# Liver Disease in Pregnancy

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# Effects of Pregnancy in Hepatobiliary System

- Bile composition: cholesterol supersaturation, decreased chenodexycholic acid. increased cholic acid, and increased bile acid pool.
- Greater residual GB volume in fasting and fed state, with less GB contractibility. Prevalence of GB stones is 2.5-12%.
- Progressive increase in blood volume, with peak at week 30, with 50% greater volume, due to increased renin, aldosterone, and steroid hormones.
- Decreased serum protein concentration by hemodilution; 20% by 2$^{nd}$ trimester. Raising AFP.
- Accelerated synthesis of CYP P450 gene superfamily products, coagulation products, globulins and ceruloplasmin.
- Progressive elevation of Alkaline phosphatase with peak of 2X ULN by end of pregnancy.
- GGT normal or slightly decreased.
- Spider nevi & palmar erythema in 50%

# Physiologic changes in Pregnancy

| Test | Effect of Pregnancy |
|---|---|
| Bilirubin | Unchanged |
| ALS & AST | Unchanged |
| Prothrombin time | Unchanged |
| Alkaline phosphatase | Increase 2-4 fold (2 X ULN) (placenta) |
| Bile acids | Increase 2-3 fold (glycocholate, taurocholate, chenodeoxycholate) |
| Fibrinogen | Increases 50% |
| Globulins | Increases alpha & beta; Decreases gamma |
| Alpha fetoprotein | Increases (specially with twins) |
| Hemoglobin | Decrease in late pregnancy |
| Leukocyte count | Increases |
| Ceruloplasmin | Increase |
| Cholesterol | Increases 2-fold |
| Triglycerides | Increase |

# Timing of Diseases Unique to, or Triggered by Pregnancy

| Disease | Trimester |
|---|---|
| Hyperemesis gravidarum | 1st. |
| Intrahepatic cholestasis of pregnancy | 2nd & 3rd. |
| HELLP syndrome | Late 2nd & 3rd. |
| Preeclampsia | Late 2nd & 3rd. |
| Acute fatty liver of pregnancy | 3rd. |
| Budd-Chiari syndrome | Post partum |

# Hyperemesis Gravidarum (HG)

- Occurs in 0.3% of pregnancies.
- Clinical Features:
  - Intractable vomiting in 1st trimester, requiring IV hydration.
  - Starts between 4-10 week of pregnancy and resolves by week 20. In 10% persists until delivery.
- Risk factors:
  - Hyperthyroidism,
  - psychiatric illness,
  - molar pregnancy,
  - preexisting diabetes, and
  - multiple pregnancies.

# Hyperemesis Gravidarum (HG)

- Pathogenesis: Immunological, hormonal, and psychological factors associated with pregnancy may play an etiologic role.
  - Increased levels of human chorionic gonadotropin (HCG) in HG may cause stimulation of secretory processes of the upper gastrointestinal tract and stimulation of the thyroid gland.
  - Elevations of estrogen, decreases in prolactin levels, and overactivity of the hypothalamic-pituitary-adrenal axis.
  - Immune and inflammatory mechanisms may also contribute to HG. Increased levels of tumor necrosis factor alpha have been observed in HG patients. Higher levels of immunoglobulin G (IgG), immunoglobulin M (IgM), C3, and C4 levels, as well as increased lymphocyte counts and natural killer and extra-thymic T cell levels have been observed in HG patients.

# Hyperemesis Gravidarum (HG)

- Laboratory:
  - Liver dysfunction occurs in 50% patients with aminotransferases up to 20-fold elevation (ALT 400-1000 U/L) and with occasional jaundice.
  - Other complications include disturbances in electrolytes and in water and acid-base balance that can usually be treated adequately with hydration.
  - Liver biopsy normal or with bland cholestasis. Needed only to exclude more serious disease.
- Effect in Fetus: Not clear.
  - Increased rates of fetal abnormalities including undescended testicles, hip dysplasia, and Down Syndrome have been reported.
  - In one large cohort study, infants of HG mothers were found to have lower birth weights and higher rates of being small for gestational age

# Hyperemesis Gravidarum (HG)

- Treatment:
  - Hospitalization is necessary for rehydration, nutritional support, and symptomatic measures with antiemetics; occasionally steroids are used.
  - Eat small, frequent, low-fat meals.
  - Naso-jejunal feeding can be very helpful.

# Safety of drugs used in pregnancy-associated liver diseases

**(Drug FDA pregnancy category Comments)**

- **Antiemetics**
  - ***Promethazine*** **C** Possible respiratory depression if drug is administered near time of delivery
  - ***Metoclopramide*** **B** Available evidence suggests safe use during pregnancy
  - ***Ondansetron*** **B** Additional studies are needed to determine safety to the fetus, particularly during the first trimester
  - ***Prochlorperazine*** **C** There are isolated reports of congenital anomalies; however, some included exposures to other drugs. Jaundice, extrapyramidal signs, hyper-/hyporeflexes have been noted in newborns

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# Intrahepatic Cholestasis of Pregnancy (ICP)

- In USA in 0.1% of pregnancies; 20% have jaundice.
- Clinical Features:
  - Severe pruritus usually with onset at week 25 or later, generalized, but most severe in palms and soles, worse at night.
  - Only 20% have mild jaundice, usually less than 5 mg/dL. Jaundice without pruritus is rare.
  - More common with advanced maternal age & multiparity.
  - May have clinical or subclinical steatorrhea that may cause deficiency of fat soluble vitamins, specially vit K.
  - There is increased risk of gallstone formation.
  - Cholestasis disappears after delivery and recurs in 60-70% of pregnancies.
  - If cholestasis does not disappear with delivery, should suspect PBC or PSC.
  - Cholecystectomy increases risk of recurrence. Have increased risk of cholestasis when taking oral contraceptives.

# Intrahepatic Cholestasis of Pregnancy (ICP)

- Laboratory Features:
  - Have high fasting bile acids, sometimes 100 fold, which correlate with fetal risk. Increase in cholic acid and decrease in chenodeoxycholic acid leads to a marked elevation in the cholic/ chenodeoxycholic acid ratio. The glycine/taurine ratio is also reduced.
  - Bilirubinuria may be present, serum alkaline phosphatase modestly elevated, GGT is normal or marginally high.
  - Serum ALT & AST usually mildly elevated, but as high as 1000 U/L or more (10-20 X ULN)
  - Liver Bx shows bland cholestasis with none or minimal hepatocellular necrosis.
- Fetal Risk:
  - Have increased risk of fetal distress, stillbirth and premature delivery (up to 60%).
  - Should monitor for placental insufficiency.
  - Fetal or perinatal mortality 0.4-1.4%.

