INTRAHEPATIC CHOLESTASIS OF PREGNANCY: CURRENT TRENDS

Authors

Dr. Vani Malhotra
Professor
Department of obstetrics & Gynaecology
PGIMS
Rohtak,India.

Dr. Parveen Malhotra
Senior professor and head
Department of Medical Gastroenterology
PGIMS
Rohtak, India.

I. INTRODUCTION

Pregnancy is affected by variety of liver disorders out of which the commonest disorder is Intrahepatic cholestatsis of pregnancy (ICP),is also called as obstetric cholestasis .[1]This multifactorial disease manifests itself by pruritis without any skin rash with deranged liver function test (above the normal range of 0-19micromol/l) which resolves after delivery.[2]It has got multifactorial etiology which is affected by genetic and environmental factors and its incidence differs geographically from 0.1%-15.65%.[2,3] Viral hepatitis is another importantreason of jaundice in pregnancy after ICP.

Obstetric cholestasis is evenly distributed among primigravida and multigravida women. It tends to recur in subsequent pregnancies. Increased associations have been observed in multiple pregnancies, women with gall stones and women seropositive for hepatitis C.[4]
ICP has got lethal outcome for unborn child but only quality of life is impaired for pregnant women. ICP is usually not given due attention and neglected , even at good obstetric centers.[5]

II. PATHOGENESIS

The women are at risk to develop ICP due to certain genetic factors.

1. **Hormonal:** Rise in levels of estrogen and progesteronecauses an accumulation of bile salts into maternal circulation resulting in biliary stasis.

The pathogenesis is complex. Hepatocytes are responsible for making bile acids and secretion of bile which reaches from liver to the gall bladder, occurs in the bile secretory unit madeup of a canalicular network. It is thought that cytotoxic bile acids will accumulate when this pump malfunctions.[6] It is the malfunction in protein carrier or transporter which occurs due to high level of sex hormone in pregnancy responsible for cholestasis in pregnancy which is provided by following observations-[7]

- The symptoms usually manifest itself in last trimester of pregnancy.
- Higher incidence of ICP in multiple pregnancy than singleton pregnancy.
- Resolution of symptoms after delivery.
- Recurrence in next pregnancy up to45 – 70% of patients.

2. **Genetic:** Certain genetic mutations encoding biliary transport proteinbecomes the basis forgenetic predisposition for ICP responsible forincreased incidence in mothers and sisters of ICP patients.[8-9]

3. **Exogenous Factors:** Some environmental and alimentary factors are believed to affect the genetically predisposed women. Low levels of selenium have been linked to increased incidence of ICP.[10]

III. FETAL PATHOPHYSIOLOGY

There is an increase chance of amniotic fluid meconium staining in ICP which results in stillbirth. Chronic placental insufficiency has not been proven responsible for fetal death as evidenced by normal birth weights for gestational age and optimum Doppler velocitimetry. However, acute anoxia causing petechial hemorrhagesin pleura, pericardia and adrenal glandsare found to be responsible for fetal deaths.[5,11]

During ICP, increased maternal levels of bile acids leads to higher levels of bile acid not only in amniotic fluid but also in cord plasma and meconium.[12]These bile acids are responsible for increase fetal colonic motility and causes vasoconstriction of human placental chorionic veins.[13]

IV. CLINICAL PRESENTATION

- Pruritis is the main presenting symptom usually observed in multiple pregnancy in third trimester, particularly involving the hands and soles spreading to extremities and trunk without rash. Pruritis may progressively worsen as gestation progresses until birth when it will rapidly clear. The pruritis is more severe at night. Pruritis may be due to deposition of bile salts in the nerve endings of skin.[14]
- Sleep disturbances are of severe nature and may be due to severe pruritis.
- Dark urine, pale stools are uncommon.
- Jaundice and steatorrhea is rare and is usually seen after two to four weeks after starting of pruritis and is manifested in around ten percent of cases.[15]
- Occasionally malaise and anorexia may also be seen.
- Intrapartum and postpartum hemorrhage
- On examination- excoriation marks may be seen. Icterus is rare. If rash is present, one should consider other diagnosis.

