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Original Research Article

To Study Maternal and Fetal Outcome Associated with Elevated Bile Acids Level in Patients of Intrahepatic Cholestasis of Pregnancy

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Abstract:

Background: The study was conducted to evaluate the maternal and foetal outcomes associated with elevated bile acid levels in patients of intrahepatic cholestasis of pregnancy.

Methods: This prospective observational study was conducted in the Department of Obstetrics and Gynaecology, LLRM Medical College associated SVBP Hospital Meerut from January 2020 to February 2021, it included 50 pregnant women with singleton pregnancy with presence of pruritus without any dermatological conditions and with elevated serum transaminases and serum bile acid levels in late 2nd and 3rd trimester of pregnancy.

Results : Out of total 50 pregnant women with cholestasis of pregnancy evaluated by serum bile acids levels, most of the women(66%) have bile acid range 10-39 micromole/lit and 34% have more than 40 micromole/lit with deranged serum transaminases levels, preterm deliveries occurred in 20% cases and 50% women were delivered by caesarean section, most of which were emergency caesarean section (64%) and most common indication of caesarean was foetal distress (32%) or MSL with foetal distress (28%) and the most common adverse perinatal outcome was MSL (20%), foetal bradycardia (16%), need of NICU admission (12%) followed by IUFD (4%). It was observed that over all adverse foetal and maternal outcomes specially proportion of neonates with APGAR less than 7 at 1 min and 5 min, low birth weight and meconium-stained liquor were significantly higher in the subjects with S. bile acid levels of 40 micromole/lit and above.

Conclusion: Serum bile acid estimation is a simple, easily available and minimally invasive test with quick results which helped to assess the severity of disease and correlated with adverse feto-maternal outcome, close monitoring of women with severe IHCP is essential to prevent adverse neonatal outcomes like foetal distress, meconium-stained liquor, preterm labour, sudden IUFD and stillbirth.

Keyword: Serum bile acid levels, serum transaminases, feto-maternal outcome.

Introduction

Intrahepatic cholestasis of pregnancy is the most common liver disease unique to pregnancy and also known as pruritus gravidarum and icterus gravidarum [1]. It is characterised by pruritus which is often intense, generalised worsen at night mostly concentrated in palm and soles with elevated in serum bile acid concentration (more than 10 micromole/lit) and transaminases, typically developing in the late or second and third trimester and often rapidly resolve after delivery.

The reported incidence of IHCP varies world wide ranging from less than 0.1 to 27.6% [2,3], it affects 1.2 to 1.5% of women of Indian Asian origin. Prevalence is influenced by genetic and environmental factors [4]. The pathogenesis of IHCP, although not well defined, is thought to be multifactorial including an environmental, genetic and hormonal basis for disease [5,6]. The hepatic transport system which is normally utilized for excretion of bile acids is saturated due to formation of large amounts of sulphated progesterone metabolites in some genetically predisposed women resulting in IHCP [7].

IHCP is relatively benign to women, but it has been reported to have important foetal complications like increased risk of preterm deliveries, meconium staining of amniotic fluids, foetal bradycardia, foetal distress, respiratory distress syndrome and sudden foetal demise [8,9,10]. The underlying mechanisms associated with poor foetal outcome are largely unknown like increasing bile acid level causes activation of myometrial oxytocin receptor pathway and initiates preterm labour. The bile acid attributable to the direct pruritogenic effect on the

skin, meconium staining of amniotic fluid occurs due to increase colonic motility by bile acids and sudden foetal distress and demise explained by vasoconstrictors effect of bile acids on placental chorionic veins and causes abnormal cardiac myocytes contraction, rhythm and desynchronisation of calcium dynamics causes bile acid induced arrhythmia in cardiomyocytes, have been shown to be associated with elevated maternal serum bile acids (more than 40 micromole/lit) in pregnancy [11], intrahepatic cholestasis of pregnancy is a challenge for health care provider because of the potential of severe foetal consequences. For women, there is a risk of recurrence and also of future hepatobiliary, cardiovascular and immunological diseases. Generally serious outcomes have been associated with serum bile acid more than 40 micromole/lit, so early obstetric management of the disease with timely delivery is essential therefore; we aimed to document maternal and foetal outcomes associated with serum bile acids level in patient with intrahepatic cholestasis of pregnancy in a tertiary care centre

Methods

This prospective observational study was conducted in the Department of Obstetrics and Gynaecology, LLRM Medical College associated SVBP Hospital Meerut from January 2020 to February 2021, 50 pregnant women with singleton pregnancy with pruritus without any dermatological condition and with elevated serum bile acid level and serum transaminases in late 2nd and 3rd trimester were included in the study. Informed consent was obtained and ethical clearance was taken from the institutional ethical committee.

