IN THE
NAME
OF GOD

INTRAHEPATIC CHOLESTASIS OF PREGNANCY

I.C.P

FARZANEH VASHGHANI FARAHANI
T.U.M.S(OB&GYN)
DEC,15,2021

Incidence and epidemiology

❖ICP is the most common liver disease unique to pregnancy .

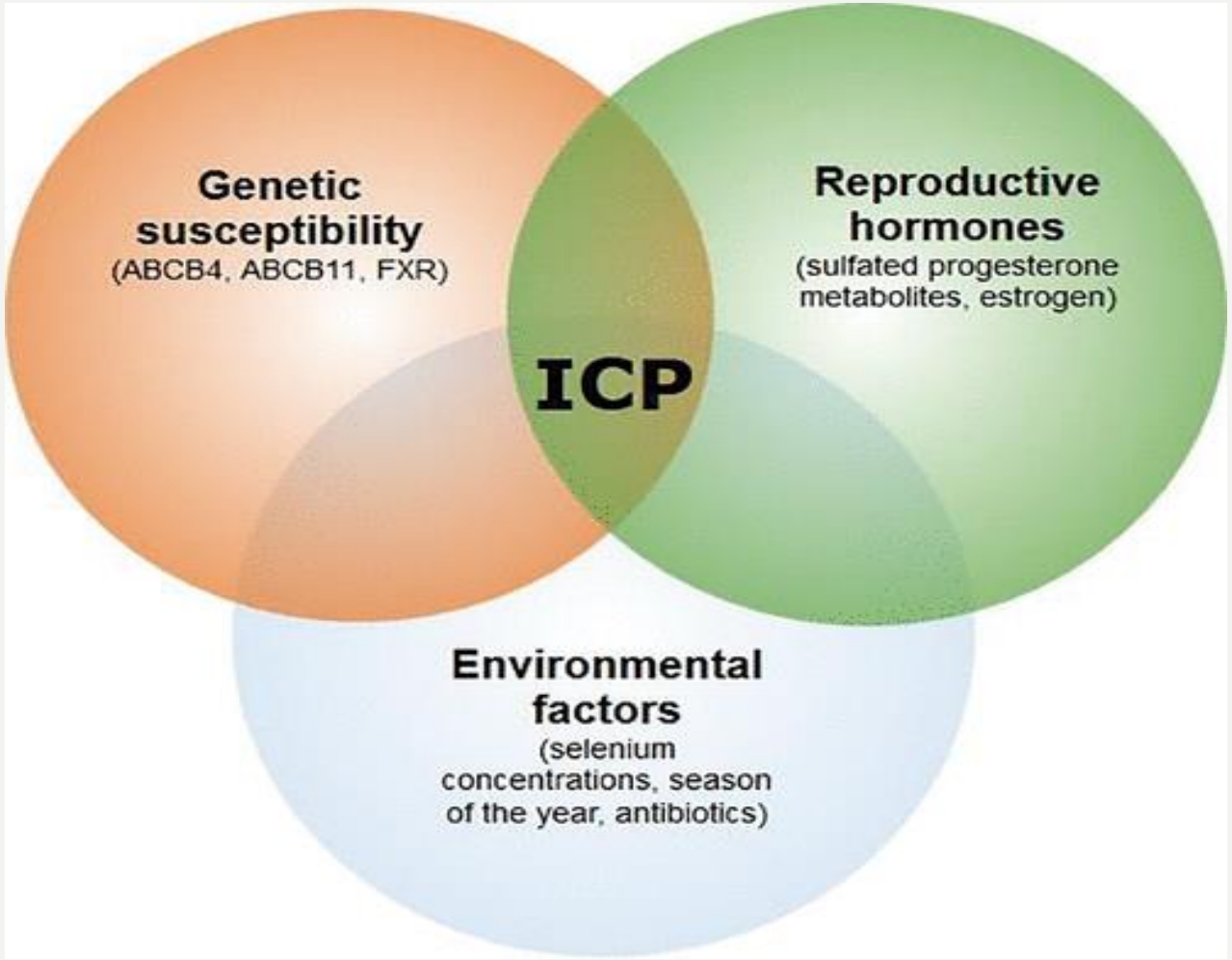
❖The reported incidence of ICP varies widely worldwide, ranging from <1 to 27.6 % .