# Laboratory in ICP

| | % Abnormal | Mean | Range |
|---|---|---|---|
| Bilirubin | 25 | 2.9 | 0.4-8.4 |
| Alk. Phosphatase | 70 | 2.4 fold | Nl – 12.5 fold |
| AST | 60 | 119 | Nl – 736 |
| ALT | 55 | 131 | Nl – 1030 |
| Bile acids | 90 | 47 mcM | Nl – 430 |
| Cholic acid | 70 | 17 mcM | Nl - 109 |

# Intrahepatic Cholestasis of Pregnancy (ICP)

- **Pathogenesis:** Unknown.
  - Most common in Chile and Scandinavia, and many have family history of ICP (genetic predisposition?).
  - More common in winter, and with low serum selenium and selenoenzyme glutathione peroxidase activity (environmental factors).
  - Elevated estrogen and/or progesterone can cause ICP in non-pregnant women, and some patients have impaired detoxification by the sulfation pathway (metabolic ?).
  - Mutations in the phospholipid translocator known as the ATP-cassette transporter B4 (ABCB4) or multidrug resistant protein-3 (MDR3) are associated with 15% of cases of ICP.
  - Increased fetal death may be due to bile acid mediated vasospasm of placental vessels, causing asphyxia.

# Intrahepatic Cholestasis of Pregnancy (ICP)

- Management:
  - **Mother:** palliative.
    - UDCA 20-25 mg/kg helps itching by changing bile acid content in maternal serum, and amniotic fluid, and also increasing placental bile acid transport. Also decreases bile acids in the fetus.
    - Exogenous progesterone must be discontinue.
    - Cholestyramine 8-24 g/d may help, but worsens steatorrhea and fat-soluble vitamin deficiency; does not help the fetus.
    - SAMe has mixed therapeutic results.
    - Ultraviolet B light may also help.

# Intrahepatic Cholestasis of Pregnancy (ICP)

- Management:
  - **Fetus:**
    - Close monitoring for chronic placental insufficiency.
    - Fetal complications correlate with maternal bile acid (BA) levels.
    - Premature delivery, asphyxial events, and meconium staining occur only in the 19% of cases with maternal BA levels greater than 40 mol/L.
    - Delivery of baby as soon as is mature.
    - Dexamethasone (12 mg/day for 7 days) has been use to promote fetal lung maturity.

# Safety of drugs used in pregnancy-associated liver diseases

**(Drug FDA pregnancy category Comments)**

- **Intrahepatic cholestasis**
  - ***Ursodeoxycholic acid*** **B** Relatively low risk
  - ***S-adenosyl-L-methionine*** Not evaluated by FDA Relatively low risk
  - ***Cholestyramine*** **C** Cholestyramine is not absorbed systemically, but may interfere with vitamin absorption

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# Preeclampsia & Eclampsia

- Hypertension, edema & proteinuria in late 2nd, or 3rd trimester.
- Occurs in 3-10% of pregnancies.
- **Hypertension:**
  - systolic pressure greater than 140 mmHg and a diastolic pressure greater than 90 mmHg
  - on at least two occasions that are at least 4 to 6 h apart
  - in a previously normotensive patient, after the 20th week of pregnancy
  - BP should be measured in a sitting position for ambulatory patients or in a semi-reclining position for hospitalized patients, with the right arm being in a roughly horizontal position at heart level.
- **Proteinuria:** equal to or greater than 300 mg of protein in a 24 h urine collection, or 1+ protein or greater on urine dipstick testing of two random urine samples collected at least 4 to 6 h apart.
- **Eclampsia:** preeclampsia + neurologic symptoms such as headaches, visual disturbances, and seizures or coma.

# Preeclampsia & Eclampsia

- **Risk factors** nulliparity, extremes of maternal age, insulin resistance, obesity, and infection.
- Liver involvement is infrequent. Indicates severe preeclampsia with significant perinatal morbidity and mortality.
- Is the commonest cause of hepatic tenderness without hepatomegaly, and liver dysfunction in pregnancy.
- Laboratory:
  - Aminotransferases are variable, from mild to 10-fold to 20-fold elevations.
  - Bilirubin is usually less than 5 mg/dL
  - May be complicated by HELLP Syndrome.

# Preeclampsia & Eclampsia

- **Liver histology:** hepatic sinusoidal deposition of fibrin along with periportal hemorrhage, liver cell necrosis, and in severe cases, infarction; these changes are likely due to vasoconstriction of hepatic vasculature. Microvesicular fatty infiltration has also been observed in some cases of preeclampsia, suggesting a possible overlap with acute fatty liver of pregnancy
- **Pathophysiology:** procoagulant and pro-inflammatory states that create glomerular endotheliosis, increased vascular permeability, and a systemic inflammatory response that results in end-organ damage and hypoperfusion.

# Preeclampsia & Eclampsia

- Maternal mortality:
  - rare in developed countries;
  - up to 15%-20% in developing countries.
- Fetal mortality rate is rare, occurring in 1%-2% of births.
- Maternal and neonatal morbidity may include:
  - placental abruption,
  - preterm delivery,
  - fetal growth restriction or
  - maternal renal failure pulmonary edema, or cerebrovascular accident.

# Preeclampsia & Eclampsia

- Treatment for preeclampsia is delivery of the fetus and placenta.
- If mild preeclampsia is evident before fetal lung maturity at 36 wk gestation, consider expectant management with intensive monitoring.
- Pharmacological agents used in preeclampsia include
  - antihypertensives such as calcium channel blockers and
  - low-dose aspirin.
- Magnesium sulfate may be administered if eclampsia develops.

# HELLP Syndrome

- Severe preeclampsia is complicated by HELLP Syndrome in 2%-12% of cases (0.2%-0.6% of all pregnancies).
- Diagnostic criteria:
  - **H**: Abnormal smear (microangiopathy), LDH > 600 U/L, High Indirect Bilirubin
  - **EL**: AST > 70 U/L, (AST/ALT elevation up to 10-20 fold)
  - **LP**: plat < 150,000;
    - Class 1: < 50K,
    - Class 2: 50-99K,
    - Class 3: 100-149K)

# HELLP Syndrome

- Symptoms:
  - Epigastric and/or RUQ abdominal pain and tenderness, nausea and vomiting, malaise, headache, edema and weight gain, hypertension, and proteinuria;
  - Less commonly renal failure (with increased uric acid), diabetes insipidus, and antiphospholipid syndrome.
  - Late findings include intravascular coagulopathy (DIC), pulmonary edema, placental abruption, and retinal detachment.
  - Jaundice is uncommon (5%); T. bili < 5 mg/dL unless has massive liver necrosis
  - Some patients have no obvious preeclampsia

# HELLP Syndrome

- Most patients present between 27 and 36 weeks' gestation, but 25% present in postpartum period.
- HELLP is commoner in white patients, multiparous, and older patients but can occur with any parity and age.
- Pathogenesis:
  - alterations in platelet activation,
  - increase in proinflammatory cytokines,
  - segmental vasospasm with vascular endothelial damage.
  - association with a defect in long-chain 3-hydroxyacyl-coenzyme A dehydrogenase (LCHAD) has been described.
- Families with known Fatty Acid Oxidation (FAO) deficiencies have shown a high incidence of HELLP, but babies of mothers with HELLP do not have a proven increased risk of FAO deficiencies.

