HEPATIC DISORDERS IN PREGNANCY

PHYSIOLOGIC CHANGES IN LIVER DURING PREGNANCY

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Marah shwayat

- 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.
- absolute hepatic blood flow remains largely 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)
- Portal vein pressure is increased in late pregnancy, and venous pressure increases in the esophagus.
- hepatic protein production increases, but, serum albumin levels decline in pregnancy due to the increase in maternal plasma volume (dilution effects)

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- alkaline phosphatase 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

- plasma cholesterol levels rise by around 50% in the third trimester and triglycerides may rise to x2 - x3 times normal levels

- 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)

Viral Hepatitis

OVERVIEW

- 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.

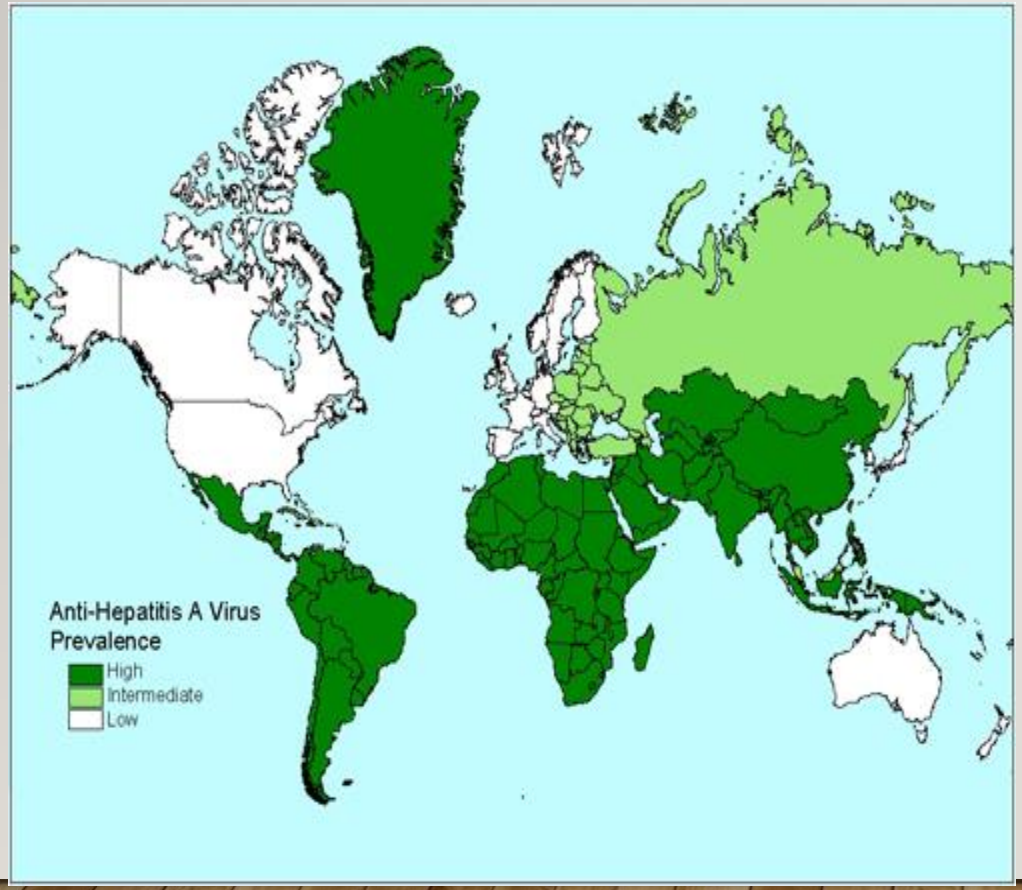
Overview of Viral Hepatitis in Children

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)

Abbreviations: HBV, hepatitis B virus; HCC, hepatocellular carcinoma.

Hepatitis A Virus (HAV)

Hepatitis A Virus



- Transmitted through feco-oral route, usually is not excreted in body fluids or urine
- Incubation period lasts from 15 to 50 days, with a short duration of viremia
- Patients at risk: travelers to endemic areas
- It affects 1:1000 of pregnant women in UK

HAV Clinical Manifestations

Maternal

- 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 labour
- Placental abruption
- premature rupture of membrane

