Hepatic disorders pregnancy

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Physiologic Changes in Liver During Pregnancy

1. The most important hepatic changes in pregnancy are the increased production and plasma levels of fibrinogen and the clotting factors VII, VIII, X and XII (hypercoagulable state)
2. Absolute hepatic blood flow is unaltered and hepatic function remains normal, (lesser portion of the cardiac output reaches the liver, but due to the effects of estrogen and progesterone (vasodilators) blood flow remains normal)
3. Portal vein pressure is increased in late pregnancy, and venous pressure increases in the esophagus.
4. Hepatic protein production increases, but serum albumin levels decline in pregnancy due to the increase in maternal plasma volume (dilution effects)

Physiologic Changes in Liver During Pregnancy

1. ALP levels increase secondary to fetal and placental production and persists postpartum, rendering it unhelpful diagnosing cholestasis during the third trimester. (cholelithiasis occurs due to gradual increase in Biliary cholesterol concentrations of gallbladder from the first to the third trimester) the incident of cholelithiasis in pregnant women is 12%. 1-3% of pregnant women undergo cholecystectomy
2. plasma cholesterol levels rise by around 50% in the third trimester and triglycerides may rise to x2 - x3 times normal levels
3. The liver, normally palpated 2 cm below the right costal margin, may become more difficult to examine because of the expanding uterus within the abdominal cavity.

Overview of viral hepatitis

- Acute viral hepatitis is the most common cause of jaundice in pregnancy.
- The course of most viral infections is not affected by pregnancy.
- It is sometimes possible for the baby to become infected with the virus around the time of birth or during their early childhood years, particularly with hepatitis B and C.
- Hepatitis E is more likely to lead to fulminant hepatic failure in pregnancy (20% of women infected in the third trimester die of fulminant hepatitis)
- Most women with hepatitis will have a normal pregnancy, but the physical process of pregnancy may cause some problems on a woman's liver. About 6% of women with hepatitis can develop cholelithiasis during their pregnancy.

Overview of viral hepatitis

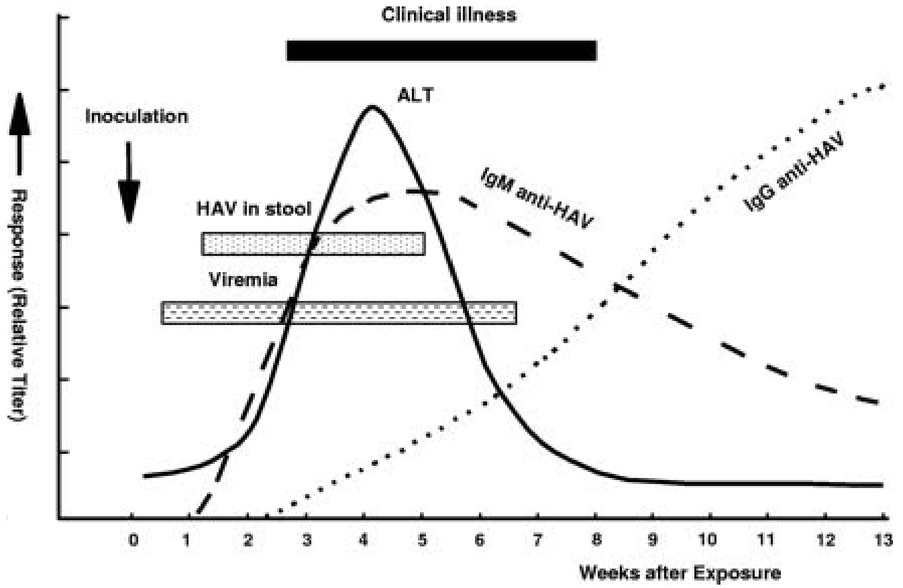
Virus	Family	Nucleic Acid	Transmission	Incubation (days)	Chronic Infection	Vaccine Available
Hepatitis A	Picornaviridae	Single-strand RNA Nonenveloped	Fecal-oral	15-50[2]	No (rare recurrent cholestatic hepatitis)	Yes
Hepatitis B	Hepadnavirus	Double-strand DNA	Parenteral, sex	30-180[8]	>90% infants <10% adults Cirrhosis, increased risk for HCC	Yes
Hepatitis C	Flaviviridae	Single-strand RNA Enveloped	Parenteral	14-180[12]	75%-80% Cirrhosis, increased risk for HCC	No
Hepatitis D	Deltavirus	Circular RNA enveloped	Parenteral, sex	42-180[21]	Superinfection: 75% Coinfection: 5% Cirrhosis, increased risk for HCC	No (prevented through HBV vaccines)
Hepatitis E	Hepeviridae	Single-strand Nonenveloped	Fecal-oral	21-56[26]	Only reported in patients posttransplant or who are immunosuppressed	Yes (approved only in China)

