**INTRAHEPATIC CHOLESTASIS OF PREGNANCY: CURRENT TRENDS**

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Pregnancy is affected by variety of liver disorders out of which the commonest disorder is Intrahepatic cholestatsis of pregnancy (ICP), also known as obstetric cholestasis .1 This multifactorial disease manifests itself by pruritis in the absence of skin rash with abnormal 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 varies geographically between 0.1%-15.65%.2,3 Viral hepatitis is second most common cause 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. Inspite of these risks, ICP is often neglected and treated expectantly, even in obstetric centers.5

**PATHOGENESIS**

There are certain genetic factors which predispose the woman to develop ICP.

HORMONAL – Rise in levels of estrogen and progesterone causes 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 from liver to the gall bladder occurs in the bile secretory unit made up 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

1. The symptoms usually manifest itself in last trimester of pregnancy.
2. Higher incidence of ICP in multiple pregnancy than singleton pregnancy.
3. Resolution of symptoms after delievery.
4. Recurrence in next pregnancy upto 45 – 70% of patients.

GENETIC – Certain mutations in genes encoding biliary transport protein becomes the basis for genetic predisposition for ICP responsible for higher incidence in mothers and sisters of patients with ICP.8-9

EXOGENOUS FATORS – 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

**FETAL PATHOPHYSIOLOGY-**

There is increase chances of meconium staining of amniotic fluid in ICP which results in stillbirth. But it has been concluded in studies that chronic placental insufficiency is not responsible for fetal death as evidenced by adequate birth weights for getational age and normal Doppler velocitimetry. However, acute anoxia causing petechial haemorrhages in pleura, pericardia and adrenal glands are found to be responsible for fetal deaths.5,11

During ICP, increased maternal levels of bile acids leads to increased bile acid levels in amniotic fluid, cord plasma samples and meconium.12 These bile acids are responsible for increase fetal colonic motility and induce vasoconstriction of human placental chorionic veins.13

**CLINICAL PRESENTATION –**

1. 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
2. Sleep disturbances are of severe nature and may be due to severe pruritis.
3. Dark urine, pale stools are uncommon.
4. Jaundice and steatorrhoea is rare and is usually seen 2-4 weeks after onset of pruritis and is seen only in 10% of cases.15
5. Occasionally malaise and anorexia may also be seen.
6. Intrapatum and postpartum haemorhage
7. On examination- excoriation marks may be seen. Icterus is rare. If rash is present, one should consider other diagnosis.

**DIFFERENTIAL DIAGNOSIS –**

1. Preexisting liver disease, alcohol or drug dependence
2. Viral hepatitis- check viral serology for hepatitis A, Hepatitis B, Hepatitis C, CMV, EBV
3. Autoimmune liver disease
4. Pruritic urticarial papules and plaques (PUPPP syndrome) or polymorphic eruption of pregnancy.
5. Pre eclampsia
6. Acute fatty liver of pregnancy
7. HELLP syndrome

**COMPLICATIONS-**

MATERNAL COMPLICATION-

1. Preterm delivery
2. Intrapartum and postpartum haemorrhage

FETAL COMPLICATIONS –

Serum bile acid levels more than 100 micromole/l defined as severe cholestasis leads to increased incidence of preterm birth, meconium passage, NICU admission, IUFD.

**DIAGNOSIS –**

Bile acids are usually elevated in ICP and their levels are strongly correlated with adverse pregnancy outcomes. In ICP, bile acid levels are typically >19micromol/l with increased cholic acid levels and decreased chenodeoxycholic acid levels.The diagnosis is more likely if itching and bile acids resolve after delievery.

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(40-99 micromol/l) and severe when bile acid values are more than 100micromol/l.16,17 Once the bile acid levels are more than 100 micromol/l, there is an increase in stillbirth risk.18

A prospective study 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 bile acid concentrations less than 40micromol/l and they were observed to increase by 1-2% per addition 1micromol/l of serum bile acids.16

Another study was conducted on 713 women presenting with severe ICP (>40micromol/l ) and found an increased risk of spontenoeous or iatrogenic preterm delivery, neonatal unit admission and 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) may be prolonged in severe cases

Liver and GB sonography to exclude obstructive disease

Liver biopsy is usually not necessary.

**PHARMACOLOGICAL TREATMENT-**

Pharmacologic treatment either in form of topical or systemic administration in ICP reduces the maternal symptoms and prevents fetal distress and sudden fetal death.

**A-TOPICAL TREATMENT**-are safe but their efficacy is low. Common topical emollients used for symptoms relief are sorbelone lotion, calamine lotion, pine tarsol solution, aqueous cream with menthol or bicarbonate of soda baths. There are no trial data to support of refute the use of these products .They are safe in pregnancy and clinical experience suggests that for some women they may provide slight temporary relief of pruritis.

**B-SYSTEMIC TREATMENT**-

It includes ursodeoxycholic acid (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 believed to protect bile ducts against injury by 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 diarohea are noted. The Royal college of obstetricians and gyanecologist guidelines states 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 as an initial dose of 12 mg four times a day for 7 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 haemorrhage 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 prothombin time is prolonged in doses of 5-10 mg daily. There are more chances of PPH in women who were not given vitamin K.

**8) ANTIHISTAMINICS** –cetrizine 10mg od to bd or promethazine 25 mg at night may be used in relieving pruritis .

**ANTENATAL MANAGEMENT-**

1-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.

2-Management should be advised in tertiary care centre.

3-Women should always be advised admission in case of severe ICP and should be counseled about adverse fetal outcomes.

4-Daily fetal kick counts should be maintained.

5-Antenatal fetal surveillance should be done more often however studies have shown still births even after normal studies.

6. LFTs should be measured weekly until delivery.

Fegan suggested that antenatal surveillance with non- stress test estimation of amniotic fluid volume and umbilical artery Doppler should be initiated from 30 week onwards till delievery and biochemical markers should be repeated weekly.20

**INTRANATAL MANAGEMENT**-

1. Timing of delievery

Many studies have examined bile acid levels in association with adverse pregnancy outcomes and it has been observed that a positive relation exists between maternal serum bile acid levels and adverse fetal outcomes.

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

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

Similarly, Ovadia et al confirmed 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 cohort study in 2015 demonstrated an increased risk of adverse perinatal outcome especially 10%risk of stillbirths with levels greater than 100 u mol/L .23

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

While the relationship of bile acid levels and adverse pregnancy outcomes is clear, the optimal time of delievery 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 labour should be individualized after weighing the risk of prematurity with the risk of sudden fetal demise. However, delievery should not be delayed beyond 37 weeks.25

**POSTNATAL MANAGEMENT**-

1-Biochemical abnormalities are usually resolved within one week of delivery. One should exclude chronic liver diseases if these abnormalities persist beyond six weeks.

2-Symptomatic relief in pruritis will usually be seen by 48 hour.

3-Risk of recurrence should be explained to the mother to the extent of 40-60%

4-Female family members should also be counselled for risk of ICP.

5-Avoid estrogen containing contraceptive devices.

6-Breast feeding is not contraindicated.

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**TABLE I- 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 is current recommended treatment first 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)
* Discuss recurrence risk (60-90%)
* Repeat bile acid, liver function tests to ensure normalization
  + Consider right upper quadrant ultrasound or referral to GI if abnormal
* Avoid high estrogen containing contraceptives