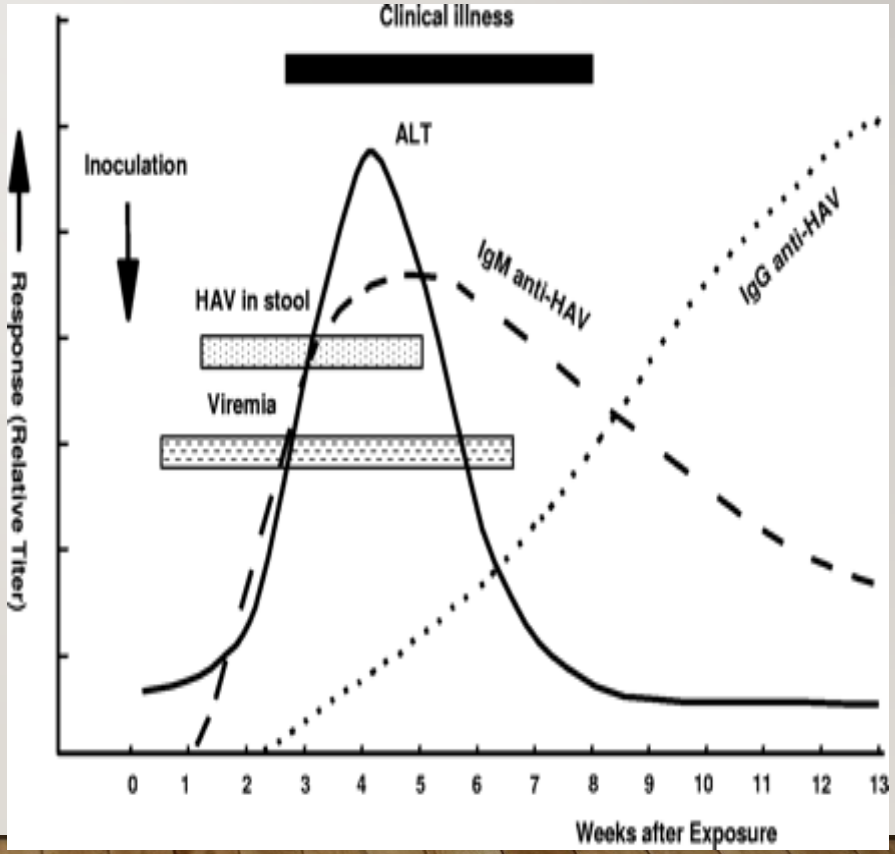
HAV Diagnosis

- Demonstration of virus in feces (immunoelectron microscopy)
- Detection of Ab (ELISA)
- Lab tests:

  -Alanine Aminotransferase (ALT)

  -Bilirubin
- Virus isolation
- Molecular Diagnosis (PCR od Feces)
- Abnormal coagulation profiles
- Hyperammoniemia may suggest