Hepatitis A Virus

- **Transmission**: feco-oral route
- **Incubation**: Period lasts from 15 to 50 days, short duration of viremia
- **Patients at risk**: travelers to endemic areas
- **Clinical manifestations**
  - **Nonspecific symptoms**: Malaise, Fatigue, Anorexia, Nausea, Abdominal pain (RUQ/Epigastric)
  - **Physical findings**: jaundice, upper abdominal tenderness, hepatomegaly
- **Effect on Pregnancy**
  - Intra-utero transmission of hepatitis A virus (HAV) is very rare, but perinatal transmission could occur.
  - Preterm labor
  - Placental abruption
  - premature rupture of membrane

Hepatitis A Virus - Diagnosis

- Demonstration of virus in feces (immunoelectron microscopy)
- Detection of Ab (ELISA)
- Lab tests:
  - Alanine Aminotransferase (ALT)
  - Bilirubin
- Virus isolation
- Molecular Diagnosis (PCR of Feces)
- Abnormal coagulation profiles
- Hyperammonemia may suggest a signifi



Hepatitis A Virus - Management

1. No specific treatment for hepatitis A. Recovery may be slow and may take several weeks or months.
2. Most important is the avoidance of unnecessary medications (Paracetamol and unsafe anti-emetics should not be given)
3. Hepatitis A virus vaccine is prepared from the inactivated virus and is considered safe during pregnancy, but there should be a clear indication for administering the vaccine during pregnancy.

- About 70% of individuals develop protective levels of antibodies 2 weeks after the first dose of the vaccine
- Partner of the patient should be given the vaccine as well
- Breast feeding is not contraindicated in HAV

Hepatitis E Virus

- **Epidemiology**
  - The severity of the infection differs depending on the country (more severe in India, less severe in Egypt, Europe and USA
  - Hepatitis E virus (HEV) infection is the most frequent cause of acute viral hepatitis (AVH) in developing countries
  - Pregnant women are more vulnerable to HEV than other hepatitis viruses
  - Can develop into a chronic infection
  - Has a maternal mortality rate of 30-53% and a fetal of 69%
- **Transmission**: feco-oral and vertical transmission
- **Clinical Manifestations**
  - A more serious course of disease than other groups with usual nonspecific abdominal complaints
  - **Effects on pregnancy**: preterm delivery, miscarriage, still birth, neonatal death

Hepatitis E Virus

- **Diagnosis**
  - Taking a full history
  - Doing a physical examination
  - Investigations
    - By detecting anti-HEV Ab
    - Western bolt is used as confirmation
- **Management**
  - Should be predominantly preventive by good sanitation and vaccination
  - Breast feeding is considered unsafe in active symptomatic infection
  - Ribavirin should be avoided for both the mother and her sexual partner. If the mother plans on getting pregnant the drug should be stopped 6months in advance
  - Treatment is mainly supportive

Hepatitis B Virus (HBV)

- **Infective organism**: DNA virus
- **Transmission**
  - body fluids of infected patients & Drug users who share needles are at high risk.
  - In some areas in the world (e.g. China), chronic hepatitis B is prevalent and vertical transmission is very common.
- **Prevalence**
  - Two billion people worldwide are infected with HBV.
  - More than 350 million have chronic (lifelong) infections.
  - The prevalence of hepatitis B surface antigen (HBsAg) in pregnant women in the UK has been found to range from 0.5% to 1%.
  - There is wide variation in prevalence among different ethnic groups, and oriental women in particular appear to have a higher prevalence of HBsAg. C

Hepatitis B Virus (HBV)