Exclusion Criteria: Previously and newly diagnosed cases of hepatitis A, B, C, D, high risk pregnancy (pregnancy induced hypertension, GDM, twin pregnancy, heart disease, acute and chronic renal disease) and any systemic diseases of hepatic-pancreatic-biliary system

All pregnant females of age group 19 to 40 years fulfilling the inclusion criteria attending outpatient clinics and emergency were enrolled for the study, irrespective of their gestational age and parity. Gestational age was established by menstrual history, clinical examinations and was confirmed by USG. A comprehensive history of each patient was taken including name, age, chief complaint, obstetric history, menstrual history, history of pruritus in previous pregnancy, skin disorder, atopic and allergic condition, liver, gallbladder diseases, history of chronic medical and surgical illness, family history and dietary history taken. General, systemic and obstetric examination was done.

All primary baseline investigations were done. Serum bile acid level and LFT done by collection of blood sample was withdrawal 2 ml venous blood from antecubital vein under full aseptic condition using a dry sterile disposable syringe and needle, after transferring the sample to plain vial, the total serum bile acid level was analysed with an enzymatic, colorimetric method. Liver enzymes were analysed with standard laboratory methods. An optimal serum bile acid level during pregnancy has not been determined and it remains an area of active research, the serum bile acid level more than 10 micromole/lit considered for diagnosis of IHCP.

The severity of IHCP was graded according to serum bile acid level, >10 to 39 was graded as mild, > 40 to 99 was moderate, more than 100 was considered severe. All women enrolled were monitored by serum bile acid level estimated in 3rd trimester or at the time of admission or delivery and all patient were followed up to 3 weeks postpartum period and outcome were studied in the term of period of gestation at the time of delivery, mode of delivery including any complication of labour if present. Foetal outcome was noted in the term of preterm birth, meconium-stained liquor, foetal distress, low APGAR score, neonatal admission, low birth weight, IUGR, still birth, PPROM and FGR

Results

In the present study, a total of 50 pregnant women with cholestasis of pregnancy were included in the study. Majority of the women present in the study belong to the 22 to 30 years age group and the mean age was 25.76 +/- 4.88 years. The average BMI was 26.07 +/- 2.93 kg/sq. and majority of women belong to lower socio-economic status i.e., 64%. Most common presenting complaint was severe itching in the whole body 40% followed by itching in the palm and sole 30%.

Table 1: Age wise distribution among study group

Age wise category	Number	Percentage
20 or less	8	16
21-25 years	17	34
26-30 years	18	36
31-35 years	4	8
36 and above	3	6

Most of the subjects were in the age group of 26-30yrs

Table 2: Socio-economic status among study group

Socioeconomic status		
Lower	5	10
Lower middle	32	64
Upper	3	6
Upper middle	10	20

Most of the subjects were from lower middle class.

Table 3: BMI of pregnant patients among study group

BMI category		
25 kg/m2 and less	18	36
25 to 30 kg/m2	25	50
30 kg/m2 and more	7	14

The average BMI of subjects was 26.07±2.93 Kg/m^2

Table 4: Gravida status among study group

Gravida		
G1	31	62
G2	5	10
G3	8	16
G4	5	10
G5	1	2

Table 5: Complaints associated with pregnancy among study groups.

Complaint Profile		
Itching in palm and sole	15	30
Itching in palm and sole at night-time	1	2
Itching whole body at night-time	14	28
Severe itching in whole body	20	40

The most common presentation was severe generalised itching, 40% followed by itching in palm and sole, 30%.

Table 6: Gestational age at pruritus onset (in weeks)

Gestational age at pruritus onset (in weeks)	
Mean	33.22
Std Dev.	2.05327

The average gestational age at pruritus onset was 33.22±2.05

Table 7: Risk factors associated with pregnancy among this study group.

Risk factor status	Number	Percentage
Family history	8	32
H/O infertility treatment (ovulation induction)	2	8
H/O OC Pills	2	8
H/O Pruritus in Previous pregnancy	11	44
Past H/O IUFD	2	8

Most common risk factor was history of IHCP in previous pregnancy i.e., 44% followed by family history of IHCP 32%.