- In the U.S.A (0.32 % to 5.6 %)
- Across Europe (0.5 to 1.5 %) with the highest rates in Scandinavia .
- Indian-Asians and Pakistani Asians (1.2 to 1.5 %).
- The Araucanos Indians in Chile have the highest incidence worldwide at 27.6 percent .

❖Geographic variations may reflect differences in susceptibility between ethnic groups, as well as differences in environmental factors .

- The disease occurs more commonly in the winter months in some countries (Sweden, Finland, Chile) .
- It is more common in multiple gestations (twins 20.9 versus singletons 4.7 %,triplets 43 % versus twins 14 % in one study from Finland).
- Other epidemiologic factors include chronic hepatitis C, prior history or family history of ICP, and advanced maternal age .
- Women with a past history of ICP frequently have ICP in subsequent pregnancies.

Etiology


Genetic susceptibility
(ABCB4, ABCB11, FXR)
Reproductive hormones
(sulfated progesterone metabolites, estrogen)
ICP
Environmental factors
(selenium concentrations, season of the year, antibiotics)

Genetic susceptibility

- This is supported by evidence of familial clustering, increased risk in first-degree relatives, increased risk in some ethnic groups, and a high recurrence rate (60 - 70 %).
- The *ABCB4* (adenosine triphosphate-binding cassette, subfamily B, member 4) gene encoding the multidrug resistance 3 (MDR3) protein (a canalicular phospholipid translocator).
- *ABCB4* is primarily involved in a subtype of progressive familial intrahepatic cholestasis (PFIC3).
- Heterozygous mutations in *ABCB4* (also called *MDR3*) have been found in a large consanguineous family in whom some women had episodes of cholestasis during pregnancy .
- The prevalence of such *ABCB4* gene mutations in Caucasian patients with ICP is 16 % .
- Some genes encoding for other canalicular transporters or their regulators may also be involved in ICP pathogenesis (*ABCB11, ATP8B1, ABCC2, NR1H4*) .

Hormonal factors

Estrogen :

Cholestasis occurs in women taking COCPs

- ICP occurs mainly in the 2nd half of pregnancy when serum concentrations of estrogen reach peak levels
- ICP is more common in multifetal pregnancies
- ICP has been reported in early pregnancy after OHSS
- ICP resolves after delivery of the placenta, which was a major source of estrogen production

Progesterone:

- Large amounts of sulfated progesterone metabolites in pregnancy may result in saturation of the hepatic transport system(s) utilized for biliary excretion of these compounds .
- Pregnancy also decreases sulfotransferase activity .

Environmental factors

- More common in the winter months in some countries(Sweden ,Finland, Chile).
- low Selenium levels due to diet and low vitamin D levels due to lack of exposure to sunlight have been implicated .

Underlying liver disease

- Hepatitis C
- Nonalcoholic liver cirrhosis .
- This suggests that some women who develop ICP have underlying liver disease revealed by pregnancy or contributing to the development of ICP.

PRURITUS

(No Rash)

