costly. UDCA was prescribed to patient along with topical emollients like calamine lotion to relief pruritus.

PROM was found in 23, 75% of cases. The reason why PROM occurs in ICP is not known. The finding was consistent with Sinha et al¹⁸ (20%). But other studies like Ghimire et al¹⁹ (10%) and Medda et al¹⁶ (10%) found lower incidences of PROM whereas Fawad et al²⁰ (47%) found highest incidence of PROM.

Mean gestational age at delivery in present study was $37W \pm 1d$ which was comparable to studies by authors Rook et al¹⁵ (37 W), Medda et al¹⁶ (37.28W), Alakananda et al¹⁷ (37+1.7W). In our hospital, we followed the patient with weekly or fortnightly LFT on the basis of values of Sr Transaminases and if decreasing trend of LFTs noticed, then patient was followed till 38-39 weeks and then induction planned. If other associated factor like PIH, GDM or twin pregnancy or no improvement or increasing levels of LFTs was found, then induction was planned at 37-38 weeks after explaining the complication that might occur due to elective early intervention.

In present study spontaneous onset of labour was found in 58.75% of cases and induction was done in 41.25% of

cases which was comparable to that observed by Mahajan et al²¹ (50.67%), Hak et al²² (50.67%) and Ghimire et al¹⁹ (51.25%).

Vaginal delivery in both spontaneous and induced cases occurred in 51.25% of cases which comprises of 42.5% Normal delivery and 8.75% instrumental delivery. The rate of LSCS was 48.75% which comprises of 16.25% elective LSCS done for either previous LSCS, multiple gestation or Primi with breech pregnancy and 32.5% of emergency LSCS which was done either for failed induction, non-progress of labour, MSL and foetal distress. Although the rate of operative delivery was high but results are statistically not significant. The results of present study is comparable to the observations made by Sultana et al²³ and Ghimire et al¹⁹ (VD 53.75%, LSCS 46.25%). Sultana et al²³ found 46.37% had vaginal delivery and 13.33% and 40% cases underwent instrumental delivery and LSCS respectively.

In present study, alteration in coagulation profile was 22.5% which was comparable to that of Medda et al (19%). Deranged coagulation was evaluated as raised PT INR in present study. All patients with deranged coagulation were given Vitamin K injection on three consecutive days and few patients in whom Sr. Bilirubin was raised, FFP was administered. The rate of PPH in present study was 8.75% which is comparable to those observed by Medda et al¹⁶ (10%) and Ghimire et al¹⁹ (11.25%) whereas Dodampahala et al²⁴ (29.6%) and Mahajan et al²¹ (16%) observed higher rates of PPH. PPH was less in present study due to active management of ICP cases with earlier UDCA prescription and administration of Vit K injection and FFP in some cases.

In present study, MSL was noticed in 23.75% of cases which is consistent with findings of Sultana et al (20%) where as other authors i.e. Sinha et al (32.5%), Ghimire et al (32.5%) and Medda et al (42%) found higher incidence of MSL and Sharma et al (8.33%) found lower incidence of MSL. This variability may be due to study population taken from regular antenatal clinic and early intervention in form of UDCA. 20% had foetal distress in terms of foetal bradycardia or foetal heart rate decelerations which is consistent with findings of Medda et al¹⁶ (23%), Ghimire et al¹⁹ (26.25%) and Sinha et al¹⁸ (17.5%). Sultana et al²³ found higher incidence of MSL i.e. 33.3% may be because they studied unbooked cases. In ICP, bile acid causes colonic motility stimulation leading to passage of meconium and foetal distress also leads to hypoxia and passage of meconium. Few researchers found correlation of Serum bile acids with foetal complication but that was not elucidated in present study because of non-availability of Sr bile acid testing. Percentage of preterm birth in present study was found to be 25% with 16 cases delivered at 36-37 weeks, 8 cases at 35-36 weeks and 6 cases at <35 weeks. The findings correlates well with studies like Padmaja et al¹¹ (24.4%), Sohail et al (25.8%), Alakananda et al¹⁷ (23%) and others. Preterm birth was mostly due to PROM and few elective induction because of complain of less foetal movement with altered S/D ratio in colour doppler in USG. LBW seen in 18.75% of cases in present study which was comparable to other studies like Sohail et al (17.1%), Singla et al²⁵ (21.5%) and Alakananda et al¹⁷ (23%) but Medda et al¹⁶ (32%) found higher LBWs rate which may be due to elective early induction in study by Medda et al¹⁶. LBW was mostly due to preterm delivery, and association with other maternal factor like PIH and twin pregnancy may be the

reason. In present study, the rate of NICU admission was 18.75% of cases which was comparable with other studies like Fawad et al²⁰ (22%), Alakananda et al¹⁷ (21%), Jain et al (17.85). Geenes et al²⁶ found less NICU admission which may be due to good antenatal surveillance and better environmental and socio-demographic factor. NICU admission was mostly due to preterm birth with low birth weight babies, respiratory distress and few with meconium aspiration syndrome. Percentage of IUFD in present study was 2.5% which was consistent with other studies like Fawad et al²⁰ (2.8%), Alakananda et al¹⁷ (2%), Medda et al¹⁶ (2%). One case of IUFD occurred in booked case admitted for induction for obstetric cholestasis with PIH with hyperuricemia and on second day of induction, foetal bradycardia noticed for which emergency LSCS was done but baby could not be revived and in other case unbooked patient came with complain of less FM with IUD for which she was admitted and investigated and previous antenatal records checked which showed that it was a case of ICP. The cause of foetal death in ICP is thought to be acute anoxia. Autopsies of still borns show signs of acute anoxia with serosal and pulmonary petechial bleeding without intra uterine growth retardation.

CONCLUSIONS

It is found that maternal complications like pruritus, sleep disturbance and risk of operative delivery are benign and don't have any significant health impact in future on women. But Foetal complications are considerable in the form of prematurity and associated low birth weight, meconium aspiration syndrome and NICU admission. Hence pregnant women with OC should be followed very vigilantly till delivery and elective early induction should be weighed considering the risk of prematurity and its further health impact on growth and development of child.

Limitations

Since this study was taken in tertiary hospital which deals with high risk pregnancy cases bit more, and on small number of patients, results cannot be extrapolated to general population. Because of frequent antenatal visits, LFT and PT INR testing, OC patients faced significant cost burden. Only UDCA was used in present study and no other drugs were studied.

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