V. DIFFERENTIAL DIAGNOSIS

- Preexisting liver disease, alcohol or drug dependence
- Viral hepatitis- check viral serology for hepatitis A, B, C, Cytomegalovirus and Epstein virus
- Autoimmune liver disease

- Pruritic urticarial papules and plaques (PUPPP syndrome).
- Pre eclampsia
- Acute fatty liver of pregnancy
- HELLP syndrome

VI. COMPLICATIONS

1. Maternal Complication

1) Preterm delivery
2) Intrapartum and postpartum haemorrhage

2. **Fetal Complications: The** serum bile acid levels of more than 100 micromole/l defined as severe cholestasis leads to increased incidence of preterm birth, meconium passage, NICU admission, IUFD.

VII. DIAGNOSIS

Bile acids are usually elevated in ICP and their levels are strongly correlated with adverse pregnancy outcomes. In ICP, bile acid levels are usually>19micromol/l with raised cholic acid levels and lower levels of chenodeoxycholic acid.The diagnosis is more likely if resolution of symptoms corresponds todecreased itching and bile acids level.

The severity of a case of ICP is defined according to the levels of bile acids. ICP is classified by mild with bile acid levels of 19-39micromol/l, moderate(40-99micromol/l) and severe when bile acid values are more than 100micromol/l.[16,17]The bile acid levels ofmore than 100 micromol/l, leads to increased chances of stillbirth .[18]

A prospectivestudy was conducted on 505 antenatal women complicated by ICP with the aim to correlate serum bile acid levels with fetal complications. It was concluded that there were fewer fetal complications associated with bile acid concentrations ofless than 40micromol/l but gotincreased by 1-2% for addition 1micromol/l of serum bile acids level.[16]

Another study was conducted on 713 women presenting with severe ICP (>40micromol/l) and found higher risk of spontaneous or iatrogenic preterm delivery, need ofneonatal unit admissionas well as still birth rate. The fetal risk was not established with mild ICP and recommended further studies to evaluate the cut off threshold.[18]

Rise in serum transaminases are usually not diagnostic. Their values should be serially checked every 1-2 weeks if initial test is negative with persistent pruritis.

- Prothrombin time (INR) can be increased in severe cases
- Liver and GB sonography to exclude obstructive disease
- Liver biopsy is usually not necessary.

VIII. PHARMACOLOGICAL TREATMENT

Pharmacologic treatment either in form of topical or systemic administration in ICP reduces the clinical manifestations of pregnant female and prevents fetal distress and sudden fetal demise.

- **Topical Treatment**: are safe but their efficacy is low.Common topical emollients used for symptoms relief are sorbelone lotion,calamine lotion,pine tarsolsolution, aqueous cream with menthol or bicarbonate of soda baths.Uptill now there are no studies which prove or disprove use of above medications but their safety profile in pregnancy is known and their use can lead to mild decrease in pruritis in pregnant females.
- **Systemic Treatment**: It includes ursodeoxycholicacid (UDCA), cholestyramine, s.adenosyl methionine, dexamethasone, rifampicin and antihistaminic agents.

1. **UDCA: I**t is hydrophilic bile acid in nature and leads to improvement in clinical and biochemical parameters in different kind of cholestatic liver disease. It is supposed to safeguard bile ducts injury from hydrophobic bile acids and promotes excretion of these compounds thus normalizing the increased CA/CDCA ratio. It also reduces the placental transfer of bile acids thus improving the fetal prognosis. It is given in doses of 10-15mg/kg and only mild side in form of nausea, vomiting and diarrhea are noted.The Royal college of obstetricians and gynecologist guidelines recommends that UDCA may give symptomatic and biochemical relief to mother yet not fully protective to the fetus.[19] Even the longest trial (PITCHES: PHASE III trial in intrahepatic cholestasis of pregnancy) in UK concluded that UDCA may not be effective in improving perinatal outcome.[20]

2. **S. Adenosyl Methionine (SAM):** It is precursor of glutathione and donates methyl group to phosphatidyl choline in liver thus promoting the biliary excretion of hormonal metabolites. There is insufficient evidence of its role in maternal and fetal relief.[21]It is usually administered orally or dose used is 1000mg /d.

3. **Phenobarbital:** It causes symptomatic relief only but not effective in improving biochemical parameters.

4. **Dexamethasone:** It is used in starting dose of 12 mg four times a day for seven days and then gradually tapered. It causes significant improvement in clinical symptoms and biochemical parameters but associated with side effects like restlessness, sleeplessness and glucose impairment and reduced fetal movements.