Elevation in serum bile acid concentrations

ICP

Typically developing in the late 2nd and/or 3rd trimester

Rapidly resolving after delivery

Clinical findings

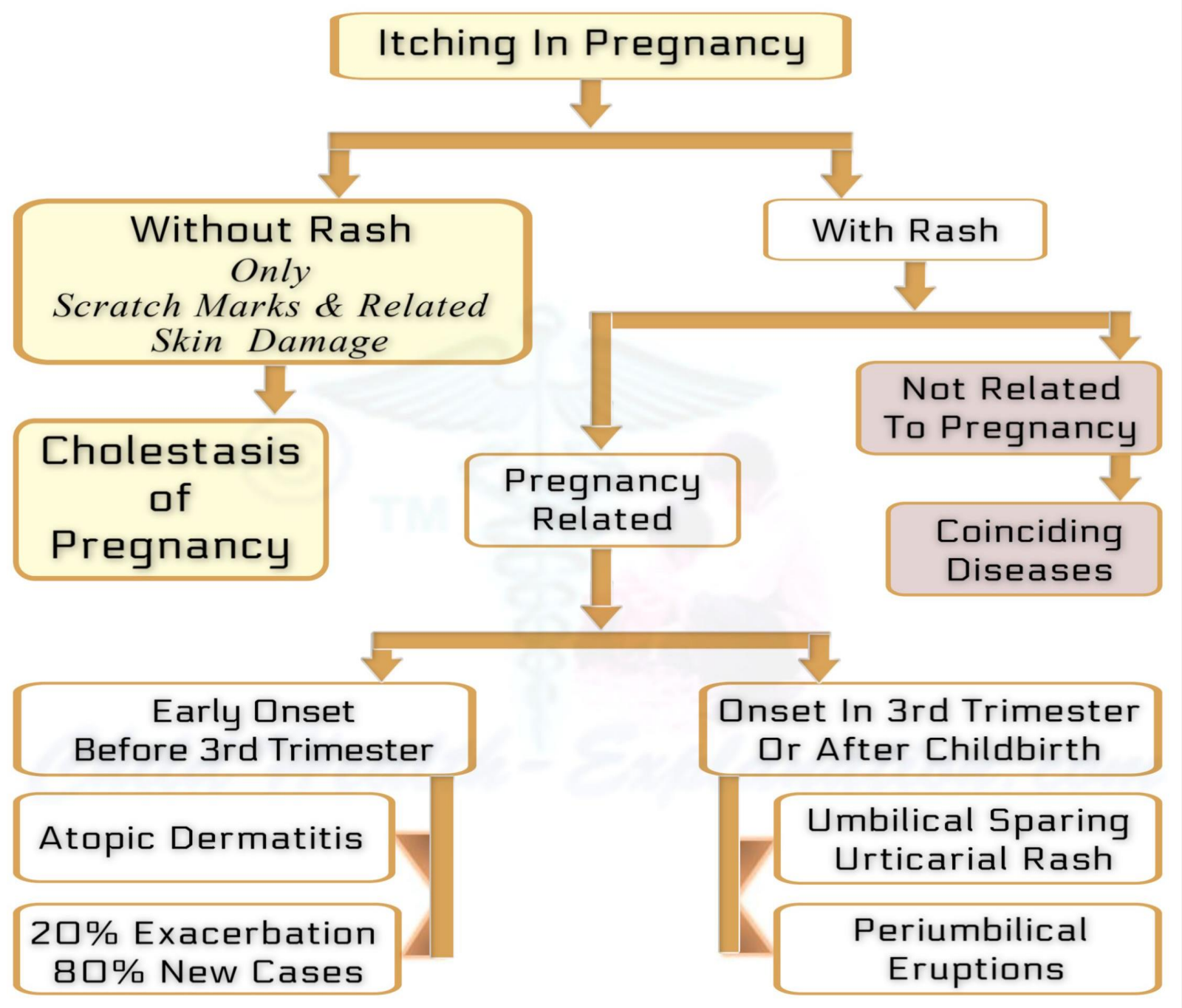
Pruritus is the hallmark of disease ,which ranges from mild to intolerable.

- It is often generalized, but starts and predominates on the palms and soles , is worse at night.
- RUQ pain, nausea, poor appetite, sleep deprivation, or steatorrhea may occur.
- It usually develop during the late second or third trimester.
- Transient first trimester symptoms have been linked to OHSS after IVF.
- Encephalopathy or other stigmata of liver failure, if present, should initiate a search for other causes of liver disease.

Physical examination

- Scratch marks, excoriations, and prurigo nodules secondary to scratching, without primary skin lesions .

- Jaundice occurs in 14 -25 % of patients, typically developing 1-4 wks after the onset of itching .