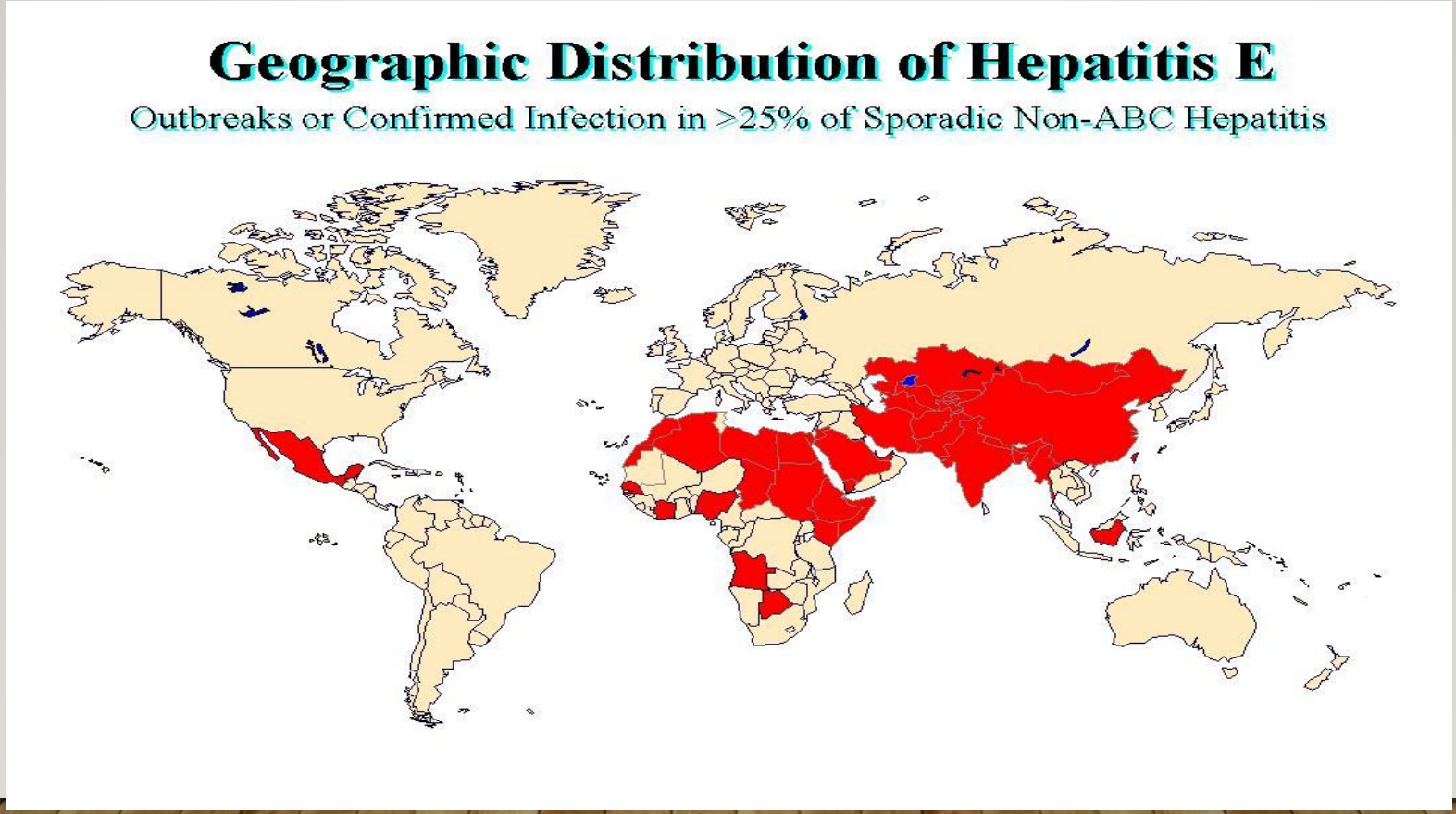
  a significant liver injury



MANAGEMENT

- There is no specific treatment for hepatitis A. Recovery from symptoms following infection may be slow and may take several weeks or months.
- Most important is the avoidance of unnecessary medications (Paracetamol and unsafe anti-emetics should not be given)
- 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



OVERVIEW

- 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
- researchers were unable to explain the high HEV morbidity in pregnancy
- Can develop into a chronic infection
- Has a maternal mortality rate of 30-53% and a fetal of 69%

HEV Clinical Manifestations

Maternal

- A more serious course of disease than other groups with usual non specific abdominal complaints

Effects on pregnancy

- Transmitted by vertical transmission

-preterm delivery

-miscarriage

-still birth

-neonatal death

Diagnosis

- Taking a full history
- Doing a physical examination

Investigations

- By detecting anti-HEV Ab
- Western bolt is used as confirmation

Management

- 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)

HEPATITIS B

Infective organism

The hepatitis B virus (HBV) is a DNA virus that is transmitted mainly in blood, but also in other body fluids such as saliva, semen and vaginal fluid. 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. In the UK, approximately 1 in 1,000 people are thought to have the virus. 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.

Screening

Serological screening for HBV should be offered 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. It has been estimated that chronic carriers of HBsAg are 22 times more likely to die from hepatocellular carcinoma or cirrhosis than non-carriers.

Mother-to-child transmission of HBV is approximately 95% preventable through administration of vaccine and Ig to the baby at birth. To prevent motherto-child transmission, all pregnant women who are carriers of HBV need to be identified. Because of the high proportion of cases of mother-to-child transmission that can be prevented through vaccination and immunization, the UK National Screening Committee recommends that all pregnant women be screened for HBV

Clinical features

Hepatitis B is a virus that infects the liver, but many people with hepatitis B viral infection have no symptoms. 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 Wight and neonatal death

Management

Women who screen positive for hepatitis B should be referred to a hepatologist for ongoing monitoring for the long-term consequences of chronic infection, for example hepatocellular carcinoma. To prevent vertical transmission of hepatitis B, a combination of hepatitis B Ig and hepatitis B vaccine may be given. Virology laboratories will usually advise on the appropriate regime. The combined treatment provides better therapy than either alone. The passive Ig provides immediate protection against any virus transmitted to the baby from contact with blood during delivery, and should be given immediately after delivery. The active vaccine provides ongoing protection from subsequent exposure in the household. The active vaccine is given in three doses: at birth, at 1 month and at 6 months of age.

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 labour without having had their booking bloods done should have hepatitis serology 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)

HEPATITIS C

Infective organism

The hepatitis C virus (HCV) is a RNA virus. Acquisition of the virus occurs predominantly through infected blood products and injection of drugs. It can also occur with tattooing and body piercing. 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.