- **Screening**
  - Serological screening for HBV should be offered all to pregnant women so that effective postnatal intervention can be offered to infected women to decrease the risk of mother-to-child transmission.
  - As many as 85% of babies born to mothers who are positive for the hepatitis e antigen (eAg) will become HBsAg carriers and subsequently become chronic carriers, compared with 31% of babies who are born to mothers who are eAg negative.
  - Mortality from liver cirrhosis and hepatocellular carcinoma is increased 22 folds in chronic carriers
  - Mother-to-child transmission of HBV is approximately 95% preventable through administration of vaccine and Ig to the baby at birth
- **Clinical features**
  - Usually asymptomatic.
  - The HBV has an incubation period of 6 weeks to 6 months.
  - The course of acute HBV is unrelated in pregnancy.
  - In chronic active hepatitis it associated with increased risk of prematurity ,low birth weight and neonatal death.

Hepatitis B Virus (HBV) - Management

- Women who screen positive for hepatitis B should be referred to a hepatologist for ongoing monitoring for the long-term complications.
- Invasive prenatal procedures should not be carried out without reviewing available blood borne virus screening tests such as human immunodeficiency virus (HIV) and hepatitis.
- If these are declined or unavailable the woman should be counselled about the potential risk of vertical transmission of infection to the fetus.
- To prevent vertical transmission of hepatitis B, a combination of hepatitis B Ig(immediately after delivery) and hepatitis B vaccine (The active vaccine is given in three doses: at birth, at 1 month and at 6 months of age)may be given.

- Hepatitis B immunization is given to all babies whose mothers have serological evidence of hepatitis B (HBV). HBV immunization should start within 24 hours of birth.
- This confers over 95% protection against chronic hepatitis B infection.

- Women who present in labor with unknown hepatitis serology should have blood samples sent urgently so that the results can prompt immunization within 24 hours of birth, if appropriate.
- In addition, HBV Ig is given to all mothers with serological evidence of hepatitis B unless the mother has antiHep e antibodies. Thus, the only babies of HBV-positive mothers who do not get HBV Ig are babies whose mothers have serological evidence that they are not infective.

Hepatitis C Virus (HCV)

- **Infective organism**: RNA virus.
- **Transmission**
  - Infected blood products and injection of drugs.. Mother-to-child transmission can occur due to contact with infected maternal blood around the time of delivery, and the risk is higher in those coinfected with HIV.
  - Sexual transmission is extremely rare.
- **Prevalence**
  - In the UK the overall antenatal prevalence has been estimated to be around 1%, with regional variation.
  - The risk of mother-to-child transmission is estimated to lie between 3% and 5% and it is estimated that 70 births each year are infected with HCV as a result of mother-to-child transmission in the UK.
  - The risk of mother-to-child transmission of HCV increases with increasing maternal viral load.

Hepatitis C Virus (HCV)

- **Screening**
  - Usually, it is not recommended to screen for HCV.
  - No effective interventions for the treatment of HCV in pregnancy, no interventions reduce vertical transmission of HCV from mother to child.
  - Screening is offered to women at high risk (current or previous intravenous drug use and hepatitis B and/or human immunodeficiency virus (HIV) infection).
  - Screening is performed by examining for hepatitis C virus immunoglobulin (Ig) G antibodies
- **Clinical features**
  - Following initial infection only 20% of women will have hepatic symptoms, 80% being asymptomatic.
  - Hepatitis C infection is associated with preterm rupture of membranes, GDM, low birthweight and neonatal unit admission
  - Liver cirrhosis, hepatocellular carcinoma and liver failure are long term complications