Itching In Pregnancy
Without Rash
Only
Scratch Marks & Related
Skin Damage
With Rash
Cholestasis
of
Pregnancy
Pregnancy
Related
Not Related
To Pregnancy
Coinciding
Diseases
Early Onset
Before 3rd Trimester
Onset In 3rd Trimester
Or After Childbirth
Atopic Dermatitis
20% Exacerbation
80% New Cases
Umbilical Sparing
Urticarial Rash
Periumbilical
Eruptions

Laboratory findings :

An increase in serum total bile acid concentration is the key laboratory finding (present in >90 % of affected pregnancies), and may be the first and only laboratory abnormality.

- Cholic and chenodeoxycholic acid levels are increased, but there is a marked elevation of the cholic/chenodeoxycholic acid ratio (>42 %) compared with pregnant women without ICP .
- Serum aminotransferases (elevated in 60 % of cases), which are usually less than two times the upper limit of normal, but may reach values greater than 1000 unit/L .
- Alkaline phosphatase, which may be elevated fourfold but is not specific for cholestasis during pregnancy due to expression of the placental isoenzyme.
- Total and direct bilirubin concentrations are elevated in 25 % of cases although T.B rarely exceed 6 mg/dL .

- The serum concentration of gamma- glutamyl transpeptidase (GGT) is normal or modestly elevated (30 % of cases).
- The prothrombin time is usually normal.
- When prolonged, it is typically secondary to vitamin K deficiency or secondary to use of bile acid sequestrants (such as Cholestyramine) rather than liver dysfunction.

Ultrasonography

- ICP is not associated with abnormalities on imaging

Pathology

- Histopathology is characterized by cholestasis without inflammation .
- Bile plugs in hepatocytes and canaliculi predominate in zone 3.
- The portal tracts are unaffected.

Diagnosis

The diagnosis of ICP is based upon the presence of pruritus associated with:

- Elevated total serum bile acid levels,
- Elevated aminotransferases,

Severe cholestasis is consistently defined as bile acids over 40 micromole /L (20 % of cases).

- Because pruritus can precede the rise in serum bile acids by several weeks, we suggest repeating laboratory tests weekly if total bile acid and aminotransferase levels are initially normal.

- If Ursodeoxycholic acid(UDCA) is started empirically, elevated bile acid and transaminase levels may never be detected.

Diagnostic evaluation and differential diagnosis

❖Laboratory studies should include:

- Total serum bile acid concentration
- Serum aminotransferases (ALT,AST)