Screening

Current recommendations are that pregnant women should not be offered routine screening for HCV. This is because there is a lack of evidence-based effective interventions for the treatment of HCV in pregnancy, and a lack of evidence about which interventions reduce vertical transmission of HCV from mother to child.

Screening for hepatitis C may be offered to women considered to be at high risk; this includes current or previous intravenous drug use and hepatitis B and/or human immunodeficiency virus (HIV) infection. The risk of transmitting the virus from mother to child is approximately 5%, but this increases significantly up to 36% if there is coinfection with HIV. Screening is performed by examining for hepatitis C virus immunoglobulin (Ig) G antibodies

Clinical features

HCV is a major public health concern due to its long-term consequences on health. It is one of the major causes of liver cirrhosis, hepatocellular carcinoma and liver failure. Following initial infection only 20% of women will have hepatic symptoms, 80% being asymptomatic. The majority of pregnant women with hepatitis C will not have reached the phase of having the chronic disease, and may well be unaware that they are infected.

Hepatitis C infection is also associated with several adverse pregnancy outcomes, such as preterm rupture of membranes and GDM, as well as adverse neonatal outcomes, including low birthweight and neonatal unit admission

Management

Testing for HCV in the UK involves detection of anti-HCV antibodies in serum with subsequent confirmatory testing by PCR for the virus, if a positive result is obtained. Upon confirmation of a positive test, a woman should be offered posttest counselling and 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. There is no strong evidence regarding mode of delivery in women with hepatitis C. Consensus groups therefore do not recommend elective caesarean section for all hepatitis C women, although it is recommended if the woman is also HIV positive.

NEW DEVELOPMENTS

Hepatitis B vaccination programmes are being extended worldwide. In some countries, such as Taiwan, this has already resulted in lower transmission rates and a reduction in childhood hepatocellular carcinoma. Further research is needed into the treatment of hepatitis C in pregnancy with antiviral agents, and into the most appropriate mode of delivery in women with hepatitis C. The development of a hepatitis C vaccination would confer long-term health benefit.

FATTY LIVER IN PREGNANCY

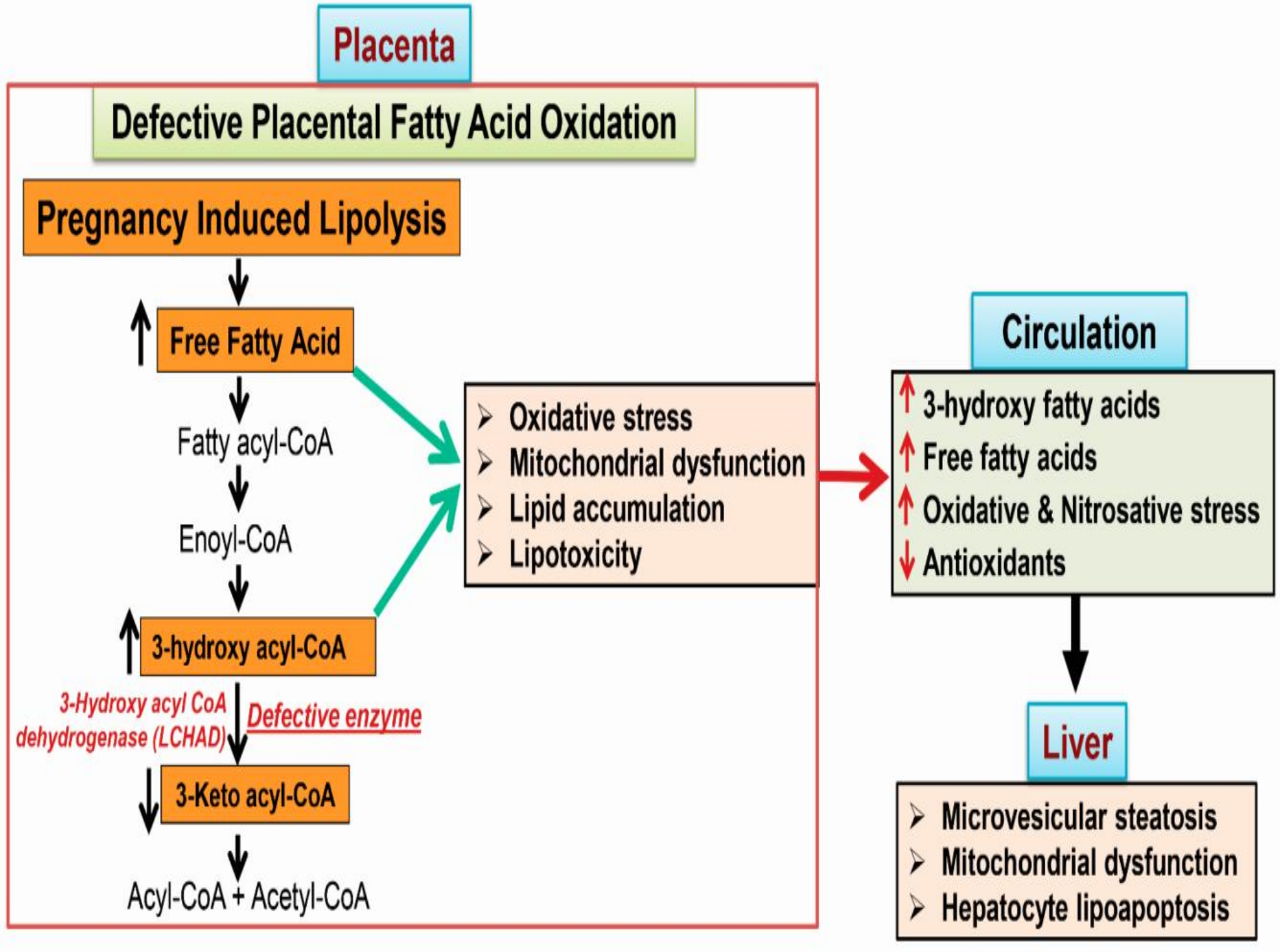
ACUTE FATTY LIVER OF PREGNANCY:

