

Pregnancy and Liver Disease

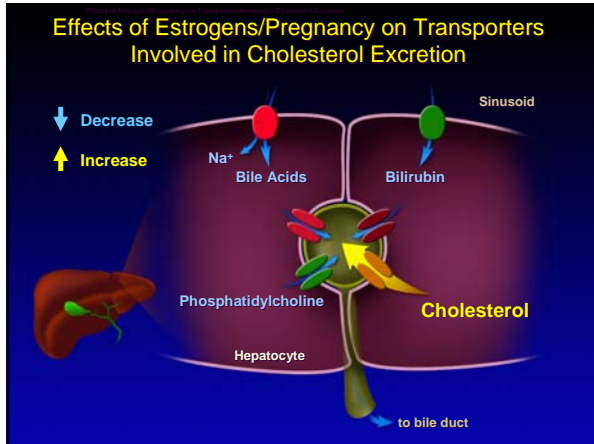
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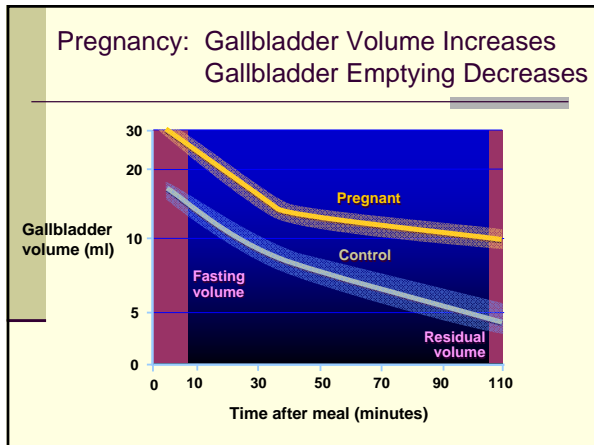
Topics

- Pre-established hepatobiliary disease and pregnancy
 - Gallstones
 - Viral hepatitis
- Unique liver diseases of pregnancy
 - Intrahepatic cholestasis of pregnancy
 - Pre-eclampsia and liver disease
 - Acute fatty liver of pregnancy

Gallstones

- Pregnancy, oral contraceptives and female gender are risk factors for gallstone formation
 - Estrogen changes biliary lipids
 - decreases bile acids and phospholipids which solubilize cholesterol
 - increases cholesterol
 - Estrogen decreases bile flow (cholestasis)
 - Progesterone decreases gallbladder motility
- Pregnancy and exogenous estrogen use increase symptomatic gallstone disease (biliary colic, acute cholecystitis)





- ### Gallstones Form During Pregnancy
- 10-31% of pregnant women develop biliary sludge
 - 2-3% of pregnant women develop gallstones
 - Biliary pain can occur in up to 28% of pregnant women with stones
 - Although 60-90% of sludge and 20-30% of new stones resolve in the first year postpartum, remaining stones/sludge contribute to future biliary problems.

Treatment of Biliary Symptoms During Pregnancy

- Evaluate patients with RUQ pain for biliary disease
- Ultrasound is safe; MRI considered safe
- Patients with recurrent biliary pain or acute cholecystitis should be treated during pregnancy. Otherwise treatment may be deferred.
- Laparoscopic cholecystectomy is preferred definitive therapy
 - usually well tolerated, especially in first two trimesters
- ERCP can be performed with limited radiation exposure and relative safety if necessary
 - Sphincterotomy, gallbladder stent
- Interventional radiology
 - Cholecystostomy or biliary tubes

Vertical Transmission of Hepatitis Viruses from Infected Mother to Baby

- Hepatitis A
very rare as the viremic period is short
- Hepatitis B
common (10-80%), especially in chronically infected mothers; rate depends on maternal viral load
- Hepatitis C
uncommon (5-8%) except in HIV co-infected women (~30%)
- Hepatitis E
estimated from small studies to be 50-100%

Prophylaxis of Vertical Transmission

Hepatitis	Maternal status	Transmission	Prophylaxis
A	Infection within 2 weeks before or after delivery	Rare	Immune serum globulin plus hepatitis A vaccine after delivery
B	HBsAg+	10-30%	HBIG + vaccine at delivery, then complete vaccine series
	HBs Ag+ and $\geq 10^8$ copies/ml	>85%	Add maternal anti-viral drug during last trimester
C	HCV RNA-positive HCV RNA and HIV-positive	5-8% up to 30%	None None
E	Active infection at the time of birth	50-100%	? Immune serum globulin