Table 8: Bile Acid levels of patients among study group

Bile acid category	Number	Percentage
40 and above	17	34
Less than 40	33	66

The average bile acid level was 44.09±25.68 micromole/lit, most of the subject had bile acid level of less than 40 micromole/lit that is 66%.

Table 9: Bilirubin levels of patients among study group.

Bilirubin	Number	Percentage
0.2-0.6	31	62
0.6-1.0	16	32
1-1.4	3	6

The average serum bilirubin level was 0.55±0.30 mg/dl and there was no clinically significant jaundice

Table 10: S.AST Levels in the study group

AST		
0-100	13	26
100-200	19	38
200-300	10	20
300 or more	8	16

The average AST level was 181.13±96.23 IU/L.

Table 11: S.ALT levels among study group

ALT		
0-100	17	34
100-200	15	30
200-300	13	26
300 or more	5	10

The average ALT level was 179.87±92.68 IU/L.

Table 12: S.ALP Levels among study group

ALP		
100-200	5	10
200-300	10	20
300 or more	35	70

The average ALT level was 435.45±205.89 IU/L.

Table 13: Gestational age at delivery

GA at delivery	Number	Percentage
Less than 37 (Preterm)	10	20
37-38	18	36
38-39	15	30
39 and above	7	14

The gestational age at delivery <37 weeks in 20% of the subjects.

Table 14: Mode of delivery among study group

Mode of delivery	Number	Percentage
Induced vaginal delivery	10	20
Vaginal Delivery	15	30
Caesarean section	25	50
Emergency LSCS	16	64
Elective LSCS	9	36

The 50% of pregnant women with IHCP delivery by vaginal route in which 20% were induced vaginal delivery and 50% were delivered by LSCS for various maternal and foetal indication.

Table 15: Indication of caesarean among study group

Indication of Caesarean	Number	Percentage
Foetal distress	8	32
MSL with FD	7	28
Previous LSCS	4	16
Cephalopelvic Disproportion	4	16
Footling breech	1	4
Placenta praevia	1	4

The most common indication for LSCS was foetal distress 32% followed by MSL with foetal distress 28%. The gestational age at delivery was less than 37 weeks in 20% women and most of the subjects were delivered after 37 weeks.

Table 16: Perinatal outcome of patients delivered among study group.

Perinatal outcomes	Number	Percentage
Foetal bradycardia	8	16
IUFD	2	4
Meconium-stained liquor	10	20
NICU Admission	6	12
Still birth	1	2

Most common adverse perinatal outcome was MSL (20%), foetal bradycardia (16%), foetal NICU admission (12%) followed by IUFD (4%).

Table 17: APGAR Score of babies at 1 minute delivered to study group

APGAR Score 1 min	Number	Percentage
Less than 7	17	34
7 or more	33	66

Majority of newborns to women with cholestasis had Apgar score more than 7 at 1 minute i.e., 66% and at 5 minutes 82%.

Table 18: APGAR Score of babies at 5 minutes delivered to study group.

APGAR Score 5 min	Number	Percentage
Less than 7	9	18
7 or more	41	82

Majority of newborns to women with cholestasis had APGAR score more than 7 at 1 minute i.e., 66% and at 5 minutes 82%.

Table 19: Baby weight of babies delivered among study group

Birth weight Category	Number	Percentage
Less than 2	3	6
2 to 2.5	18	36
More than 2.5	29	58

The average birth weight was 2.53±0.38 kg and 58% had foetal weight more than 2.5 kg.

Table 20: Correlation of bile acid levels and fetomaternal outcome

Bile acid and fetomaternal outcomes	Less than 40	40 and above	P value
Number of patients	**n 33**	**n 17**	
APGAR <7 at 1 min	5 (15.15)	12 (70.58)	**0.0001**
APGAR <7 at 5 min	1 (3.03)	8 (47.05)	**0.0001**
Low birth weight	8 (24.24)	13 (76.47)	**0.0004**
Foetal bradycardia	2 (6.06)	6 (35.29)	**0.0082**
IUFD	0	2 (11.76)	**0.0465**
Meconium-stained liquor	2 (6.06)	8 (47.05)	**0.0007**
NICU Admission	2 (6.06)	4 (23.52)	0.0748

A comparative assessment of feto-maternal outcome on the basis of bile acid was done, it was seen that over all adverse feto-maternal outcomes were significantly higher in subject with bile acid level more than 40 micromole/lit and above.