- It's a rare condition that occurs in pregnancy about 1 in 10000 pregnancies.
- Acute fatty liver of pregnancy is a term used for late pregnancy liver dysfunction which may end up as liver failure and it may result as a complication in the 3rd trimester or sometimes even after the delivery.
- Its abnormal metabolism of fatty acids usually due to unknown cause but it may result from an fetal mutation and maternal mitochondrial defect.
- And it's a life-threatening condition for both fetus and mother .

PATHOPHYSIOLOGY:

- This condition may happen due to fetal deficiency of an enzyme 3-hydroxyacyl-CoA dehydrogenase which cause the accumulation of medium and long chains fatty acids this cause the return of the non metabolized fatty acids (3-hydroxyacyl CoA) which is toxic to the maternal liver from the fetal circulation in to the maternal circulation through the placenta causing an overload on the maternal liver .

- The mutation that cause this condition is a missense mutation (point mutation were one nucleotide is replaced which make the codon coding an other amino acid).
- The maternal liver will start to oxidize these fatty acids by beta –oxidation enzymes which will cause the collection of fat within the hepatocytes which is called(micro vesicular steatosis)


Placenta
Defective Placental Fatty Acid Oxidation
Pregnancy Induced Lipolysis
Free Fatty Acid
Fatty acyl-CoA
Enoyl-CoA
3-hydroxy acyl-CoA
3-Hydroxy acyl CoA dehydrogenase (LCHAD)
Defective enzyme
3-Keto acyl-CoA
Acyl-CoA + Acetyl-CoA
Oxidative stress
Mitochondrial dysfunction
Lipid accumulation
Lipotoxicity
Circulation
3-hydroxy fatty acids
Free fatty acids
Oxidative & Nitrosative stress
Antioxidants
Liver
Microvesicular steatosis
Mitochondrial dysfunction
Hepatocyte lipoapoptosis

- There are some condition which may increase the risk for AFL to occur like:

1. Multiple pregnancy : twine (9-12%)
2. In male more female by (3:1).
3. The presence of mild preeclampsia (30-60%).
4. Previous history of AFL.

- AFL is associated with 18% risk for maternal mortality if diagnosed late and 23% risk of fetal mortality.

SWANSEA CRITERIA:

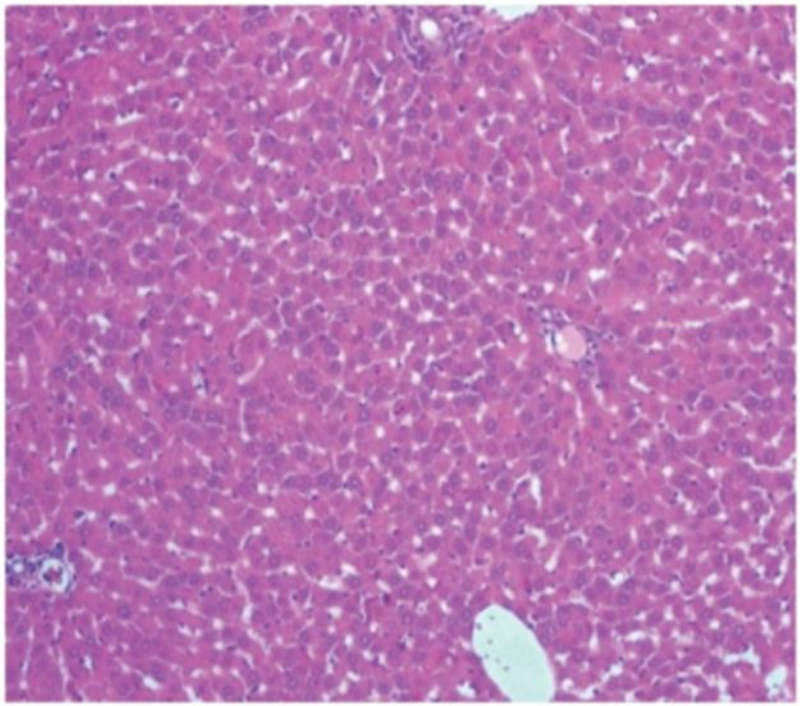
- This criteria has been validated for the diagnosis of AFL of pregnancy by identifying 6 or more of the following in the absence of other cause and it include clinical features, lab findings ,radiographic features and histological features .

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

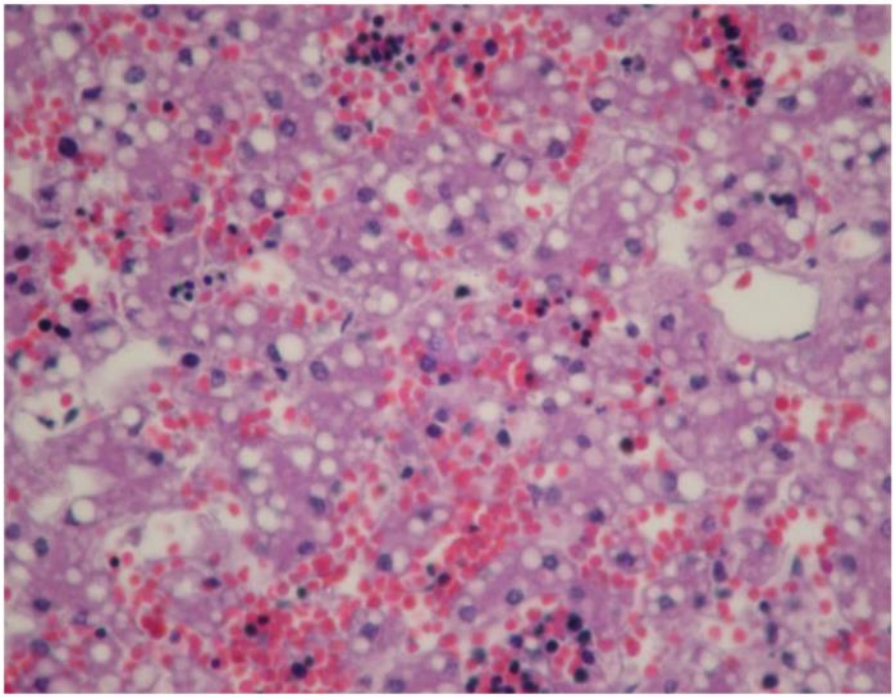
*In the absence of other causes, six or more features must be fulfilled in order to meet criteria.

- The maternal kidneys might be affected due to elevated creatinin and uric acid which may lead to metabolic acidosis.
- And there is a risk of developing DIC due to abnormal coagulation profile.
- The definitive diagnosis is done by liver biopsy which allow us to see the steatosis (micro vesicular collection of lipid between the hepatocytes) but its rarely preformed due to the risk of bleeding .

HISTOLOGICAL FINDINGS:



Normal liver



Liver of AFLP

MANAGEMENT:

- If the patient is suspected for AFLP then admission should be done .

1. Then a group of blood tests should be started with fetal monitoring.
2. Give the patient I.V fluids and glucose to prevent dehydration and hypoglycemia.
3. If DIC started then we should give the patient FFP or cryoprecipitate (not vit.k supplement cause its not effective).

- 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.