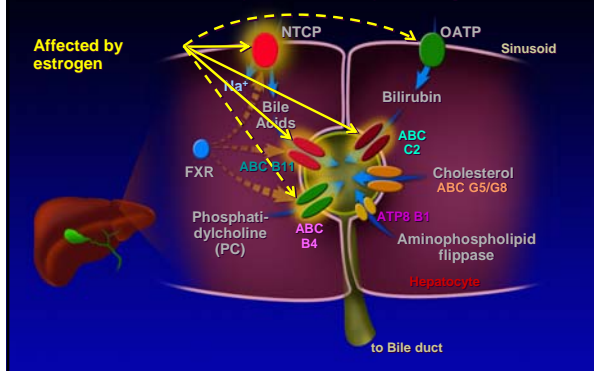
Intrahepatic Cholestasis of Pregnancy

- Mild cholestatic disease that occurs in <2% of pregnancies in the United States and up to 6% in some countries
- Also occurs with oral contraceptives
- Variable severity in subsequent pregnancies
- Strong genetic component, 10-15% of first degree female relatives affected

Intrahepatic Cholestasis of Pregnancy: Pathophysiology

- Estrogens present in oral contraceptives or pregnancy are known to impair bile formation
- Women who develop ICP likely have mild underlying abnormalities in genes that affect bile formation or bile flow
- Clinical cholestasis is more likely when both factors are present

Intrahepatic Cholestasis of Pregnancy: Transporters Likely Affected by Estrogen



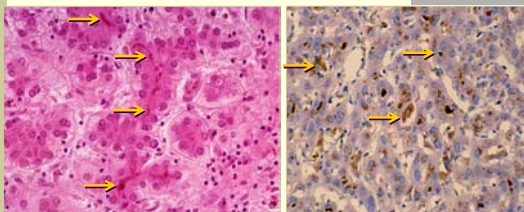
Clinical Presentation of ICP

- Onset is usually in the third trimester
- Resolves within few days of delivery
- Symptoms
 - Pruritus occurs in virtually all patients
 - May be very severe
 - Jaundice occurs in ~25%
- Benign disease for mother
- May cause increased intrauterine death for fetus

Laboratory Presentation of ICP: cholestatic hepatocytes

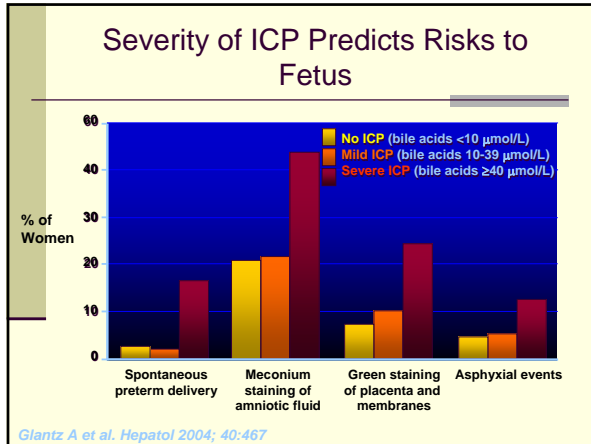
- Laboratory abnormalities
 - Elevated bile acids (> 10 $\mu\text{mol/L}$)
 - modest elevations of alkaline phosphatase, AST/ALT and bilirubin
- Radiologic findings - none
- Liver biopsy is diagnostic but rarely needed

ICP Pathology



Cholestasis: centrilobular cholestasis
canalicular bile plugs (arrows)
retained biliary pigment in hepatocytes
lack of inflammation or necrosis

Image courtesy of Dr. J. Greenson



- ### ICP Treatment
- Ursodeoxycholic acid
 - 15 mg/kg/day (or more than 1g per day) reduces maternal pruritus and improves laboratory tests
 - Safe for mother and fetus
 - Monitor pregnancies beginning at 32-34 weeks and deliver fetus early
 - Deliver by 37 weeks for mild disease
 - Deliver by 36 weeks for cases with jaundice
 - Deliver as soon as possible if fetal distress is identified
 - May need to deliver earlier if mother has disabling pruritus

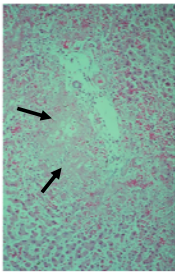
- ### Pre-Eclampsia and the Liver
- Pre-eclampsia affects 5-10% of all pregnancies
 - More common in first pregnancies and in women with hypertension, organ transplant or pro-coagulant disorders (especially lupus anticoagulant)
 - Liver is affected in 10-20% of women with pre-eclampsia
 - Liver disease related to pre-eclampsia accounts for:
 - ~5% of jaundice
 - ~20% of mortality in pregnancy