# Clinical Characteristics of HELLP Syndrome

## Symptoms, Signs, & Complications

| | % |
|---|---|
| RUQ/Epigastric Pain | 65 |
| Nausea & Vomiting | 36 |
| Headache | 31 |
| Bleeding | 9 |
| Jaundice | 5 |
| Disseminated Intravasc Coag | 21 |
| Abruptio placentae | 16 |
| Acute Kidney Injury | 8 |
| Hepatic hematoma | 1 |
| Death | 1 |

## Laboratory Findings

| | % Abnl | Median | Range |
|---|---|---|---|
| ALT | 100 | 239 | 49-700* |
| AST | 99 | 250 | 70-630* |
| T. Bilirubin | 42 | 1.5 | 0.5-25 |
| Platelets | 100 | 57 | 7-99 |

Am J Obstet Gynecol 169:1000; 1993

*AST up to 2300, ALT up to 700 have been reported

# HELLP Syndrome

- Computed tomography  or MRI of the liver may show subcapsular hematomas, intraparenchymal hemorrhage, or infarction or hepatic rupture (thrombocytopenia of less than 20,000).
- **Management:**
  - Hospitalize for antepartum stabilization of hypertension, management of DIC, seizure prophylaxis, and fetal monitoring.
  - Transfer to a tertiary care center if possible.
  - Obtain hepatic computed tomography (limited views).
  - If fetus greater than 34 weeks' gestation or if there is any evidence of multiorgan dysfunction, DIC, renal failure, abruptio placentae, or fetal distress, here is consensus that immediate delivery should be effected.
  - If fetus < 34 weeks and case is mild, give IV betamethasone or dexamethasone for 24-48 h before delivery.
  - Well-established labor should be allowed to proceed in the absence of obstetric complications or DIC, but many patients (40%-50%) will require caesarean section.

# HELLP Syndrome

- Maternal mortality from HELLP is 1%.
- Perinatal mortality rate ranges from 7%-22% and may be due to premature detachment of placenta, intrauterine asphyxia, and prematurity.
- Liver transplantation need is rare: persisting bleeding from a hematoma or hepatic rupture or liver failure from extensive necrosis.
- Hepatic hemorrhage without rupture is managed conservatively in a hemodynamically stable patient with close hemodynamic monitoring in an intensive care unit:
  - correction of coagulopathy,
  - avoid all trauma: abdominal palpation, convulsions, emesis, unnecessary transportation.
  - immediate availability of large volume transfusion of blood products,
  - immediate intervention for rupture or rapid expansion of hematoma, on diagnostic hepatic imaging.

# HELLP Syndrome

- Hepatic rupture mortality is 50%, with 10-60% perinatal mortality.
- Budd-Chiari syndrome can occur with HELLP syndrome.
- **Recurrence:** 4-19%. Subsequent pregnancies in patients with HELLP syndrome carry a high risk of complications:
  - pre-eclampsia,
  - recurrent HELLP,
  - prematurity,
  - intrauterine growth retardation,
  - abruptio placentae,
  - No long-term effect on renal function has been noted.

# Safety of drugs used in pregnancy-associated liver diseases

**(Drug FDA pregnancy category Comments)**

- **Antihypertensives**
  - ***ACE inhibitors* C/D** First trimester exposure to ACE inhibitors may cause major congenital malformations. Second and third trimester use of an ACE inhibitor is associated with oligohydramnios and anuria, hypotension, renal failure, skull hypoplasia, and death in the fetus/neonate
  - ***Beta blockers* C/D** Fetal bradycardia, hypotension, risk of intrauterine growth retardation
  - ***Calcium channel blockers* C** Teratogenic and embryotoxic effects have been demonstrated in small animals. There are no adequate and well-controlled studies in pregnant women

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# Safety of drugs used in pregnancy-associated liver diseases

**(Drug FDA pregnancy category Comments)**

- **Anticoagulation**
  - Aspirin **C** (1st/2nd trimesters) **D** (3rd trimester). Adverse effects in the fetus include intrauterine growth retardation, salicylate intoxication, bleeding abnormalities, and neonatal acidosis. Use of aspirin close to delivery may cause premature closure of the ductus arteriosus. Data have shown low-dose aspirin (60-150 mg/day) may be safe in pregnancy
  - Enoxaparin **B** No adequate and well-controlled studies using enoxaparin. Postmarketing reports include congenital abnormalities and also fetal death
  - Heparin **C** Does not cross the placenta

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# Acute Fatty Liver of Pregnancy

- Sudden, catastrophic illness with hepatic failure, manifested as coagulopathy and hepatic encephalopathy, in a pregnant woman without known liver disease, liver biopsy showing microvesicular fatty infiltration.
- Occurs in the third trimester of pregnancy (wk 34-37). Rarely occurs after delivery.
- Incidence of 1 in 10 000 to 1 in 15000 pregnancies.
- Maternal mortality rate of 18% and a fetal mortality rate of 23%.
- AFLP is more commonly seen in nulliparous (40-50%) women and with twin or multiple gestation.

# Acute Fatty Liver of Pregnancy

- **Presentation:** from asymptomatic to fulminant liver failure.
  - Typical patient has 1 to 2 weeks of anorexia, nausea and vomiting, headache, and right upper quadrant pain, and is ill-looking with jaundice, hypertension, edema, ascites, a small liver, and hepatic encephalopathy. Pruritus may be an early symptom.
  - Intrauterine death may occur.
  - About 50% (21-64%) of patients with AFLP have preeclampsia, and there is some overlap with the HELLP syndrome.
  - The fetus ratio male:female is 2.7:1

# Acute Fatty Liver of Pregnancy

- **Laboratory:**
  - ALT & AST from near-normal to 1000, usually about 300 to 500; as high as 1300
  - high ammonia
  - bilirubin usually less than 5mg/dL but higher in severe or complicated disease (elevated in 98%, up to 36 mg/dL)
  - hypoglycemia in 25%
  - hyperuricemia in 81% (up to 18.5 mg/dL)
  - normochromic, normocytic anemia,
  - high white blood cell count in 97%,
  - normal to low platelets (low in 86%, as low as 5000),
  - coagulopathy with or without DIC,
  - metabolic acidosis,
  - renal dysfunction (often progressing to oliguric renal failure) in 75%,
  - biochemical pancreatitis in 33%

# Acute Fatty Liver of Pregnancy

- **Definitive diagnosis**: is histological;
  - frozen tissue stained with oil-red O shows microvesicular fatty infiltration (free fatty acids) predominantly in zone 3 with lobular disarray and mild portal inflammation with cholestasis .
  - Occasionally the histological picture, cannot be differentiated from viral hepatitis or preeclampsia.
- **Presumptive diagnosis**:
  - In presence of coagulopathy precluding biopsy, the diagnosis is made on compatible clinical and laboratory features, and the need for expeditious therapy.
  - Imaging studies, including ultrasound and computed tomography (CT), are inconsistent in detecting fatty infiltration.

