Management of Intrahepatic Cholestasis of Pregnancy

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Epidemiology

- Most common liver specific disorder during pregnancy.
- 0.2% and 2%
  - South Americans and Northern European
  - Multiples
  - IVF
  - Age greater than 35
  - Cholelithiasis
  - Hepatitis C

Etiology

- Defect involving the excretion of bile salts
- Increased serum bile acids
- Deposited within the skin, causing intense pruritus
  - Genetic
  - Hormonal
  - Environmental involvement

Etiology

- End products of hepatic cholesterol metabolism \(\rightarrow\) Bile Acids
- Transport of bile salts from the liver to the gallbladder is disrupted
- Compensatory transport of bile salts from the hepatocytes into the blood
Diagnosis

- Pruritus
- 80% cases occur after 30 weeks
  - abnormal liver function
  - raised maternal serum bile acids
  - onset of pruritus / abnormal labs is not clear
Diagnosis

- 10 and 14 micromoles/L total serum bile acids non-fasting
- Reduced to 6 and 10 micromoles/L in fasted women
- ALT is more sensitive x 2-fold to 30-fold
- Alkaline phosphatase not useful – produced by the placenta

Diagnosis

- Gamma glutamyl transferase (GGT) may be elevated but is more commonly normal
- Bilirubin is elevated in 10 % cases (conjugated)
- Steatorrhea → clotting profiles should be checked
- Symptoms of Cholestasis
  - Pale stools
  - Dark Urine
  - Rare – jaundice
- Diagnosis of exclusion – differential diagnosis
Pregnancy specific causes of pruritus

- Pruritus gravidarum
- Atopic eruption of pregnancy – dry red rash; affects trunk and limb

Pruritus gravidarum

Atopic eruption of pregnancy – dry red rash; affects trunk and limb


Differential Diagnosis

PUPPS

The incidence is about 1 in 200 pregnancies, but increases with multifetal gestations. In addition, PUPPP is more common in white and nulliparous women. Although most note symptoms in late pregnancy, up to 15 percent of cases will begin postpartum. It seldom recurs in subsequent pregnancies.


Differential Diagnosis

PUPPS

This figure shows PUPPP extending to the thigh and leg. Although PUPPP may resemble herpes gestationis, there is no evidence that perinatal morbidity is increased.
Pregnancy specific causes of pruritus

- Pemphigoid gestationis (herpes gestationis)

Differential Diagnosis

Pemphigoid Gestationis

www.dermnetnz.org/immune/pemphigoid-gestationis.html

Cutis. 2015 May;95(5):268, 270.
Pemphigoid Gestationis

- Incidence 1/50,000-60,000 pregnancies
- Occurs most commonly during the 2nd or 3rd trimester or in the postpartum period
- Typical Course:
  - Rash begins on the trunk as urticarial plaques or papules surrounding the umbilicus
  - Vesicles may be present
  - Rash typically spares the face
  - Mucous membrane involvement in only 20% of cases
  - Rapid progression to bullae formation

Diagnosis of Pemphigoid Gestationis

- Skin biopsies: histology and direct immunofluorescence
- Higher degree of peripheral eosinophilia may correlate with disease severity

Complement 3 (C3) in a homogenous, linear band at the basement membrane zone.
Treatment of Pemphigoid Gestationis

• For localized lesions:
  – Mid to high potency topical glucocorticoids

• Oral antihistamines

• If these do not control symptoms, treat with systemic glucocorticoids
  – Prednisone 0.5mg/kg/day

Fetal Effects of Pemphigoid Gestationis

• Risk for intrauterine growth restriction and prematurity
  – Placental insufficiency results from an immune response between placental antigens and the antibodies targeted against the skin antigen

• Antepartum fetal assessment is indicated

• Neonatal pemphigous have a mild course that resolves within weeks although higher mortality rate has been reported

Prognosis of Pemphigoid Gestationis

• Lesions may remit intrapartum.
• 75% of patients flare postpartum, although most patients experience resolution in the weeks to months following delivery.
• 25% of patients flare with use of OCPs or during menses.
• In future pregnancies, the disease recurs and is typically worse and occurs at an earlier gestation.
• Women are at an increased lifetime risk of Graves’ disease.

Pregnancy specific causes of pruritus

• Prurigo of Pregnancy – red-brown papules on abd + extensor surface of limb

Pregnancy specific causes of pruritus

- Pruritic folliculitis of pregnancy – Acneform follicular papules and pustules

Preexisting causes of pruritus

- Systemic Diseases
  - Atopic dermatitis
    - History of atopy
  - Allergic or drug reactions
    - Exposure

Pregnancy-specific causes of hepatic impairment

- Acute Fatty liver of pregnancy
  - Unwell, N/V, renal impairment, coagulopathy, hypoglycemia
- HELLP
  - Hypertension and proteinuria
- Hyperemesis gravidarum
  - First trimester

Preexisting Causes of hepatic Impairment

- Viral Hepatitis
- Primary biliary cirrhosis
  - Immunologic attack on the intralobular bile ducts
- Primary sclerosing cholangitis
  - Unknown etiology; inflammation, fibrosis, and stricturing ducts of biliary tree
- Autoimmune hepatitis
  - ANA, anti-smooth muscle antibodies, antimitochondrial antibodies
**Differential Diagnosis**

**Preexisting Causes of hepatic Impairment**

- Drug-induced liver injury
- Biliary obstruction
  - Liver ultrasound
- Venoocclusive disease
  - Imaging/History of thrombophilia

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**Family History**

- ~14% ICP have a family history
- Pedigrees have suggested autosomal dominant, sex-linked inheritance pattern.