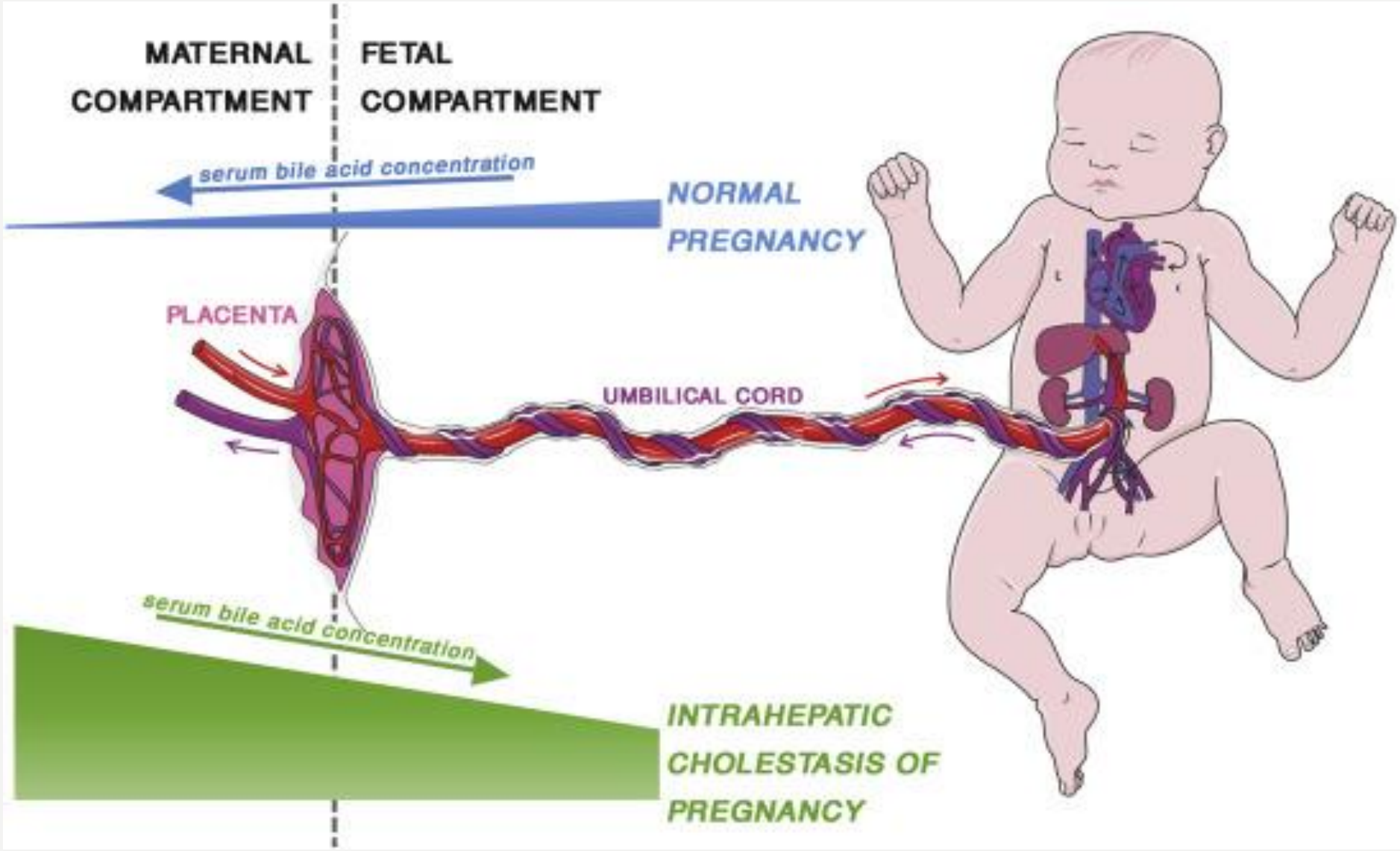
❖Pruritus

- Pruritus affects 23 percent of pregnancies, but only a small proportion are due to ICP .

- Pruritus helps distinguish ICP from other types of pregnancy-related disorders characterized by elevated transaminase levels (HELLP syndrome, preeclampsia, acute fatty liver of pregnancy).

- The lack of primary skin lesions in ICP helps to differentiate it from most pregnancy-specific pruritic dermatoses and skin conditions unrelated to pregnancy.

Bile acid metabolism in pregnancy



Fetal effects

Intrauterine demise(IUFD)

- The incidence of stillbirth after 37 weeks of gestation attributed to ICP is reported to be 1.2 percent .
- The risk of IUFD appears to increase with higher bile acid levels and with advancing gestational age.
- In a series of fetal deaths associated with ICP, the median gestational age was 38 weeks, and only two fetal deaths occurred before 37 weeks

❖Meconium-stained amniotic fluid,

❖preterm delivery (spontaneous and iatrogenic),

❖Neonatal respiratory distress syndrome (associated with bile acids entering the lungs) .

Pathophysiology of fetal death

- The sudden development of a fetal arrhythmia or vasospasm of the placental chorionic surface vessels induced by high levels of bile acids.

- Coexistent pregnancy complications (GDM,PIH) may also play a role .

- Prematurity varies greatly among studies (6 to 60 %):
  - Iatrogenic (induction of labor)
  - Spontaneous preterm labor(Bile acids appear to increase expression of Myometrial oxytocin receptors).
  - High rate of multiple gestations in patients with ICP.
  - Pregnancies complicated by spontaneous preterm birth appear to have earlier onset of pruritus .

- Fetal growth restriction and oligohydramnios are not features of the disease .

Predictive value of maternal bile acid level :

Higher serum total bile acid concentration appears to predict adverse fetal outcomes .