# Acute Fatty Liver of Pregnancy

- **Etiology:** It is unknown.
  - LCHAD (long chain 3-hydroxyacyl-CoA dehydrogenase deficiency) has been identified in about 20% of babies of mothers with AFLP.
  - Maternal heterozygosity for LCHAD deficiency may reduce the maternal capacity to oxidize long-chain fatty acids both in liver and placenta, and this, together with the metabolic stress of pregnancy and fetal homozygosity for LCHAD deficiency, may causes accumulation in the maternal circulation of potentially hepatotoxic LCHAD metabolites.
  - Even with a normal maternal genotype, a fetus with at least one G1528C or E474Q mutation causing LCHAD, can produce AFLP in the mother.
  - Carnitine palmitoyltransferase I deficiency has been associated with AFLP.
  - Prenatal diagnosis can be done by chorionic villous sampling.
  - Perhaps external factors, such as carnitine deficiency or other dietary factors, exacerbate this situation.

# Acute Fatty Liver of Pregnancy

- **Management:**
  - delivery of the fetus.
  - many laboratory abnormalities may persist after delivery and may initially worsen during the first postpartum week.
  - rarely patients progress to fulminant hepatic failure needing liver transplantation.
  - infant should be watched for risk of cardiomyopathy, neuropathy, myopathy, non-ketotic hypoglycemia, hepatic failure, and death associated with fatty acid oxidation defects in newborns.
  - affected patients should be screened for defects in fatty acid oxidation as recurrence in subsequent children is 25%, and recurrence of AFLP in mothers is also possible.
  - mother, father and child should be tested for LCHAD (G1528C or E474Q), and Carnitine palmitoyltransferase I deficiency

# Acute Fatty Liver of Pregnancy

- **Evolution & Prognosis :**
  - patients are better managed in an ICU with liver failure expertise.
  - most patients improve in 1 to 4 weeks postpartum,
  - a cholestatic phase with rising bilirubin and alkaline phosphatase may persist.
  - recovery can occur in days or be delayed for months but is complete with no signs of chronic liver disease.
  - With good supportive management, the maternal mortality is now 7%-18% and fetal mortality 9%-23%.
  - infectious and bleeding complications remain the most life threatening

| | ICP | HG | PE/E | HELLP | AFLP |
|---|---|---|---|---|---|
| **% Preg** | 0.1 | 0.3 | 3-10 | 0.2-0.6 | 0.005-0.01 |
| **Onset** | 25-32 w | 4-10 w | After 20 w | 27-36 w | 34-37 W |
| **Fam. Hx** | Often | No | No | No | Occasional |
| **Pre-eclamp** | No | No | Yes | Yes | 50% |
| **Clinical Features** | Pruritus, high bile acids | Nausea/ vomiting | HBP, edema proteinuria | Hemolysis, low plat, high Liver enzymes | ALF, coagulop high ammonia & uric acid |
| **AST & ALT** | Mild - 20X | Normal - 20X | Normal - 20X | Mild - 20X | Mild - 1000 U |
| **Bilirubin** | < 5 mg/dL | Occasional < 5 mg/dL | < 5 mg/dL | < 5 (up to 25) | < 5 (up to 25) |
| **Maternal mortality** | 0 | Rare | Rare (15-20% in 3rd W) | 1-25 % | 7-18 % |
| **Fetal/perin mortality** | 0.4-1.2 % | Rare | 1-2 % | 4-19 % | 9-23% |

# Gallstone Disease

- Biliary sludge and gallstones is associated with parity. Stones or sludge develop by the postpartum period in 10% of pregnancies.
- Prevalence of gallstones in pregnancy is:
  - 18.4%-19.3% in multiparous women and
  - 6.9%-8.4% in nulliparous women.
  - Symptomatic stones in 0.1-0.3% of pregnancies
- Etiology for  biliary sludge and gallstones in pregnancy is multifactorial:
  - Increased estrogen levels, especially in the second and third trimesters, lead to increased cholesterol secretion and supersaturation of bile
  - increased progesterone levels cause a decrease in small intestinal motility
  - fasting and postprandial gallbladder volumes are larger
  - gallbladder emptying time is reduced.
- The large residual volume of supersaturated bile in the pregnant woman leads to biliary sludge and the formation of gallstones.

# Gallstone Disease

- Pre-pregnancy risk factors :
  - high body mass index,
  - high serum leptin levels,
  - low high-density lipoprotein (HDL) levels, and
  - insulin resistance
- Clinical Presentation:
  - Biliary colic: causes 5% of jaundice episodes in pregnancy
  - Gallstone pancreatitis: 50% of women < 30 with pancreatitis are pregnant; 0.05-0.1% of pregnancies.
  - Acute cholecystitis: Least common presentation
  - right upper quadrant pain that may radiate to the flank, scapula, or shoulder.
  - nausea, vomiting,
  - anorexia,
  - fatty food intolerance,
  - low-grade fever.