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**Pharmacotherapy**

- Significant reduction in pruritus
- Decrease in ALT, GGT, Bilirubin
- No change in bile acids
Pharmacotherapy

Meta-analysis

**Ursodeoxycholic acid (Ursodiol or UDCA)**
- Prescribe 300 mg three times a day (or 15 mg/kg per day) until delivery.
- Titrate to symptoms: 500 mg to 2 g/day
- Side Effects: 16% of patients vs. 9% in placebo
  - Nausea
  - Vomiting
  - Loose stools

**Ursodeoxycholic acid (Ursodiol or UDCA)**
- Mechanism of action not fully understood
- Reduction in total serum bile
  - Mother
  - Cord serum
  - Amniotic fluid
  - Colostrum
- Improves placental morphology

**Therapies**
- Hydroxyzine 25 to 50 mg/day can improve pruritus
  - Antihistamines can aggravate respiratory difficulties in preterm babies
- Cholestyramine 8 to 16 g/day
  - Decreases ileal absorption of bile salts
  - Increase steatorrhea and exacerbate vitamin K deficiency
  - Less effective than UDCA trial

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Fetal Monitoring

- Unable to predict
- Non-stress tests: detection of the effects of chronic placental insufficiency on the fetus may not be useful in ICP
- Mechanism of intrauterine fetal demise is thought to be a sudden event
- Absence of high-quality evidence
  - lack of value of non-stress testing
  - proven mechanism for fetal death

*Most experts recommend antenatal testing*

Timing of Delivery

- Controversial
- Expert opinion and limited data:
  - Deliver women with ICP at 36 weeks 36\(\frac{6}{7}\)ths to 36\(\frac{6}{7}\)ths of gestation
  - Upon diagnosis if ICP is diagnosed at ≥37 weeks of gestation
  - Do not perform an amniocentesis to check fetal pulmonary maturity prior to delivery

Elective Early Delivery

- ACOG – no guideline
- Royal College of Ob and Gyn – no evidence to support or refute

Timing of Delivery

- Some providers wait until 38-39 weeks gestation to deliver if:
  - there is resolution of pruritus symptoms with treatment
  - bile acid levels are not significantly elevated (less than 40 micromole/L)
Timing of Delivery

- > 1.6 million pregnancies with and without ICP
- California 2005 and 2008
- In women with ICP Risk of fetal, neonatal, or infant mortality:
  - Lowest with delivery at 36 weeks (4.7 per 10,000 fetuses at risk, 95% CI 0.0-10.5) versus expectant management at 36 weeks (19.2 per 10,000 fetuses at risk, 95% CI 7.6-30.8).
  - The lower risk of mortality with delivery versus expectant management:
    - 37 weeks (12.3 versus 21.7 per 10,000 fetuses at risk)
    - 38 weeks (13.7 versus 23.1 per 10,000 fetuses at risk)
    - 39 weeks (18.3 versus 33.6 per 10,000 fetuses at risk)

Intrauterine Demise

Clinical outcome in a series of cases of obstetric cholestasis identified via a patient support group

Catherine Williamson, Laura M. Hems, Dimitrios G. Gouills, Ian Walker, Jennifer Chambers, Oscar Donaldson, Michael de Swiet, Desmond G. Johnston

Objective: To explore the clinical features of obstetric cholestasis pregnancies in UK white Caucasians.

Design: A questionnaire survey.

Setting: Study coordinated at Queen Charlotte’s Hospital.

Population: Clinical features of 352 affected pregnancies in 227 Caucasian women identified via a patient support group.

Methods: Evaluation of the gestation at which prematurity and intranatal death occur, and recording of additional clinical features in pregnancies complicated by obstetric cholestasis.

Main outcome measures: The timing of pregnancies complicated by intranatal death and prematurity.

Results: Among the affected pregnancies, 25 (7.1%) were complicated by intranatal death (20 singletons and 5 twins) and 133 (38%) were delivered prematurely (56 spontaneous and 77 iatrogenic). Eighteen of the 20 singleton intranatal deaths occurred after 37 weeks. All three intranatal deaths in twin pregnancies occurred before 37 weeks. Prematurity was more common in pregnancies complicated by spontaneous prematurity, but not in those complicated by intranatal death.

Conclusions: Intranatal death in singleton pregnancies complicated by obstetric cholestasis death mainly occurs after 37 weeks. The gestation at which prematurity is first reported may help to predict spontaneous prematurity.

Intrauterine Demise
Complications

- Fetus produces bile acids ~12 weeks
- Transplacental gradient for bile acids facilitates excretion
- ICP gradient reversed

- Every 1–2 micromoles/L increase in the bile acid level........1–2% increase in risk of adverse outcome
- Increase in risk only became statistically significant in severe intrahepatic cholestasis of pregnancy
  – bile acid level exceeded 40 micromoles/L
Complications

- Higher rates of GDM and preeclampsia
- Bile acids can lead to fetal arrhythmia
- Bile acids can cause vasoconstriction of placental chorionic vessels

Postpartum

- Liver function and serum bile acids recommended 6 to 8 weeks postpartum
- If abnormal labs, primary biliary cirrhosis and hepatitis C

Counseling

- Advise patients 10% of developing pruritus or hepatic impairment use hormonal contraception
- Rate of ICP recurrence is 40% to 90%
Conclusion

• ICP most common liver disorder of pregnancy
• Bile acid levels should be followed evidence higher levels associated with increased risk
• Complications risk levels exceed 40 micromoles/L
• Treatment ursodeoxycholic acid improves pruritus and liver function
• Active management with early elective delivery