Gall bladder disorders in pregnancy

Cholelithiasis

- Is the presense 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 lead to increased cholesterol secretion & supersaturation of bile
  2-increased progesterone level cause decrease small intestinal motality

Acute cholecystitis

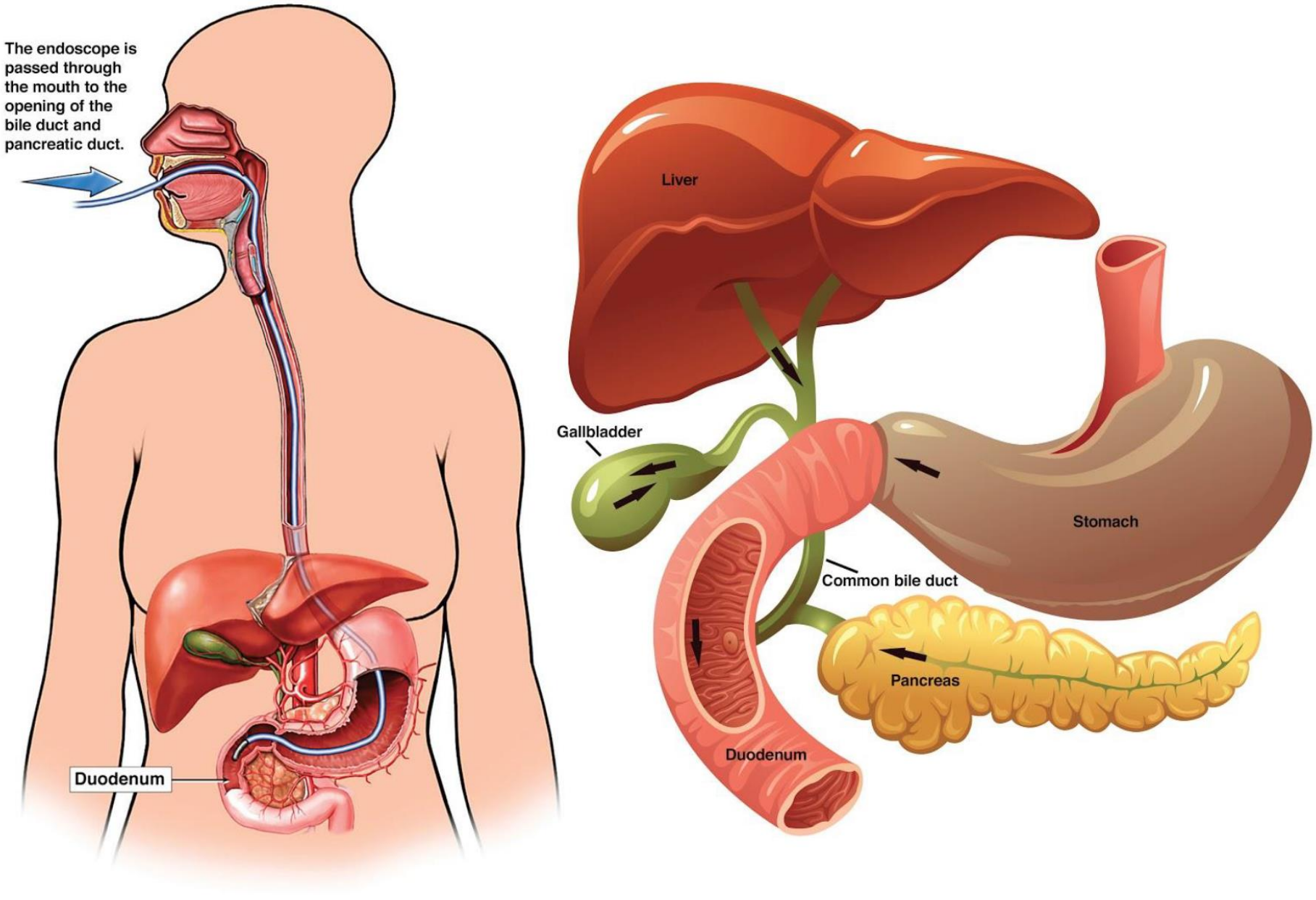
- Is much less common occurring in pregnancy in around 0.1% of pregnant women