# Gallstone Disease

- Medical Management:
  - Conservative management is recommended initially, especially during the first and third trimesters, in which surgical intervention may confer risk of abortion or premature labor, respectively.
  - Medical management involves intravenous fluids, correction of electrolytes, bowel rest, pain management, and broad spectrum antibiotics.
  - Relapse rates (40%-90%) are high during pregnancy; thus, surgical intervention may be warranted.
- Surgical Management:
  - Laparascopic cholecystectomy in the second trimester is preferred.;
    - should be done in all symptomatic patients who present in 2$^{nd}$ trimester.
    - $CO_2$ insuflation should be minimized, and
    - hyperventilation should be induced to minimize acidosis and $PaCO_2$ in mother.
  - ERCP may also be required if there are concerns about choledocholithiasis, and this can be performed safely in pregnancy by shielding the fetus and minimizing fluoroscopy time

# Viral Hepatitis

- Viral hepatitis, due to hepatitis A, B, C, D, E, herpes simplex, cytomegalovirus, and Epstein-Barr viruses, accounts for 40% of jaundice in pregnant women in the United States.
- Hepatitis A, B, and C have the same frequency in the pregnant and nonpregnant populations and during each of the 3 trimesters of pregnancy.
  - Acute hepatitis A occurs in 1 per 1000,
  - Acute hepatitis B in 2 per 1000 pregnant women, and
  - Hepatitis D is rare.
- The clinical and serologic course of acute hepatitis in the Western world is generally the same as in the nonpregnant patient

# Viral Hepatitis

- With few exceptions, hepatitis usually does not appear to affect the pregnant state adversely
  - Hepatitis A during the second or third trimesters may increase gestational complications.
  - Hepatitis E is extremely rare in the United States but is endemic to large areas of Asia, Africa, and Central America, where, in the third trimester of pregnancy, it becomes fulminant with a high mortality (up to 25%), probably influenced by malnutrition.
  - Herpes simplex hepatitis is rare but must be diagnosed because antiviral therapy with acyclovir or vidarabine is life-saving; these patients present with a severe or fulminant “anicteric” hepatitis in the third trimester.

# Viral Hepatitis

- Management of the patient with acute viral hepatitis is supportive, and viral hepatitis is not an indication for termination of pregnancy, caesarean section, or discouragement for breastfeeding.
- Congenital malformations in the fetus occur only with early cytomegalovirus infection.
- Vertical transmission of hepatitis A and D is rare and occurs only with high viral levels at the time of delivery.
- Newborns of mothers with hepatitis A in the third trimester should be given passive immunoprophylaxis with immune globulin within 48 hours of birth.
- Hepatitis E is associated with intrauterine death and abortion, in any trimester. Maternal-fetal transmission can occur, and give neonatal hepatitis.

# Viral Hepatitis B

- All pregnant women are tested for hepatitis B on first antenatal visit;
- Pregnant women without immune antibodies and at high risk for HBV infection during pregnancy (for example, multiple sex partners, intravenous drug use), vaccine can be given in pregnancy with little risk to the fetus.
- Perinatal transmission of hepatitis B is highest in those with acute hepatitis, especially with hepatitis B e antigen positivity in the third trimester (50%- 80%).
- Transmission is lower in mothers with anti-HBe (25%), and lowest in carriers (5%); 80%-90% of these babies have persistent hepatitis B surface antigen positivity.
- Hepatitis B virus DNA levels typically increase late in pregnancy or in the early postpartum period, with 1 retrospective study showing a mean increase of 0.4 log

# HBV & Pregnancy

- Pregnancy is well tolerated by HBV carriers
- HBV reactivation with exacerbation of disease is rare during pregnancy or post-partum.
- Intrauterine transmission of HBV is rare, but may occur during “threatened abortion” by transplacental leakage.
- Transmission by amniocentesis is low (</= 4%).
- If mother is HBeAg(+), risk of vertical transmission is 90% without prophylaxis.
- Post-partum “flare up” is common and due to decrease of cortisol levels. Up to 12-17% may have post-partum “e” seroconversion.

# HBV & Pregnancy

- If mother has HBV-DNA < $10^8$ IU/ml:
  - neonatal immuno-prophylaxis [HBIG + HBV immunization] prevents transmission in 95%.
- Cesarean section decreases vertical transmission rate, but:
  - is not indicated because [HBIG + HBV immunization] is very effective.
- If mother is “highly infectious” with HBV-DNA > $10^8$ IU/mL
  - risk of HBV transmission is 30-40% despite [HBIG + HBV immunization]

# HBV & Pregnancy

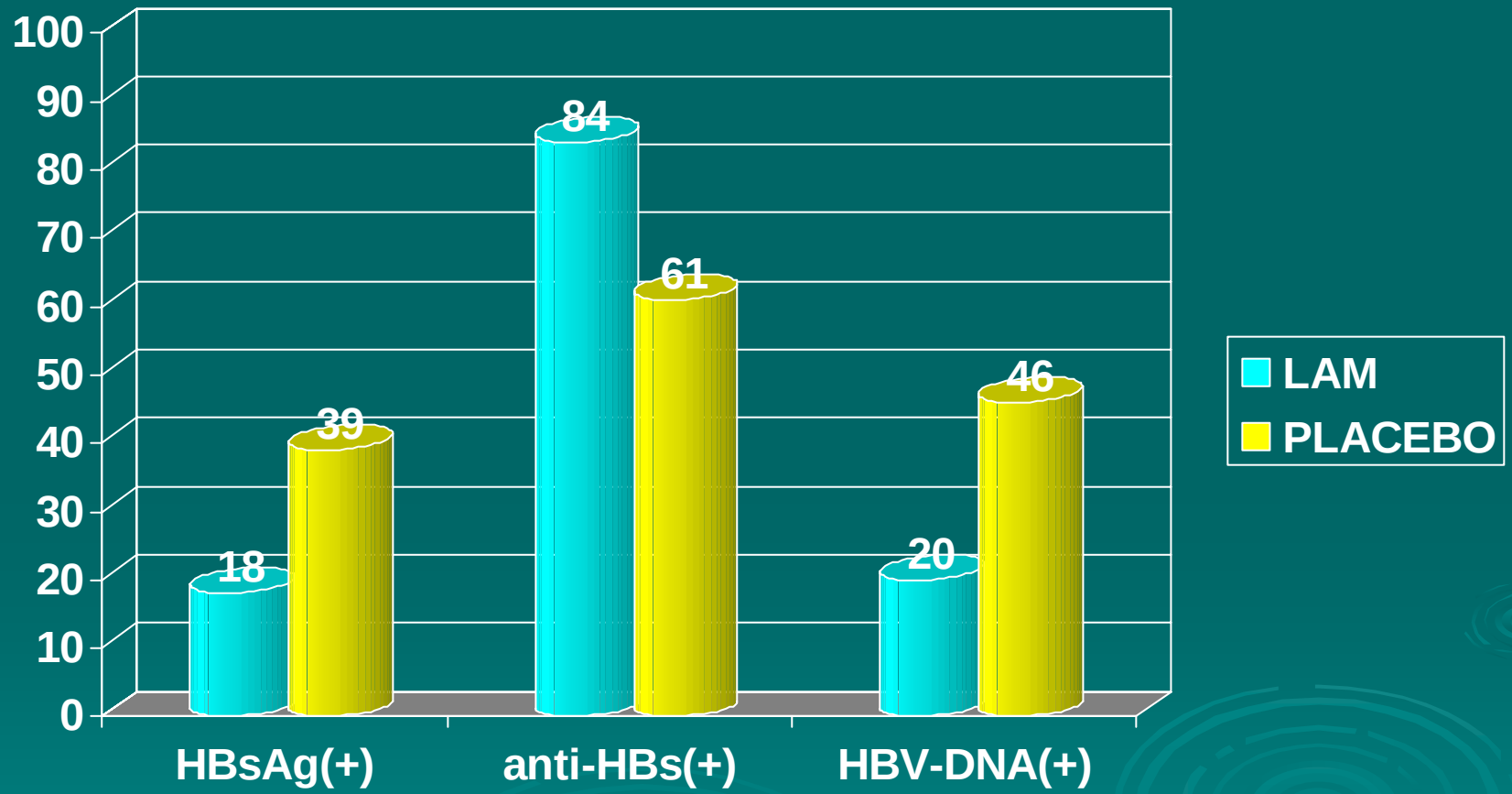
- If mother is infected with HBeAg(-) and HBV-DNA > $10^8$ IU/mL ("very high load precore mutant HBV"):
  - infant is at risk of fulminant hepatitis B during initial 2 to 4 months of life.
- Mothers with HBV/HDV co-infection:
  - may vertically transmit both infections to the neonate.
  - HBIG + HBV immunization can protect from both.
- Post-vaccination testing of infant should be done at age 9-15 months.
- Telbivudine and Tenofovir are safe during pregnancy. Lamivudine has been used safely in the 3$^{rd}$ trimester.