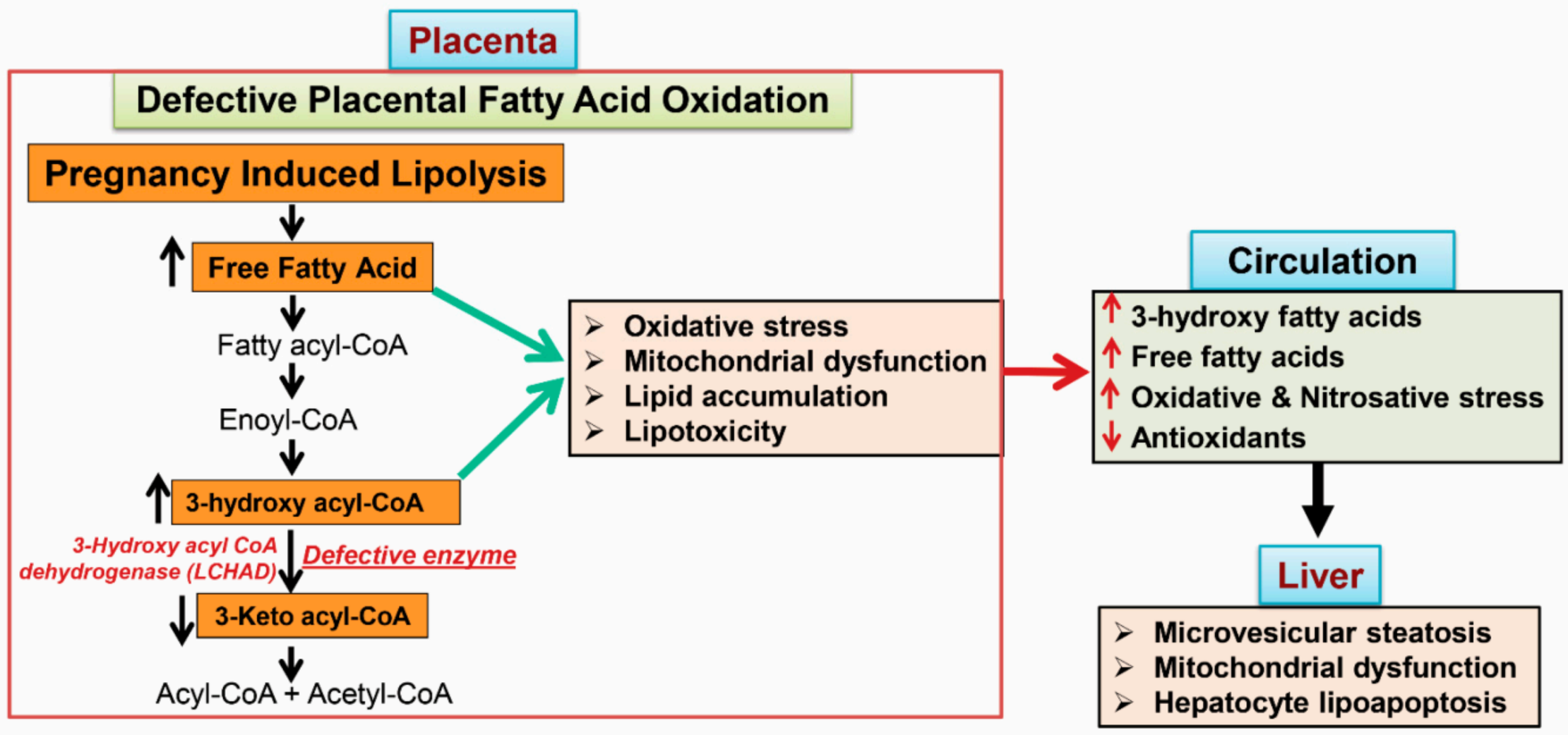
Hepatitis C Virus (HCV) - Management

- Testing for HCV in the UK involves detection of anti-HCV antibodies in serum with subsequent confirmatory testing by PCR for the virus
- Upon confirmation of a positive test, referral to a hepatologist for management and treatment of her infection.
- In non-pregnant adults, interferon and ribavirin can be used to treat hepatitis C infection, but these are contraindicated in pregnancy.
- Elective CS delivery is not recommended in all hepatitis C women, although it is recommended if the woman is also HIV positive.