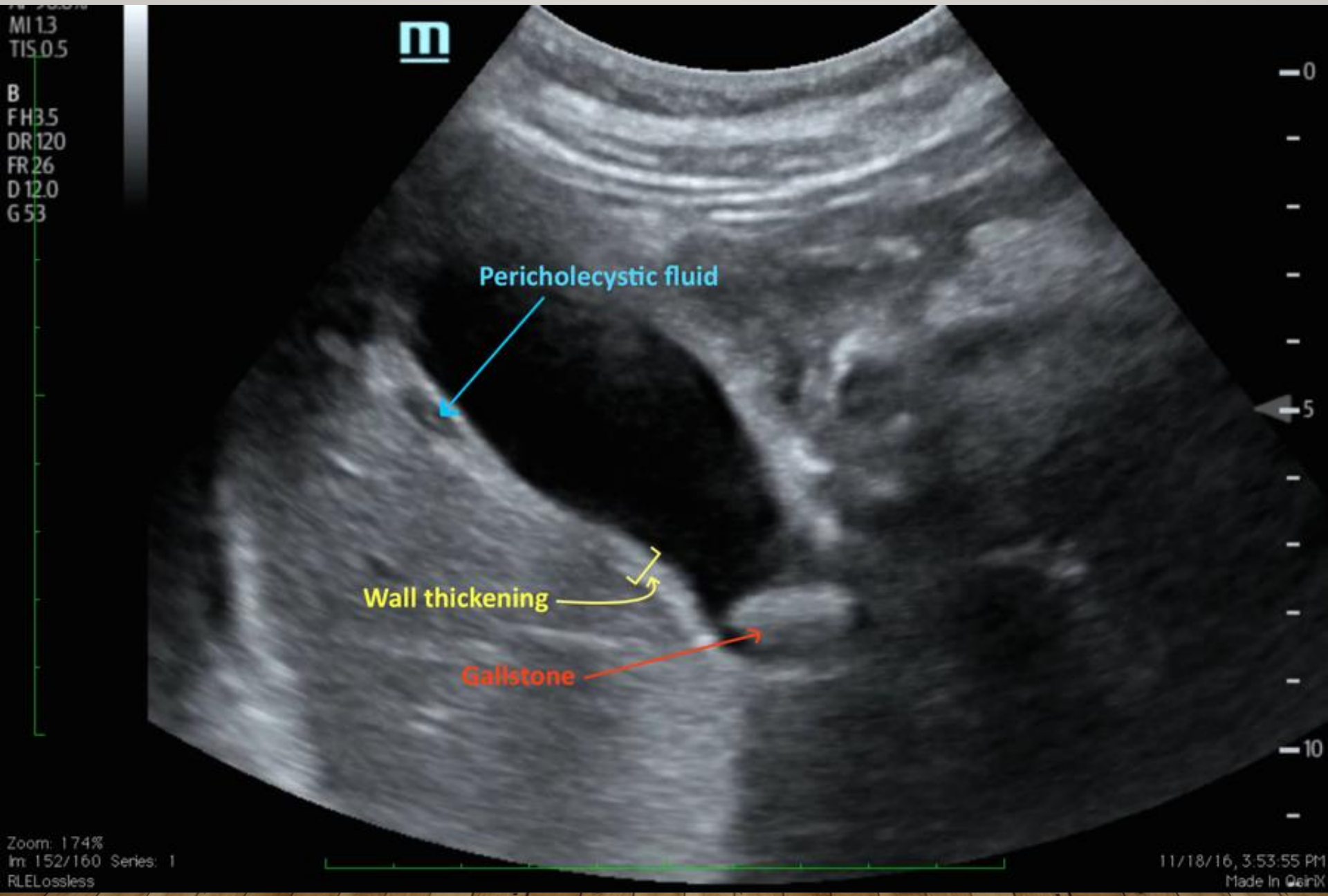
- **clinical presentation**
  symptoms: 1- pain may be localized to flank, scapula or right shoulder
  2-nausea & vomiting
  3-anorexia
  4-fever
  signs
  1-murphy sign is seen less frequently in pregnancy or may be displaced
  2-fever
  3-tachycardia

Acute cholecystitis

- **Diagnosis**
  leukocyte count
  Total bilirubin
  Ultrasound
  ERCP

- Differential diagnosis
  acute fatty liver of pregnancy
  HELLP syndrome
  peptic ulcer
  pancreatitis
  lower lobe pneumonia
  abruption placenta


The endoscope is passed through the mouth to the opening of the bile duct and pancreatic duct.
Duodenum
Liver
Gallbladder
Stomach
Common bile duct
Pancreas
Duodenum


MI 1.3
TIS 0.5
B
FH 3.5
DR 120
FR 26
D 12.0
G 53
Pericholecystic fluid
Wall thickening
Gallstone
0
5
10
Zoom: 174%
Im: 152/160 Series: 1
RLELossless
11/18/16, 3:53:55 PM
Made In QuinX

Acute cholecystitis

- Management
- Concervative initial management include
  1-bowel rest , IV fluid , analgesia & fetal monitoring
  antibiotics are warrented 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

- Complication
  gangrenous cholecystitis
  choledocholithiasis

  Perforation
  fistula
  ascending cholangitis
  pancreatitis

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

Thank you