Pathophysiology of Pre-Eclampsia

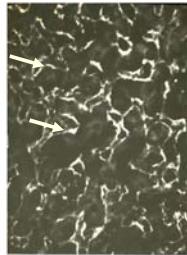
- Abnormal placental formation
 - Failed development of high capacity, low resistance vessels
 - Fetal ischemia and intrauterine growth retardation
- Local and systemic endothelial dysfunction
 - Release of soluble anti-angiogenic factors
 - sFlt1, sEndoglin
 - Decrease in VEGF and other angiogenic factors
 - Vasoconstriction
 - Reversal of the usual low systemic vascular resistance
 - Increased sensitivity to vasoconstrictors
 - Angiotensin II, Catecholamines
- Systemic endothelial injury, fibrin deposition, ischemic infarcts

Pre-Eclampsia Liver Pathology: patchy ischemic necrosis and fibrin deposition

Hepatocyte necrosis



Fibrin deposition in sinusoids
(fluorescent stain)



Pre-Eclampsia-Related Liver Disease: Clinical Presentation

- Extent of necrosis determines extent of liver damage
- HELLP syndrome is the most common form of pre-eclampsia-related liver disease:
 - Hemolysis (intravascular)
 - Elevated Liver tests (AST/ALT)
 - Low Platelets

Clinical Presentation of HELLP Syndrome

- Onset usually third trimester (range 23-40 weeks)
- May start immediately post-partum in up to 28%
- Common signs/symptoms of pre-eclampsia
 - Hypertension/headache
 - Proteinuria
 - Edema
- Other signs and symptoms
 - Nausea / vomiting
 - Epigastric / right upper quadrant pain

Laboratory Tests in HELLP Syndrome: necrotic hepatocytes

- RBC hemolysis occurs in all cases
- Hepatocellular injury
 - AST/ALT elevation in all (usually 100-300 U/L, may exceed 1000 U/L)
 - Hyperbilirubinemia in 5-40%
- Thrombocytopenia ($\leq 150,000$) is universal
- Fibrin deposition / DIC
 - Low fibrinogen
 - Elevated fibrin degradation products
 - Elevated prothrombin time with DIC

HELLP Syndrome Clinical Course

- HELLP syndrome can worsen quickly and other organs can be affected (kidney, heart, CNS)
- Fetus at great risk due to placental involvement and fetal anoxia
- Treatment:
 - Urgent delivery of the baby
 - Terminates maternal disease
 - Prevents sudden intrauterine deaths
 - Supportive care

HELLP Syndrome Outcomes

- Fetal mortality is ~3-23%
- Maternal mortality is ~ 0-3.5%
- Pre-eclampsia without or with liver involvement can recur in subsequent pregnancies at ~3-27%

Hepatic Hematoma or Rupture

- Confluent hepatic necrosis related to pre-eclampsia may cause intrahepatic hematomas or rupture with intraperitoneal bleeding
- Affects 1-2% of all women with pre-eclampsia
- Hematomas or rupture may occur up to 48 hours after delivery
- Free hepatic rupture is reported in 1 in 15,000 to 45,000 deliveries

Radiologic Appearance of Hepatic Hematoma or Rupture

- Liver infarct and contained right lobe subcapsular hematoma
- The hematoma (arrow) is less dense than the remaining well perfused liver during IV contrast administration

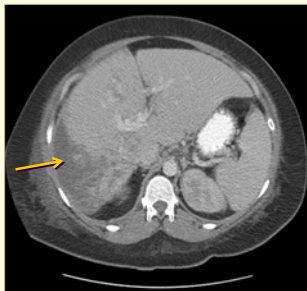


Image courtesy of Dr. P. Knechtges

Acute Fatty Liver of Pregnancy (AFLP): Epidemiology

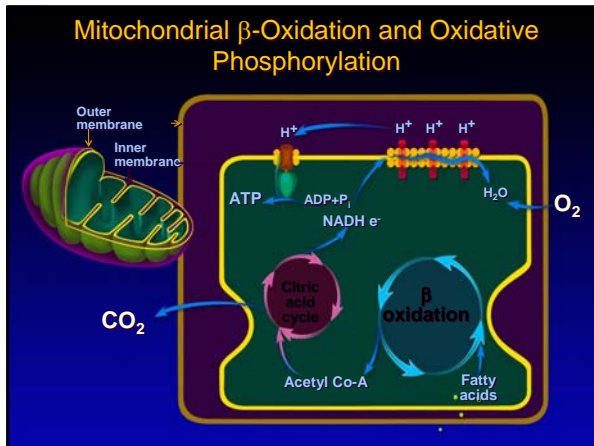
- Occurs in about 1 in 1000 pregnancies
- Accounts for 16-70% of severe liver disease and maternal and fetal deaths during pregnancy