# Effect of Lamivudine on HBV Vertical Transmission from Highly Infectious Mothers

Xu WM et al. AASLD Abstr # 246, 2004
Xu WM et al. J. Viral Hepat 2009:16, 94-103

- Multicenter, double blind, randomized, placebo controlled.
- **Population**: 114 pregnant women with HBsAg(+) & HBV-DNA > $10^9$ genome Eq/mL (Chiron bDNA) (aprox > 200 million IU/mL).
- **Treatment**: Lamivudine 100 mg/d vs. placebo starting @ wk 32 until 4 wks post-partum
- All neonates received: HBIG 200 IU + HBV vaccine @ birth, 4 & 24 weeks.
- **End-point**: HBsAg(+) & HBV-DNA(+) @ age 53 wks

# RESULTS # 246


100
90
80
70
60
50
40
30
20
10
0
84
61
39
46
18
20
HBsAg(+)
anti-HBs(+)
HBV-DNA(+)
LAM
PLACEBO

# CONCLUSION

Abstr # 246

- In mothers with HBV-DNA > $10^9$ genome Eq/ml (> 200 million IU/mL), the addition of Lamivudine 100 mg/d in the 8 weeks prior to delivery plus 4 weeks post-partum, to the regimen of HBIG & Vaccination, decreased the rate of vertical transmission of HBV.
- No safety concerns were observed on mothers nor infants.
- Lamivudine was well tolerated.

# Vertical Transmission of HCV

(Obstet Gynecol Surv 2006; 61:666-72)

- Risk if mother anti-HCV(+) is approximately 2%;
  - If mother is HCV-RNA (+), risk is 4-5%.
  - Scalp electrodes increase risk of transmission.
- Up to 30% of infected neonates may have acquired HCV "in utero" (Arch Dis Child Fetal Neonatal Ed 2005;90:F156-60)
- A cohort study of 506 HCV-positive pregnant women found that HCV infection was associated with:
  - development of gestational diabetes mellitus,
  - lower birth weight,
  - lower Apgar scores,
  - more admissions to the neonatal intensive care unit for respiratory problems, prematurity, and infections

# Vertical Transmission of HCV

(Obstet Gynecol Surv 2006; 61:666-72)

- In HCV/HIV co-infection the transmission risk is higher (15-18%) but HAART may decrease the risk.
- HCV-RNA viral load >/= $10^{18}$ U/mL have up to 36% vertical transmission rate.
- There is no association between vertical transmission of HCV, gestational age at delivery, nor chorioamnionitis.
- Data are conflicting about duration of ruptured membranes and risk of HCV transmission (increased after 6 h ?)

# Vertical Transmission of HCV Cesarean Section vs Vaginal Delivery

- The “Cochrane Pregnancy and Childbirth Group’s Trial Register”, and the “Cochrane Central Register of Controlled Trials” were analyzed until April 2006.
- No randomised controlled trials were found (Cochrane Database Syst Rev 2006; Oct 18).
- Systematic review of observational studies (subject to biases) or RCT’s are needed.

# Vertical Transmission of HCV

(Obstet Gynecol Surv 2006; 61:666-72)

- **In HCV(+)/HIV(-) mothers:**
  - Route of delivery does not influence vertical transmission.
  - There is no need to discourage breast feeding.
- **In HCV(+)/HIV(+) mothers:**
  - Mode of delivery should be based in HIV status.
  - Breast feeding should be discouraged.

# HSV Hepatitis

- Subclinical HSV due to “primary” infection is common.
- Primary infection during pregnancy, specially in the 3rd trimester, may cause severe and fulminant hepatitis.
- Clinical presentation:
  - Patient is usually anicteric, obtunded, with high aminotransferases, and coagulopathy.
  - May have subtle oropharyngeal or genital vesicular lesions.
  - May have associated HSV encephalitis.
- Liver Bx shows intracytoplasmic inclusions.
- Serum HSV by PCR is positive.
- Treatment is urgent, with Acyclovir. Prevents transmission to the fetus.

# Primary Biliary Cirrhosis (PBC)

- PBC is a chronic cholestatic disease that affects persons in their 30s to 60s.
- Causes destruction of intrahepatic bile ducts and is likely autoimmune, with than two thirds of patients having an associated autoimmune disease.
- The course of PBC may be insidious, often presenting with fatigue and pruritus.
- Serum aminotransferase, bilirubin, cholesterol, IgM, and erythrocyte sedimentation rate levels are often elevated, and an elevated bilirubin level often portends poor prognosis.
- Portal hypertension and liver failure may develop.

# Primary Biliary Cirrhosis (PBC)

- Early reports suggested that PBC is associated with reduced fertility, amenorrhea, repeated pregnancy loss, endometriosis, and premature ovarian failure, as well as worsening liver function during the course of pregnancy. More recent data suggest that women with PBC may be able to have normal pregnancies.
- One study of nine pregnancies in six patients with UDCA-treated PBC showed that:
  - all women remained asymptomatic during pregnancy with no recurrence of pruritus.
  - improvements were seen in laboratory tests including antimitochondrial antibody titers and levels of alkaline phosphatase, ALT, serum bile acid, bilirubin, immunoglobulin G, and immunoglobulin M.
  - a flare in disease with increases in liver biochemistries was observed 3 mo postpartum.
  - UDCA has been shown to be safe in pregnancy.