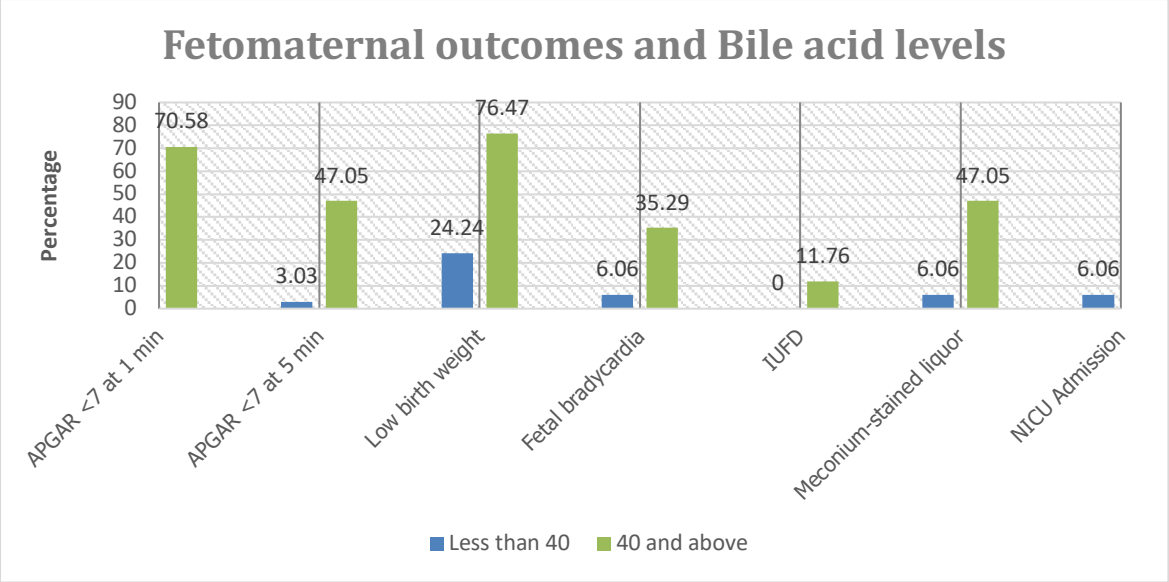

Figure 1: Bile Acid and Feto-Maternal Outcome

Discussion

The mean age in our study was 25.76±4.88 and the maximum number of cases were in the group of 26 to 30 years (36%)[table1], which was correlated well with study conducted by M rook et al, Skaur et al, Lt. col G Singh et al, M Padmaja et al, Dang Arbinder et al, Kavita et al respectively 27.5 year, 25.4 year, 25.8 year, 28.7 year, 26.5 year, 25.9 year and 31.7 year in the study conducted by Nighat Atftab et al, the lesser age was attributed to early marriage leading to early child bearing in our state. Most of the women in our study belong to the lower socioeconomic category (64%) [table2].

The average BMI of women in our study was 26.07±2.93 kg/sq.[table3] which was lower than study conducted by Nighat Aftab was 31.31±6.05. The lower BMI in our study is mainly due to low socio-economic status in our population. [12] Majority of women in our study were primigravida (62%) [table 4] and rest were multigravida, our study correlated well with M Padmaja et al, Dang Arbinder et al, Nina Mishra et al was 68.8%, 72.3%, 72.9% primigravida. Our finding was contrary to normal belief that IHCP is more common in multiparous women with advanced age, indicating possibly different presentation of IHCP in north India. [13]

In our study the most common complaint was severe itching in the whole body (40%) followed by itching in the palm and sole 30%[table5]. Most of the women in our study had onset of pruritus at 32 to 36 weeks of pregnancy and average of 33.22±2.5 weeks [table 6] which correlated well with the study by Dang Arbinder et al, M Padmaja et al, Amita Gupta et al, Nalini Sharma et al was respectively 33.4 weeks, 32 weeks, 30 weeks and 30 weeks. [14] The most common risk factor was history of IHCP in previous pregnancy was 44% followed by positive family history of IHCP (32%) and other were history of IUFD, history of OCP usage, history of infertility treatment [table 7], our study correlated well with M Padmaja et al, Amitagupta et al, Alaknanda et al where history of pruritus in previous pregnancy was 64.3%, 50% 61.3% respectively, positive family history was similar to the study by Nina Mishra et al 31.4%, Ruqqiya et al 30% and the incidence of oral contraceptive usage by Nina Mishra et al 8.6% and Ruqqiya et al 3.3%.