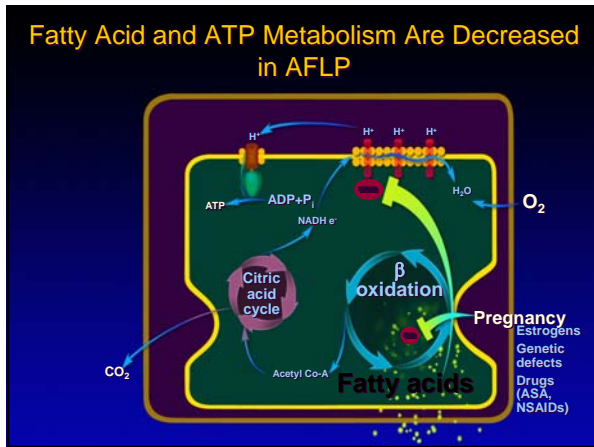
AFLP - Pathophysiology

- Microvesicular steatosis similar to Reye's syndrome, Jamaican vomiting sickness and valproic acid hepatotoxicity
- Impaired mitochondrial β -oxidation of fatty acids leads to fatty acid toxicity of mitochondria and of oxidative phosphorylation
- The resulting decrease in ATP production leads to liver cell failure

AFLP - Pathophysiology

- Normal pregnancy causes increased hepatic influx of triglycerides and fatty acids.
- Pregnancy itself may cause mild defects in mitochondrial β -oxidation of fatty acids - possibly due to estrogens
- Possible triggering factors for AFLP include
 - Genetic mutations in genes affecting fatty acid metabolism
 - Long-chain acyl CoA-dehydrogenase (LCHAD) deficiency
 - Pre-eclampsia
 - Drugs that impair β -oxidation or oxidative phosphorylation (aspirin, NSAIDs)
 - ?? Inflammatory cytokines



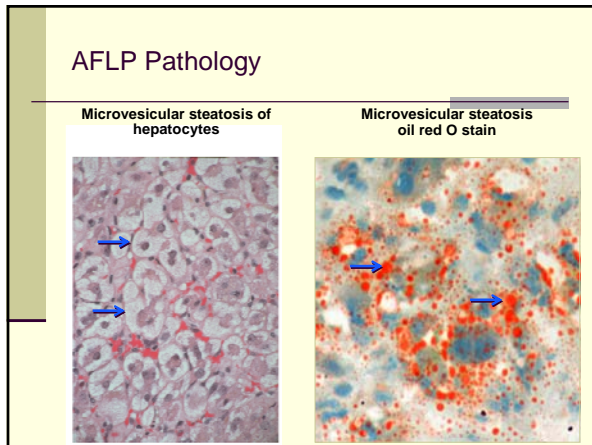


Acute Fatty Liver of Pregnancy Clinical Presentation

- Usually appears in third trimester of pregnancy and terminates quickly after delivery
- May occur as late as 1-2 days post-partum
- Severe cases present as fulminant liver failure with modest increase of AST / ALT
- May recur in subsequent pregnancies, especially if genetic mutations are present

AFLP - Laboratory Abnormalities in Severe Cases

Test	Value	Range
AST / ALT	200-300 IU/l	Normal to ~1000
Bilirubin	12 mg/dl	1.8-36 mg/dl
Alkaline Phosphatase	4.4x - elevated	Normal to 10x-elevated
Creatinine	3.0 mg/dl	Normal to 6.6 mg/dl
Prothrombin	22 sec.	Normal to 78 sec.
Antithrombin III	11%	0-30% of normal



- ### AFLP Outcomes
- Can worsen rapidly and lead to fulminant hepatic failure (FHF) with DIC
 - Maternal mortality is 5-26%
 - Intrauterine fetal death rate is 9-32%

AFLP Treatment

- Urgent delivery improves maternal and fetal outcomes
- If appropriate, transfer to hospitals with experience in liver failure and high-risk pregnancies
- Infants should be tested for LCHAD mutations

Summary

- Pregnancy may impact upon pre-existing liver diseases.
- Unique liver disease of pregnancy may appear unexpectedly and need to be considered
- The unique liver diseases of pregnancy all terminate rapidly with delivery and this is often the optimal treatment, in conjunction with best supportive care.