Bile acid level ≥40 micromol/L :

- In a large prospective cohort study of women with ICP and total bile acid concentrations ≥40 micromol/L, the incidence of stillbirth was 1.5 percent (10/669), which was higher than the control population incidence of 0.5 percent (11/2208) .

- Preterm birth
- Asphyxia or respiratory distress syndrome
- Meconium stained amniotic fluid

Bile acid level ≥100 micromol/L :

The risk for fetal demise appears to be particularly high with bile acid levels ≥100 micromol/L: 10 % (2/21) in one study and 15 % (4/26) in another .

Maternal treatment

Goals

- Reducing bothersome symptoms
- Reducing the risk of perinatal morbidity and mortality

Although pruritus is bothersome, ICP is not associated with other serious maternal sequelae.

Candidates for treatment :

- We offer treatment to all patients with ICP.
- For patients with characteristic clinical symptoms but normal serum bile acid and aminotransferase levels:
  - Either empiric treatment may be initiated
  - Or laboratory tests can be repeated weekly with initiation of treatment once the total bile acid or serum transaminase levels or both are elevated.

Ursodeoxycholic acid

UDCA

- Results in complete resolution of pruritus (42 %) and an improvement in approximately (61 %).
- It improves laboratory abnormalities in both the maternal and fetal compartments.
- It may improve perinatal outcome, and has no known fetal/neonatal toxicity .

Dosage:

- 300 mg TID (15 mg/kg per/ day) until delivery, but 300 mg BID(10 mg/kg / day) is also reasonable.

- If pruritus is not relieved to a tolerable level within about two weeks, the dose is titrated every week or two , to a maximum dose of 21 mg/kg / day .
- Pruritus is usually improves within 1-2 wks
- Biochemical improvement is usually seen within 3-4 wks.

- The drug is well-tolerated by most patients, but mild nausea and dizziness have been reported in up to 25 % of patients.

❖In a meta-analysis of 12 randomized trials :

- Patients who received UDCA had better outcomes than those who received an alternative agent (S- adenosyl-methionine ,Cholestyramine, or placebo).

- Children exposed to UDCA in utero and examined at 1 to 12 years of age reported all were healthy.

- Although meta-analyses support the efficacy of UDCA, they are limited by small numbers of patients and adverse fetal events; heterogeneity in patient populations, interventions, and assessed outcomes; and moderate to high risk of bias .

Pretreatment and post treatment laboratory monitoring

- No need for additional laboratory tests before starting treatment.
- Total bile acid concentration and transaminases are not rechecked before delivery.

- In women diagnosed remote from term or with severely elevated total bile acid concentration or transaminases, repeating laboratory tests 2-3 Weeks after beginning UDCA .

- Clinical decision making is based on maternal symptoms and on the highest total bile acid level before treatment was initiated.

- We would not increase the UDCA dose to reduce elevated laboratory results if pruritus has been relieved .

- We would not revise the planned time of delivery if laboratory abnormalities improve.

Refractory cases

❖S-adenosyl-methionine (SAMe)

- SAMe increases the methylation and biliary excretion of hormone metabolites .
- It is usually administered intravenously, which is inconvenient as prolonged therapy is required.

❖Cholestyramine

- Decreases ileal absorption of bile salts, thereby increasing their fecal excretion.
- Cholestyramine is given orally in divided doses starting at 2 - 4 g /day and gradually increased to a maximum dose of 16 g / day, if needed for symptom control .
- Its effect on pruritus in ICP is limited .
- It may cause constipation, abdominal discomfort, and malabsorption of fat including fat-soluble vitamins (vitamin K), especially at high doses (>4 grams per day).

Other drugs:

- Hydroxyzine (25 mg every 6-8 hrs) or Cholorpheniramine (4 mg every 4-6 hrs) has been used to treat pruritus with minimal efficacy, but provides sedation at night.

- Calamine Lotion or aqueous cream with 2 percent menthol may also relieve pruritus.

  (None of these therapies improves laboratory abnormalities).