In our study the average bile acid level were 44.09±25.68 micromole/L[table8], most of the women had bile acid levels of less than 40 micromole/L (66%), our study correlated with Amitakant et al, Kavita et al, Nighat Aftab et al respectively 32±7.3 mg/dl, 26.81±9.85, 29±4.3. In our study the average serum bilirubin was 0.55±0.30 mg/dl and there was no case of clinical jaundice [table 9] and average AST level were 188.13±96.24 IU/L [table 10], average ALT level was 179±92.8 IU/L[table11] and average ALP level were 435.45±205.89 IU/L[table12] [15]

In our study 36% women get delivered between 37 to 38 weeks, 20% get delivered before 37 weeks which went into spontaneous preterm labour, 30% delivered between 38 to 39 weeks. Higher rate of preterm delivery was observed among patients with moderate and severe IHCP. In our study the mean age at delivery was 37.14±2.24 weeks [table 13] which correlated well with M. Rook et al, Anita Kant et al 36.63±2.57 weeks preterm deliveries frequently were significantly higher by Dang Arbinder et al i.e., 19.14.

In our study 50% women were delivered by LSCS out of which 64% were emergency LSCS and 36%

were elective LSCS, 30% had spontaneous vaginal delivery and induction was done in 20%. [table 14]. Most common indication for LSCS was foetal distress (32%) and followed by MSL with foetal distress (28%), increased chance of operative deliveries (50%) due to increased incidence of meconium-stained liquor and induction of labour [table 15]. There was no maternal mortality reported in this study.

In our study 54% cases were associated with adverse pregnancy outcome in which 16% were delivered with foetal distress, 20% preterm babies and 20% had meconium staining of amniotic fluid which was significantly higher in our setup, our setup is tertiary care centre and many patients were referred from small centres [table 16].

Our study correlated well with S Kaur et al, Arora et al where foetal distress was present in 16% and 15.6% cases and preterm delivery in Siddhu et al, Nina Sharma et al were 14.8% and 12.8% respectively and meconium staining were noted in Lt. Col. G Singh et al i.e., 18.52% and M Padmaja et al i.e., 17.8% and lower in S. Kaur et al and Anita Kant et al 6.3% and 9% respectively, 2% of patient came with IUFD which were unbooked and result correlated with Kavita et al, Ghimire et al, Nighat Aftab et al were 2%, 6.25%, 7.1% respectively. [16]

Apgar scores less than 7 at 1 min were found in 34% of neonates [table 17] and 9% at 5 minutes [table 18]. Our result correlated well with Ghimire et al, Nighat Aftab et al were 13.75%, 8.2% respectively, despite high incidence of meconium staining Apgar score is nearly normal in the studies it shows that meconium staining of amniotic fluid seen in IHCP was not due to foetal distress it is because of bile acids increased colonic mortality and meconium passage. In our study average birth weight was 2.53±0.83 kg, low birth weight was seen in 21% babies, most of the babies have birth weight of 2-2.5 kg (36%), only 3 babies have birth weight less than 2kg [table 19]. our study correlated well with Ghimire et al, Nighat Aftab et al, Anita Kant et al were 22.5%, 27.1%, 22.7% babies were low birth weight.

In our study NICU admission rate was 12% due to meconium aspiration, respiratory distress, low birth weight, prematurity, similar results were found in the study conducted by Ruqqiya et al, Nina Mishra et al, Nighat Aftab et al was 13.6%, 10%, 11.8% respectively. A comparative assessment of fetomaternal outcomes on the basis of bile acid levels was done,2 categories were made i.e., TSBA <40 µmol/lit and >40µmol/lit. It was seen that the proportion of cases of low APGAR score, low birth weight, fetal bradycardia, meconium-stained liquor, NICU admission was significantly higher in the cases with bile acid levels >40µmol/lit. Similar results were shown in the study conducted in the UK where women with severe IHCP had significantly higher chances of preterm delivery, stillbirth, and NICU admission. [table 20, fig 1]

Conclusion

Intrahepatic cholestasis of pregnancy is a most common liver disorder seen in pregnancy. The etiology of IHCP is not fully understood but likely involves a combination of genetic susceptibility, hormonal factors and environmental factors. It is typically a reversible cholestatic disease presenting in the 2nd and 3rd trimester of pregnancy. Recurrence during subsequent pregnancy has been reported.