# Primary Sclerosing Cholangitis (PSC)

- There are only a few published case reports on PSC in pregnancy; thus, the natural history of PSC in pregnancy is not well understood.
- Pregnant patients with PSC may experience pruritus, biliary strictures and choledocholithiasis.
- If a patient with PSC develops symptoms worrisome for biliary obstruction, an ultrasound should be performed, as it is thought to be safe in pregnancy and may detect the presence of stones or dominant strictures.
- Endoscopic retrograde cholangiopancreatography (ERCP) may be considered with caution regarding exposure to radiation and the use of sedation.
- Empiric use of UDCA should be considered, as it is felt to be safe in pregnancy and may improve maternal symptoms and fetal complications.

# Autoimmune Hepatitis

- The natural history of AIH in pregnant women is variable.
- Candia *et al reviewed 101 cases of AIH in* pregnant women reported in the literature between 1966 and 2004:
  - 47 women experienced AIH flares, with 35 occurring during pregnancy and 12 occurring after delivery.
  - fetal deaths occurred in 19% of pregnancies, and the majority of the fetal deaths occurred before the 20th wk of gestation.
- A recent review of 42 pregnancies in women with AIH reported a fetal loss rate of 24%. Range in several studies is 14-24%.
- Fetal death in pregnant women with AIH has been associated with the presence of prematurity and low birth weight.
- Factors associated with worsening of AIH in pregnancy include:
  - changes in the relative concentrations of various hormones during pregnancy
  - specific autoantibodies, including antibodies to SLA/LP and Ro/SSA.

# Autoimmune Hepatitis

- AIH may by exacerbated by pregnancy
  - Intrapartum flare is 12.5% to 21%.
  - Postpartum flares are 12.5% to 86%.
  - Discrepancy in data may be due to inconsistent alteration of therapy during pregnancy, with dosing being maintained, reduced, or even discontinued.
- Patients with AIH undergo caesarian section at higher rates than the general population, ranging from 16.1% to 43%.
- Women of childbearing age with AIH should be advised to consider pregnancy only if their disease is well-controlled.

# Autoimmune Hepatitis

- Pregnancy or the contemplation of pregnancy does not contraindicate immunosuppressive therapy.
- Pregnant women with AIH are often treated with a combination of steroids and azathioprine.
- Azathioprine crosses the placenta, but data have suggested that azathioprine and its metabolites do not have toxic effects on the fetus.
- Expectant mothers typically respond as well to treatment as others, and there have been only theoretical concerns regarding teratogenicity associated with azathioprine treatment but have not been reflected in the human experience. The use of prednisone alone during pregnancy eliminates any concern.
- Patients must be monitored closely throughout pregnancy and in the early postpartum period given the unpredictability of the course of AIH in the setting of pregnancy.

# Autoimmune Hepatitis

- A modest decrease in immunosuppression can often be performed after the third month of pregnancy, when liver test typically improve. However, this is usually followed by a need for increased doses just before delivery and in the postpartum period
- Women with AIH typically tolerate pregnancy satisfactorily unless their disease is advanced and complicated by ascites and esophageal varices. Under such circumstances, the risk of variceal hemorrhage may be increased.
- Patients with advanced liver disease and portal hypertension are commonly amenorrheic and/or infertile, and pregnancy is uncommon.
- Effective contraception should be advised in those rare, actively menstruating women with AIH and advanced liver disease.

# Wilson Disease

- Autosomal recessive disorder of copper metabolism.
- Occurs in 1:30 000 to 1:50 000 persons,
- Due to a mutation of gene, ATP7B, on chromosome 13q14. ATP7B codes for a P type ATPase that controls copper transportation in the liver. More than 100 forms of this mutation have been found to cause WD. This mutation leads to copper excess and deposition in the liver and brain.
- Hepatic disease may present as chronic hepatitis, cirrhosis, or fulminant failure.
- Neurologic abnormalities occur in 40%-50% and include an akinetic-rigid tremor similar to Parkinson's disease, tremor, ataxia, and a dystonic syndrome.
- Studies of WD effects on pregnancy are limited to small case series.
  - WD may adversely affect fertility due to hormonal fluctuations causing amenorrhea;
  - copper deposition in the uterus may cause miscarriage due to improper implantation of the embryo.
  - the rate of recurrent spontaneous abortions is higher among untreated women with WD, compared to those treated.

# Wilson Disease

- Penicillamine, trientine, and zinc are drugs approved by the United States Food and Drug Administration (FDA) as treatment for WD.
- Penicillamine acts by chelation and enabling excretion of copper in the urine. Penicillamine has been reported to cause teratogenicity in humans.
- Trientine works similarly but is less effective than penicillamine. There is one report of a chromosomal abnormality occurring in a baby delivered by a woman with WD who took trientine during pregnancy
- Zinc induces intestinal cell metallothionein that binds to copper and prevents transfer of copper into the blood. Brewer *reported that the use of zinc in 26* pregnancies of 19 pregnant women with WD resulted in 24 healthy pregnancies; one baby was born with a heart defect requiring surgery at 6 mo, and a second baby was born with microcephaly.

# Wilson Disease

- **In WD pregnant women, treatment must be maintained throughout the course of pregnancy.**
- **Interruption of treatment during pregnancy has resulted in acute liver failure.**
- Chelating agents (both penicillamine and trientine) and zinc salts have been associated with satisfactory outcomes for the mother and fetus.
- A few birth defects has been noted infrequently in offspring of treated patients; however, the rarity of this disorder has made it difficult to determine whether this is different from the frequency of these defects in the population at large.

# Wilson Disease

- The dosage of zinc salts is maintained throughout without change.
- Dosages of chelating agents should be reduced to the minimum necessary during pregnancy, especially for the last trimester to promote better wound healing if cesarean section is performed. Dose reduction might be on the order of 25%-50% of the pre-pregnancy dose.
- Patients should be monitored frequently during pregnancy.
- Women taking D-penicillamine should not breast-feed because the drug is excreted into breast milk and might harm the infant.
- Little is known about the safety of trientine and zinc in breast milk.

# Pregnancy in Cirrhosis

- Only 45 cases of cirrhosis occur in every 100,000 women of reproductive age.
- Cirrhosis results in metabolic and hormonal derangements that lead to anovulation and amenorrhea
- Morbidity and mortality likely remains higher than that of the general pregnant population.
- Spontaneous abortion rate in patients with cirrhosis is 30% to 40% versus 15% to 20% in the general population.
- In patients with extrahepatic portal obstruction unrelated to cirrhosis, the rate of spontaneous abortion is 3% to 6%.
- Patients with cirrhosis who have undergone portal decompressive procedures prior to conception have spontaneous abortion rates comparable to patients with extrahepatic obstruction.

