CHOLESTASIS OF PREGNANCY

Background
1. Definition: pruritus with elevated serum bile acids during pregnancy
2. General Information: also called pruritus gravidarum, intrahepatic cholestasis of pregnancy

Pathophysiology
1. Pathology of Disease: etiology unclear. Female sex hormones induce cholestasis, and abnormal biliary transport across canalicular membranes may decrease bile salt export.1
   - Multidrug resistant protein-3 (MDR3) or ATP-cassette transporter B4 (ABCB4) mutations may lead to increased estrogen sensitivity2
   - Different mutations across ethnic and familial groups
   - Increased progesterone in third trimester, multiple gestation3
   - Leads to toxic bile acid levels in the fetus
   - May increase myometrial contractility and vasoconstriction of chorionic veins in placenta
2. Incidence: 1 in 1000 to 1 in 10,000, higher incidence in twin pregnancies
3. Risk Factors: women who develop cholestasis with oral contraceptive pills (OCP), history of cholestasis in previous pregnancy, family history, multiparous, advanced maternal age, possibly hepatitis C and selenium insufficiency4
4. Morbidity / Mortality:
   - Leads to placental insufficiency causing increased risk of prematurity, anoxia, fetal distress, perinatal death, stillbirth5
   - Maternal hemorrhage
   - RDS in neonates due to bile acids directly causing lung inflammation, surfactant depletion
   - Increased meconium passage in utero

Diagnostics
1. History: pruritus, especially on the palms and soles, progressively severe, worse at night; usually presents in third trimester, resolves post partum6
   - 80% present after 30 weeks gestational age, but may present as early as 8 weeks7
   - Anorexia, malaise, abdominal pain
   - Pale stools, dark urine may occur
   - Mild jaundice may occur
2. Physical Examination
   - Excoriations due to scratching
   - Jaundice in 10-15%8
3. Diagnostic Testing
   - Laboratory evaluation:
     - Fasting total bile acids elevated 10-100 times normal6,9
     - AST and ALT may be elevated, bilirubin is generally normal
     - Alkaline phosphatase elevated, 10x normal
     - Diagnostic imaging: liver ultrasound
     - Other studies: screening for hepatitis A, B, C; EBV; CMV; autoimmune hepatitis
4. Diagnostic “Criteria” (If indicated)
   - Mild disease: fasting bile acids > 10 umol/L and <40 umol/L
   - Severe disease: fasting bile acids >40 umol/L

5. Recommendation (GRADE)
   - Use pregnancy specific reference ranges for liver function tests (SOR:C)\textsuperscript{10}
   - Rule out other causes of pruritus and abnormal liver function tests (SOR:C)\textsuperscript{10}
   - Confirm postpartum resolution of symptoms (SOR:C)\textsuperscript{10}

Differential Diagnosis
1. Key Differential Diagnoses
   - Preexisting liver disease
   - Viral Hepatitis
   - Autoimmune liver disease
   - Drug-induced hepatitis
   - Pruritic Urticarial Papules and Plaques of Pregnancy (PUPP)
   - Dermatitis
   - Urticaria

Therapeutics
1. Acute Treatment
   - Management of pruritus
     - Diphenhydramine
     - Hydroxyzine
     - Topical lanolin lotion
     - Cholestyramine – monitor for fat soluble vitamin malabsorption, especially vitamin K
     - Phenobarbital – enhances hepatic microsomal function
   - Insufficient evidence for treatment
     - 2-5 ursodeoxycholic acid 15mg/kg/day divided BID; relief within 1-2 weeks in one of 3 trials\textsuperscript{11}
     - ii. S-adenosylmethionine (SAMe) showed improvement in pruritus, bile acid levels and liver enzymes in one of 4 trials\textsuperscript{11}

2. Further Management
   - Vitamin K administration post partum to prevent PP hemorrhage if cholestasis has been severe or prolonged

3. Long-Term Care
   - May include appropriate important signs of complications to watch for

4. Recommendation (GRADE)
   - There is insufficient evidence to support widespread use of SAMe or ursodeoxychoic acid. (SOR:A)\textsuperscript{10}
   - Fetal monitoring is not proven to prevent intrauterine demise (SOR:C)\textsuperscript{10}
   - Ultrasound is not reliable for preventing fetal death (SOR:B)\textsuperscript{10}
   - Induction of labor at 37-38 weeks is often done to reduce the incidence of stillbirth, but there is no evidence to support or refute this practice (SOR:B)\textsuperscript{8,12}
Follow-Up
1. Return to Office
   - Time frame for return visit
     - Weekly LFT, bile acids may be considered (SOR:C)\(^{10}\)
     - Postpartum LFT, at least 10 days postpartum (SOR:C)\(^{10}\)
   - Recommendations for earlier follow-up
2. Refer to Specialist
   - NICU should be available at delivery site
3. Admit to Hospital
   - Recommendations / urgency

Prognosis
1. Hepatic impairment resolves postpartum with normal liver enzymes 2-8 weeks post partum.
   - Pruritus resolves within 48 hours post partum.
2. Fetal Complications
   - May be related to level of maternal bile acids
   - Meconium staining of amniotic fluid, higher incidence with higher maternal bile acid level
   - FHT abnormalities
     - Decreased variability, tachycardia, bradycardia
   - Preterm Delivery
     - 30-40%
   - Respiratory Distress Syndrome
     - 28% of infants with maternal high bile acid levels\(^{13}\)
   - Intrauterine Demise
     - Incidence increased between 37-38 weeks gestation
     - 1-2% increased risk for every umol/L of bile acid above 40 umol/L\(^{14}\)
3. Recurrence with future pregnancies or OCP use is likely

Prevention
1. Not applicable

Patient Education

References

Authors: Heather Ho, MD, & Camille Garrison, MD, Medical College of Wisconsin

Editor: Edward Jackson, MD, Saginaw FMRP, MI