Laboratory analysis includes elevated serum bile acid level > 10 µmol/lit with elevated transaminases level, depending upon serum bile acid levels IHCP categorized into mild (10-39 µmol/lit), moderate (40-99 µmol/lit), severe (>100 µmol/lit) which having serious perinatal morbidity and mortality. Awareness of this complex disorder which is associated with poor perinatal outcome is essential and a challenge to obstetricians to ensure its prompt diagnosis and risk assessment for developing specific plans for any antenatal intervention, management of delivery and neonatal outcome.

In our study we found a positive correlation between elevated serum bile acid levels and adverse fetomaternal outcomes. Close monitoring of women with severe ICP is essential to prevent adverse neonatal outcomes like fetal distress, meconium-stained liquor, preterm labor, sudden IUFD and stillbirth. Bile acid estimation is a simple, easily available and minimally invasive test with quick results which help to assess the severity of disease. Hence the better understanding of pathophysiology of conditions associated with elevated serum bile acid levels brings hope for future therapeutic strategies.

References

1. Clinical Updates in Women's Health Care Summary: Liver Disease: Reproductive Considerations. Obstet Gynecol. 2017; 129:236.
2. Geenes V, Williamson C. Intrahepatic cholestasis of pregnancy. World J Gastroenterol. 2009; 15:2049.
3. Bacq Y. Intrahepatic cholestasis of pregnancy. Clin Liver Dis 1999; 3:1.
4. Abedin P, Weaver JB, Egginton E. Intrahepatic cholestasis of pregnancy: prevalence and ethnic distribution. Ethn Health. 1999; 4:35.
5. Reyes H, Gonzalez MC, Ribalta J, et al. Prevalence of intrahepatic cholestasis of pregnancy in Chile. Ann Intern Med. 1978; 88:487.
6. Wikström Shemer E, Marschall HU, Ludvigsson JF, Stephansson O. Intrahepatic cholestasis

of pregnancy and associated adverse pregnancy and fetal outcomes: a 12- year population-based cohort study. BJOG. 2013; 120:717.
7. Abu-Hayyeh S, Ovadia C, Lieu T. Prognostic and mechanistic potential of progesterone sulfates in intrahepatic cholestasis of pregnancy and pruritus gravidarum. Hepatology. 2016; 63:1287–1298.
8. Kondrackiene J, Beuers U, Zalinkevicius R, TauschelHD, Gintautas V, et al. Predictors of premature delivery in patients with intrahepatic cholestasis of pregnancy. World J Gastroenterology. 2007; 13(46): 6226–6230.
9. Kondrackiene J, Kupcinskas L. Intrahepatic cholestasis of pregnancy- current achievements and unsolved problems. World J Gastroenterology. 2006; 14(38): 5781–5788.
10. Pusl T, Beuers U. Intrahepatic cholestasis of pregnancy. Orphaned Journal of Rare Diseases. 2007; 2: 26.
11. Glantz A, Marschall HU, Mattsson LA. Intrahepatic Cholestasis of Pregnancy: Relationships between Bile Acid Levels and Fetal Complication Rates. Hepatology. 2004; 40(2): 467–474.
12. Lt Col G Singh, Maj K Sidhu. Cholestasis of Pregnancy: A Prospective Study (2007) MJAFI. 2008; 64: 343-345
13. Padmaja M, Bhaskar P, Kumar GJ, Seetha R, Mahasweta C. A study of obstetric cholestasis. The Journal of Obstetrics and Gynecology of India. 2010 Jun 1; 60(3):225-31.
14. Dang A, Agarwal N, Bathla S, Sharma N, BalaniS. Prevalence of liver disease in pregnancy and its outcome with emphasis on obstetric cholestasis: An Indian scenario. The Journal of Obstetrics and Gynecology of India. 2010 Oct 1; 60(5):413-8
15. Amita G, Tania K, Yudhishtervir G, Jyoti H. Cholestasis of pregnancy. J Obstet Gynecol India. 2009; 59:320-323.
16. Sharma N, Panda S, Santa Singh A. Obstetric Outcome during an Era of Active Management for Obstetrics Cholestasis. The Journal of Obstetrics and Gynecology of India. 2015:1-4 17.