- Dexamethasone (12 mg / day)did not improve pruritus or reduce the serum aminotransferase levels, and was less effective than UDCA 1000 mg/day at reducing bilirubin and bile acids .

- Other treatments, including Charcoal, Ultraviolet light, Herbal remedies, and Phenobarbital , have been used, but few patients have been treated and with uncertain efficacy.

Pregnancy management

Antepartum fetal assessment

We recommend Twice weekly modified biophysical profiles.

The mechanism of intrauterine fetal demise is thought to be a sudden event rather than the result of a chronic placental vascular process.

Therefore:

- NST,
- Biophysical profile score,
- Daily fetal kick count,

❖ Do not improve detection of placental insufficiency and reduce the risk of fetal morbidity and mortality.

Timing of delivery

❖We deliver most women with ICP at 36+0 to 36+6 weeks of gestation or upon diagnosis if ICP is diagnosed at ≥37+0 weeks of gestation.

❖We consider delivery prior to 36 weeks of gestation in women with ICP and:

- Excruciating and unremitting maternal pruritus not relieved with pharmacotherapy
- Jaundice
- A prior history of fetal demise before 36 weeks due to ICP with recurring ICP in the current pregnancy
- High total serum bile acid concentration ≥100 micromol/L .

- The timing of delivery in these situations is empirical and generally delayed as long as possible after 34 weeks of gestation, depending on the individual patient's particular circumstances.

Delivery

- No special considerations related to delivery are required in women with ICP.
- Continuous fetal monitoring during labor is indicated, given increased frequency of fetal death and non-fatal asphyxial events .
- Labor induction does not necessarily lead to an increased risk of cesarean delivery compared with expectant management.
- There does not appear to be an increased risk for postpartum hemorrhage when ICP is managed with UDCA .

❖In rare refractory cases, the prothrombin time can be checked and vitamin K administered if it is prolonged .

Maternal outcome

Postpartum course

- Pruritus usually disappears in the first few days following delivery, accompanied by normalization of serum bile acid concentrations and other liver tests .
- Postpartum, total bile acids, and transaminases are rechecked to make sure biochemical improvement has occurred.

Breastfeeding

ICP is not a contraindication to breastfeeding.

UDCA is discontinued when labor begins.

Follow-up

❖Check LFT and bile acid concentration 6-8 weeks after delivery .

❖ICP may be associated with subsequent diagnosis of :

- Gallstone disease
- Hepatitis C
- Cholangitis
- Hepatobiliary cancer
- Immune-mediated disease
- Cardiovascular disease

Recurrence in subsequent pregnancies

- Cholestasis recurs during subsequent pregnancies in 60 to 70 % of women with ICP..

Contraception

Any Nonhormonal contraceptive may be used.

Estrogen-progestin

- The administration of COCP to women with a history of ICP rarely results in recurrent cholestasis.
- COCP can be initiated after normalization of liver function tests.
- Routine Check –up of liver function tests after 3-6 months of such contraception is recommended.
- The CDC consider COCP an acceptable choice for women with a past history of ICP since the benefits generally outweigh the risks .
- In women with cholestasis related to past use of COCP , non-estrogen methods of contraception are preferred due to the increased risk for recurrent cholestasis.

Progestin-only

- The CDC consider progestin-only contraceptives an acceptable choice for women with a history of ICP or cholestasis related to use of estrogen-progestin contraceptives .

Special populations

❖Women with a history of cholestasis undergoing ovarian stimulation for ART.

❖ Progesterone supplementation in women with a history of previous preterm birth or a short cervical length in current pregnancy with a previous history of ICP.

- In placebo-controlled randomized trials of progesterone supplementation for reducing the risk of spontaneous preterm birth, an increased frequency of ICP has not been specifically reported.

- The package insert for Hydroxyprogestrone Caproate (Makena) describes an 8 % incidence of pruritus in treated women and lists cholestatic jaundice of pregnancy, liver tumors (benign or malignant), or active liver disease as contraindications to therapy .

THANK YOU FOR YOUR ATTENTION!

ANY QUESTIONS ?


Thank You
For Your Atten