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 sensitivity[2]
    - Different mutations across ethnic and familial groups
    - Increased progesterone in third trimester, multiple gestation[3]
    - 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 insufficiency[4]
4. Morbidity / Mortality:
    - Leads to placental insufficiency causing increased risk of prematurity, anoxia, fetal distress, perinatal death, stillbirth[5]
    - 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 partum[6]
    - 80% present after 30 weeks gestational age, but may present as early as 8 weeks[7]
    - 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 normal[6,9]
    - 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[5]
    - Severe disease: fasting bile acids >40 umol/L
5. Recommendation (GRADE)
    - Use pregnancy specific reference ranges for liver function tests (SOR:C)[10]
    - Rule out other causes of pruritus and abnormal liver function tests (SOR:C)[10]
    - Confirm postpartum resolution of symptoms (SOR:C)[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.[11]
        - ii. S-adenosylmethionine (SAMe) showed improvement in pruritus, bile acid levels and liver enzymes in one of 4 trials[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)[10]
    - Fetal monitoring is not proven to prevent intrauterine demise (SOR:C)[10]
    - Ultrasound is not reliable for preventing fetal death (SOR:B)[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)[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

1. http://www.mayoclinic.com/health/cholestasis-of-pregnancy/DS01033

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