Acute fatty liver of pregnancy

- **Definition**: idiopathic, rare, life-threatening obstetric emergency most commonly arising in the third trimester, characterized by extensive fatty infiltration of the liver, which can result in acute liver failure
- **Epidemiology**: 1–3 cases per 10,000 pregnancies
- **Risk factors**: low BMI, multiple pregnancy, preeclampisa, and previous attacks.
- **Clinical features**
  - Sudden onset of jaundice
  - RUQ pain, nausea, and vomiting
  - Coagulopathy with an increased risk of DIC
  - Hypoalbuminemia → ascites
  - Encephalopathy
  - Polyuria and polydipsia
  - 50% of patients have concurrent preeclampsia

Pathophysiology: dysfunction of fatty acid β-oxidation



Acute fatty liver of pregnancy

- **Laboratory findings**
  - CBC: ↑ WBC; platelet count variable
  - Liver chemistries: ↑ AST, ↑ ALT , hyperbiliru binemia
  - Hyperuricemia
  - Hypoglycemia
  - Coagulopathy (prolonged PT/aPTT)
  - Renal function test: may show acute renal failure
- **Imaging**: used to help confirm the diagnosis and rule out differentials (e.g., liver hematoma)
  - Modality of choice: ultrasound
  - Findings: The liver appears bright white; ascites may also be present.
- **Liver biopsy**
  - Consider in diagnostic uncertainty (e.g., atypical presentation) and in patients with persistent liver dysfunction postpartum.
  - Findings: microvesicular steatosis
- **Differential diagnosis**
  - HELLP syndrome, preeclampsia with severe features, other causes of acute liver failure
  - It is often difficult to differentiate between AFLP, HELLP, and preeclampsia with severe features, and these conditions can also coexist. Renal failure, hyperuricemia, and hypoglycemia are more common and severe in AFLP than in HELLP and severe preeclampsia.

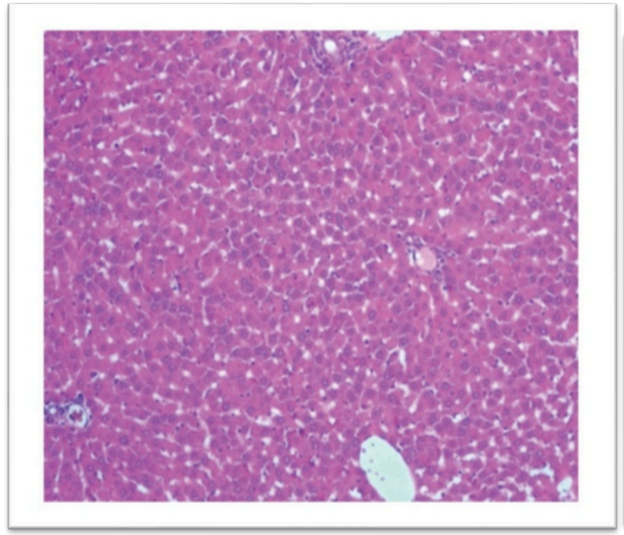
Swansea Criteria

This criteria has been validated for the diagnosis of AFL of pregnancy by identifying 6 or more of the following in the absence of other cause and in include clinical features, lab findings, radiographic features and histological features.

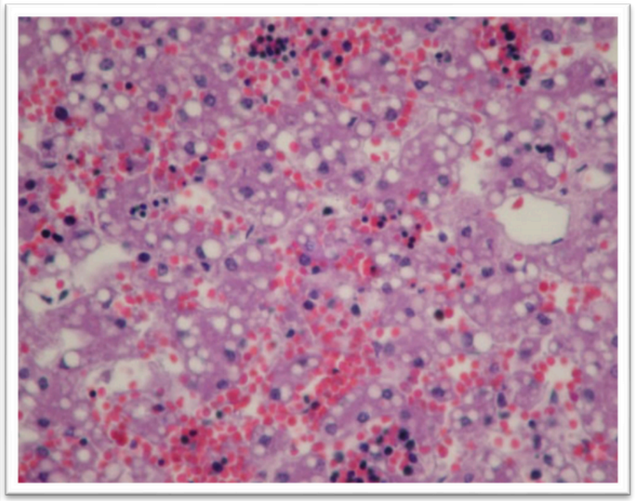
Class	Feature*
Clinical features	Vomiting
	Abdominal pain
	Polydispsia/polyuria
	Encephalopathy
Laboratory features	Elevated bilirubin (>14 μmol/L)
	Hypoglycemia (<4 mmol/L)
	Elevated urea (>340 μmol/L)
	Leukocytosis (>11 × 10^9/L)
	Elevated transaminases (>42 IU/L)
	Elevated ammonia (>47 μmol/L)
	Elevated creatinine (>150 μmol/L)
	Coagulopathy (prothrombin time >14 seconds or activated partial thromboplastin time >34 seconds)
Radiographic features	Ascites or bright-appearing liver on ultrasound
Histologic features	Microvesicular steatosis on liver biopsy

*In the absence of other causes, six or more features must be fulfilled in order to meet criteria.