5. **Cholestyramine:** They interrupt enterohepatic circulation by binding to bile acids. They should not be combined with UDCA. Increased feto-maternal hemorrhage is seen as a result of Vitamin K deficiency.

6. **Rifampicin:** A recognized liver enzyme inducer should be given to women who fails to respond to UDCA.

7. **VIT K:** Women should be advised vit k when prothrombin time is prolonged in doses of 5-10 mg daily. There are more chances of Post partum hemorrhage in women who do not receive vitamin K.

8. **Antihistaminics:** Cetirizine 10mg od to bd or promethazine 25 mg at night may be used in relieving pruritis.

IX. ANTENATAL MANAGEMENT

- Physician/hepatologist should always be involved in the management of ICP especially when biochemical parameters fall in the severe range or early or atypical presentation.
- Management should be advised in tertiary care centre.
- Women should always be advised admission in case of severe ICP and should be counseled about adverse fetal outcomes.
- Daily fetal kick counts should be maintained.
- Antenatal fetal surveillance should be done more often however studies have shown still births even after normal studies.
- LFTs should be measured weekly until delivery.
  Fegan suggested that antenatal surveillance with non- stress test calculation of amniotic fluid volume and umbilical artery Doppler should be initiated from 30 week onwards till delivery and biochemical markers should be repeated weekly.[20]

X. INTRANATAL MANAGEMENT

1. **Timing of Delivery**: Many studies have examined bile acid levels in association with adverse pregnancy outcomes and a positive relation between maternal serum bile acid levels and adverse fetal outcomes has been documented.

Glantz et al estimated that there is increased risk ofone to two percent of adverse events for an increment of micromole/L of bile acid level above 40umol /l .[16]

A meta-analysis by Cui and colleagues reported an increased association of raised serum bile acid levelsin pregnant female (>40 micromole/L) and adverse perinatal outcomes but not still births.[21]

Similarly, Ovadia et alconfirmed increase risk of stillbirths with maternal bile acid levels more than 100 micromole/L. Women with level below this threshold can be reassured and needed frequent bile acid testing.[22]

A cohortstudy in 2015 demonstrated an increased risk of adverse perinatal outcomeespecially 10%risk of stillbirths with levels greater than 100u mol/L.[23]

Further, Kawakita et al showed increased risk of meconium-stained liquor and stillbirth with bile acid levels greater than 40u mol/l and 100u mol/L respectively.[24]

The relationship of bile acid levels and adverse pregnancy outcomes is well known but the timing of delivery for pregnant patients complicated with ICP is not clear

but from above mentioned studies, optimal timing of delivery in ICP patients can be formulated as shown in Table I.

2. Continuous fetal monitoring should be done in labour.
3. Active management of third stage of labour should be considered.
4. Coagulation studies should be advised in severe cholestasis.

Henderson recommended that decision to induce labourhas to be individualized after weighing the prematurity risk with the risk of sudden fetal demise. However, delivery should not be delayed beyond 37 weeks.[25]

XI. POSTNATAL MANAGEMENT

- Biochemical abnormalities are usually resolvedwithin one week of delivery. One should exclude chronic liver diseases if these abnormalities persist beyond six weeks.
- Symptomatic relief in pruritis will usually be seen by 48 hour.
- Risk of recurrence should be explained to the mother to the extent of 40-60%
- Female family members should also be counselled for risk of ICP.
- Avoid estrogen containing contraceptive devices.
- Breast feeding is not contraindicated.

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Table 1: Plan of Termination of Pregnancy

ICP	Bile Acid Level(Micromole/L)	Termination
Mild	19-40	40 weeks
Moderate	40-99	38-39 weeks
Severe	>100	35-36 weeks

HIGHLIGHTS OF ICP

- UDCA isfirst line therapy
- All therapies primarily aimed at maternal itching
- Ursodeoxycholic acid500mg BID or 300mg TID, titrate to symptoms max 2g/d
- Antihistaminics- Hydroxyzine or Chlorpheninamine (less sedating)
- The recurrence risk (60-90%) should be kept in mind
- Watch on bile acid and liver function tests should be kept for ensuring normalization
- Ultrasound abdomen and on detection of any abnormality Gastroenterologist consultation should be taken
- The contraceptives with high estrogen level should be avoided.