# Pregnancy in Cirrhosis

- Termination of pregnancy most often occurs as a result of maternal death, variceal hemorrhage, stillbirth, intrauterine growth retardation, and maternal complications during delivery.
- In those pregnancies that do result in live births, the risk of prematurity is significantly increased, with a rate of up to 25%, compared with 12.8% in the general population.
- From old literature, the perinatal death rate is likewise elevated and may be as high as 18% versus 1.08% in the noncirrhotic population. We do not know if current outcomes are better.

# Pregnancy in Cirrhosis

- Esophageal Varices:
  - Esophageal variceal bleeding is reported in 18% to 32% of pregnant women with cirrhosis and in up to 50% of those with known portal hypertension.
  - With preexisting varices, up to 78% will have gastrointestinal bleeding during pregnancy, with a mortality rate of 18% to 50%. In non-cirrhotic portal hypertension with pregnancy, mortality rate is 2-6%.
  - Bleeding is most common during the second and third trimesters when maternal blood volume is maximally expanded and the larger fetus causes increased compression of the inferior vena cava and collateral vasculature
  - Primary prophylaxis with nonselective beta blockers such as propranolol, nadolol, or carvedilol (category C), may outweigh the risks of potential fetal harm. Side effects of these drugs include fetal growth retardation, neonatal hypoglycemia, and neonatal bradycardia

# Pregnancy in Cirrhosis

- Esophageal Varices:
  - Up to 24% of pregnant patients with cirrhosis will experience hepatic decompensation , usually due to variceal bleed. With fulminant failure, liver transplantation may be the only option, which may be successful for mother and fetus.
  - Treatment of choice is Endoscopic Band Ligation, plus cefotaxime (category B), plus Octreotide (category B).
  - TIPS placement is generally contraindicated during pregnancy because of the risk of radiation exposure to the fetus. It may be an appropriate rescue therapy . The risk of fetal malformations from radiation increases at doses above 150 mGy and is negligible if  below 50 mGy. TIPS can be done with as little as 0.1-5.49 mGy.
  - Repetitive Valsalva maneuver during labor increases variceal bleed risk. Many experts advocate  elective c-section or forceps delivery under extradural analgesia in order to decrease this risk. During C-section a surgeon with experience with cirrhosis should be available in case of collateral circulation bleed.

Absorbed dose per unit of weight  is measured in gray (GY); 1 Gy = 100 rad
Biological risk depends in type of radiation, is measured in sievert (Sv); 1 Sv = 100 rem

# Pregnancy in Cirrhosis

- Ascites and SBP
  - Ascites rarely occurs during pregnancy because of increased intra-abdominal pressure, which acts to resist the extravasation of fluid from splanchnic vessels and organs.
  - If therapy is required, however, sodium restriction and diuretics can be used, as in nonpregnant patients with cirrhosis. Amiloride (category B), and Torsemide (category B) are reasonable choices. Metolazone and HCTZ are also category B, but are reserved as third line, to add to other regimens.
  - Cases of spontaneous bacterial peritonitis have not been reported during pregnancy.

# Pregnancy in Cirrhosis

- Hepatic Encephalopathy
  - May develop due to predisposing medications, hypotension, hypoxia, infection, hypoglycemia, or gastrointestinal hemorrhage.
  - Spinal and general anesthesia should be avoided during delivery because of the potential for hypotension and the risk of precipitating encephalopathy.
  - Treatment remains frequent small meals, lactulose (category B), Zinc, L-carnitine (category B) and/or rifaximin (category C). Metronidazol is category B, and neomycin is category D

# Splenic Artery Aneurism Rupture

- Splenic artery aneurisms are increased in pregnancy related to:
  - increased splenic blood flow from both pregnancy and portal hypertension.
  - high estrogen levels during pregnancy which effects the elastic tissue of the tunica media
- Pregnant patients with cirrhosis have an increased risk of splenic artery aneurysm rupture, which occurs in 2.6%.
- 20% of all splenic artery aneurysm ruptures occur during pregnancy, with 70% occurring during the third trimester.
- Clinical Presentation: Rapid intra-abdominal bleeding and hypovolemic shock often ensue, resulting in substantial maternal and fetal mortality rates of 70% and 80%, respectively.

# Splenic Artery Aneurism Rupture

- Management options:
  - emergency splenectomy,
  - transcatheter embolization of the aneurysm, or
  - stent-graft placement.
- Transcatheter embolization, and stent-graft placement, are usually the preferred options in cases of portal hypertension, as an extensive collateral circulation in these patients makes surgery more difficult.

# Post-Partum Uterine Hemorrhage

- Occurs in 7% to 10% of pregnancies in patients with cirrhosis.
- Likely related to a higher incidence of coagulopathy and thrombocytopenia.
- Treatment is similar to that in patients without cirrhosis.
  - blood and coagulation factors
  - oxytocin or other uterine contractile agents.
  - surgical therapy to ligate the bleeding vessels or hysterectomy is indicated when these measures fail.

# Pregnancy after Liver Transplantation

- As of January 2006, 202 pregnancies and 205 outcomes have been reported in 121 female liver transplant recipients in the National Transplantation Pregnancy Registry.
- Children born to female liver transplant recipients have, compared with the regular population:
  - greater risk of prematurity (35% versus 11.0%-12.7%) and
  - greater risk of low birth weight (34% versus 8.2%)

# Pregnancy after Liver Transplantation

- No associated malformation patterns reported thus far, but recent data indicates that mycophenolate may be associated with first trimester pregnancy loss and an increased risk of congenital malformations.
- Maternal complications are increased in liver transplant recipients:
  - pregnancy- induced hypertension (34% versus 4%-10%),
  - preeclampsia (22% versus 6%-8%), and
  - caesarian section (35% versus 20%-25%).

# Pregnancy after Liver Transplantation

- The incidence of pregnancy- induced or exacerbated hypertension is highest with cyclosporine, followed by tacrolimus and then corticosteroids.
- The rate of acute rejection in pregnant liver recipients is not substantially different, from that of their nonpregnant counterparts.
  - In 121 liver recipients, 7% developed acute rejection during pregnancy, and 8% suffered graft loss within 2 years of delivery.
  - Risk was highest in women who conceived within 6 months of their transplant.

# Pregnancy after Liver Transplantation

- Experts recommend that pregnancy be postponed for at least 1 year post-transplant, when graft function is optimal on lower doses of immunosuppression and the risks of acute rejection and opportunistic infection are lower. Until then, contraception is advised, preferably using barrier methods, which confer a lower risk of infection or potential drug interaction.
- Physicians should discuss with all patients considering pregnancy, as part of pretransplant counseling:
  - the timing of pregnancy,
  - methods of contraception, and
  - safety and adverse effects of immunosuppressants