HISTOLOGICAL FINDINGS:



Normal liver



Liver of AFLP

Acute fatty liver of pregnancy

- **Management**
  - If the patient is suspected for AFLP then admission should be done.
  - Then a group of blood tests should be started with fetal monitoring.
  - Give the patient IV fluids and glucose to prevent dehydration and hypoglycemia.
  - If DIC started, then we should give the patient FTP or cryoprecipitate.
  - After stabilization of the definitive management of AFL of pregnancy is delivery as soon as possible.
  - After the delivery a carful evaluation should be done for the genital tract to detect ant laceration and maintain hemostasis after cesarean due to the coagulation abnormality.
- **Complications**
  - Acute liver failure
  - Acute renal failure
  - Encephalopathy, pulmonary edema, pancreatitis
  - Maternal death (2%)
  - Fetal demise (10–20%)
  - Infection
- **Prognosis**
  - Clinical improvement is typically seen within 4 days of delivery.
  - Laboratory abnormalities may persist for > 1 week.

Intrahepatic cholestasis of pregnancy

- **Definition**: common pregnancy-associated liver disease, most commonly manifesting in the second and third trimesters with pruritus and elevated serum bile acid levels
- **Epidemiology**: occurs in 0.4–10% of pregnancies
- **Risk factors** :
- A past history of ICP is a strong risk factor for recurrence
- multiple gestation
- chronic hepatitis C virus
- family history of intrahepatic cholestasis
- advanced maternal age

Intrahepatic cholestasis of pregnancy

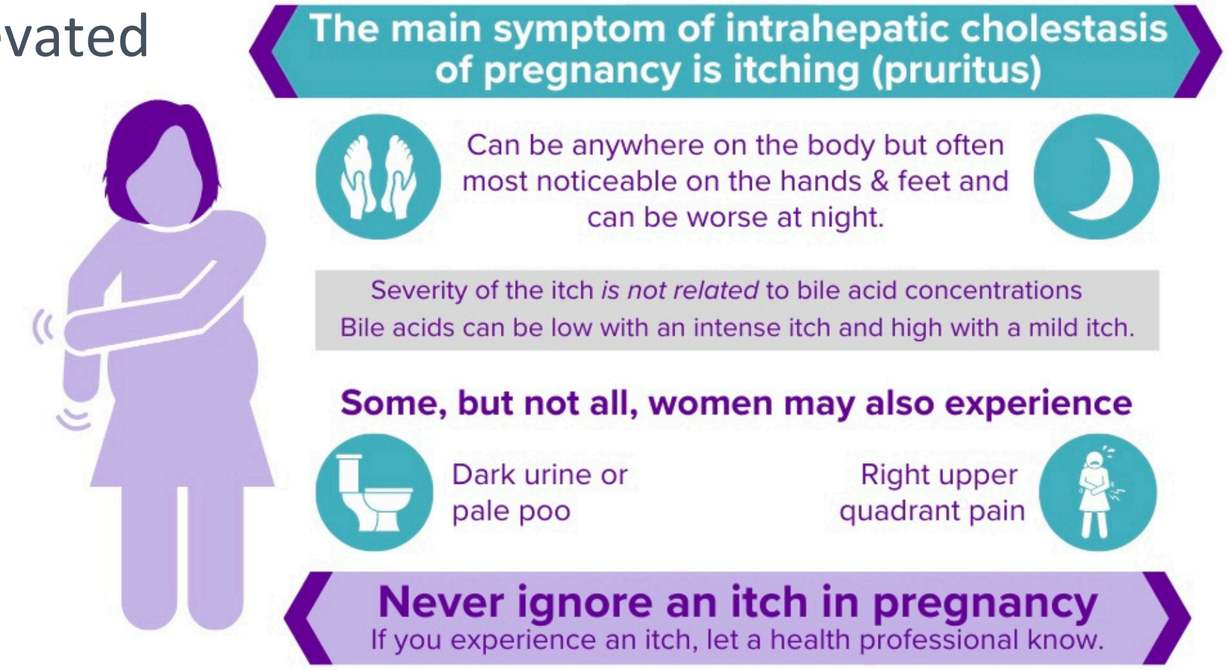
- **Etiology**: multifactorial

The etiology of ICP is not completely understood but likely involves a combination of genetic susceptibility, hormonal factors, and environmental factors.

- Pregnancy-associated increase in Estrogen and Progesterone.
- Up to 15% of ICP cases are associated with defect in the multi-drug resistance 3 (MDR3) gene, which encodes for a canalicular phospholipid trans-locater involved in bile duct secretion from hepatocyte

Intrahepatic cholestasis of pregnancy

- **Clinical features**: Pruritus, Jaundice, Steatorrhea (uncommon)
- **Diagnostics**
  - ↑ Total serum bile acid levels (> 10 mcmol/L) called hypercholanemia
  - ↑ ALT, ↑ AST
  - Normal or mildly elevated bilirubin
  - GGT is typically normal or mildly elevated



Intrahepatic cholestasis of pregnancy

- **Medical management**
  - First line: ursodeoxycholic acid (reduces bile acid levels and pruritus)
  - Consider first-generation antihistamines, e.g., hydroxyzine for severe pruritus.
  - Administer corticosteroids for fetal lung maturity if preterm delivery is anticipated.
- **Obstetric management**
  - Antenatal surveillance 1–2 times per week
  - Monitor serum bile acid levels regularly.
  - Deliver at 36–39 weeks' gestation depending on severity
    1. If Bile acid levels ≥ 100 mcmol/L
       - Deliver at 36 weeks' gestation.
    2. If Bile acid levels between 10 and 100 mcmol/L:
       - Deliver between 36- and 39-weeks' gestation.
  - Continuous fetal monitoring is recommended during labor because of the increased risk of stillbirth.

Intrahepatic cholestasis of pregnancy

- **Prognosis**: The condition is fully reversible postpartum.
- **Complications**
  - Intrauterine fetal demise (1.2% after 37 weeks)
  - Fetal growth restriction
  - Premature labor and increased preterm birth rates
  - Meconium-stained amniotic fluid
  - Neonatal respiratory depression
  - Recurrence in subsequent pregnancies (60%–90%)
- Elevated total serum bile acid level (> 10 mcmol/L) in a patient with pruritus in the second or third trimester (without other causes of pruritus) is diagnostic for intrahepatic cholestasis of pregnancy. Elevated transaminases are not required for diagnostic confirmation.
- Early initiation of therapy with ursodeoxycholic acid may reduce the risk of preterm birth and stillbirth.

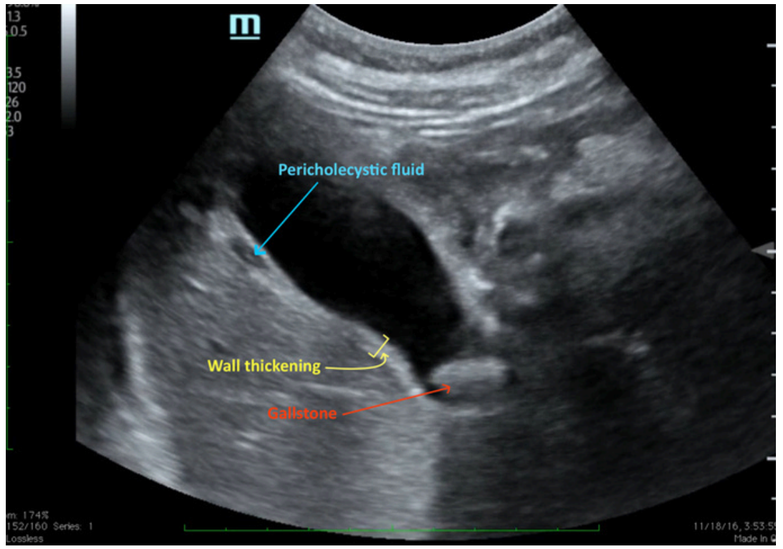
Cholelithiasis

- Is the presence of one or more of calculi in the gallbladder
- The prevalence of gall stones in pregnancy is around 19% in multiparous & 8% in nulliparous women

- **The causes of gall stones in pregnancy are**
  1. Increased estrogen level led to increased cholesterol secretion & supersaturation of bile
  2. Increased progesterone level cause decrease small intestinal motality

Acute cholecystitis

- **Clinical presentation**
  - **Symptoms**: pain may be localized to flank, scapula or right shoulder, nausea & vomiting, anorexia, fever
  - **Signs**: murphy sign is seen less frequently in pregnancy or may be displaced, fever, tachycardia
- **Diagnosis**: leukocyte count, Total bilirubin, Ultrasound, ERCP
- **Differential diagnosis**
  - Acute fatty liver of pregnancy
  - HELLP syndrome
  - Peptic ulcer
  - Pancreatitis
  - Lower lobe pneumonia
  - Abruption placenta



Acute cholecystitis - Management

- **Conservative initial management include**
  - bowel rest
  - IV fluid
  - Analgesia & fetal monitoring
  - Antibiotics are warranted if symptoms persist for 12-24 hours coverage for enteric gram(-) flora is desired by metronidazole & ceftriaxone
- **Surgical management**
  - Is required in 25% of cases & indicated for failure of conservative management , recurrence in same trimester or complicated cholecystitis
  - Intraoperative cholecystectomy even in uncomplicated cases decreases the length of hospital stay & rate of preterm delivary

Acute cholecystitis - Complications

1. Gangrenous cholecystitis
2. Choledocholithiasis
3. Perforation
4. Fistula
5. Ascending cholangitis
6. Pancreatitis

   The last two complications are associated with 15% maternal mortality & 60% fetal loss

Overview of liver disease in pregnancy

		HELLP syndrome	Acute fatty liver of pregnancy	Intrahepatic cholestasis of pregnancy	Acute viral hepatitis
Trimester		• Third trimester			• Any trimester

Clinical features		• Preeclampsia
		• Rapid clinical deterioration
		• RUQ pain
		• Nausea, vomiting, diarrhea
			• Sudden onset of jaundice
			• Nausea, vomiting
			• RUQ pain
			• Ascites
				• Jaundice
				• Pruritus
					• Prodromal phase (1–2 weeks)
					  ◦ Fever, malaise
					  ◦ Nausea, vomiting, anorexia
					  ◦ RUQ pain
					  ◦ Tender hepatomegaly
					• Icteric phase (~ 2 weeks)
					  ◦ Jaundice
					  ◦ Pruritus
					  ◦ Dark urine and pale stools

Diagnostics		• **H** = hemolysis (↓ hemoglobin, ↓ haptoglobin, ↑ LDH, ↑ indirect bilirubin) • **EL** = elevated liver enzymes (↑ AST, ↑ ALT) • **LP** = low platelets	• ↑ WBC, possible ↓ platelets • ↑ ALT, ↑ AST • Hyperbilirubinemia • Hypoglycemia • Coagulopathy (prolonged PT and/or aPTT)	• ↑ Total serum bile acid levels: > 10 mcmol/L • ↑ ALT, ↑ AST • ↑ ALP, ↑ GGT • ↑ Direct bilirubin	• ↑ AST, ↑ ALT • AST/ALT ratio < 1 • ↑ Total bilirubin • ↑ ALP, ↑ GGT

Treatment		• Stabilization
		  ◦ IV fluids
		  ◦ Blood transfusions
		  ◦ Antihypertensive agents
		  ◦ Magnesium sulfate
		• Delivery if ≥ 34 weeks' gestation or at any gestational age with deteriorating maternal or fetal status
			• Stabilization
			• Immediate delivery
				• Ursodeoxycholic acid
				• Delivery at 36–39 weeks' gestation based on severity
					• Supportive care

Complications	**Maternal**	• Placental abruption • DIC • Pulmonary edema • Acute renal failure • Stroke • Acute respiratory distress syndrome (ARDS) • Hepatic subcapsular hematoma • Maternal death	• Acute liver failure • Acute renal failure • Encephalopathy • Death	• Recurrence in following pregnancies	• Hepatitis E: acute liver failure • Death
	Fetal	• Fetal growth restriction • Preterm birth • Seizure-induced fetal hypoxia • Death	• Death	• Fetal growth restriction • Death • Preterm birth	• Death

Thank you