2 COMPLICATIONS OF PREGNANCY

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2.18 Cholestasis in pregnancy
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2.18 CHOLESTASIS IN PREGNANCY

BACKGROUND INFORMATION

Obstetric cholestasis is a condition in pregnancy which is characterized as pruritis in the absence of a skin rash with increased total serum bile acid levels[1] (≥10µmol/L) and abnormal liver function tests (LFTs). The diagnosis is made when other causes are excluded.[2] The condition rarely presents before 25 weeks gestation[3, 4], with 80% of women presenting after 30 weeks gestation.[5] A significant number of women may have pruritis for days or weeks prior to developing abnormal liver function.[2, 5, 6] The incidence varies according to geographical location and ethnic background with rates of up to 15% in Chile and Bolivia and less than 1% in Europe.[5, 7] A higher incidence is seen in twin pregnancies, following *in vitro* fertilisation, women over 35 years of age[5], women with a history of cholestasis in a previous pregnancy,[7] and in women with a history of biliary disease.[6]

The aetiology of obstetric cholestasis is unknown but it is believed to be multifactorial with genetic, environmental or hormonal factors being involved.[4, 5, 6, 7, 8] The main maternal impact for women with cholestasis is pruritis[4, 5, 7, 8] and they have increased risk for postpartum haemorrhage.[8, 9] Adverse fetal outcomes associated with the condition include preterm labour[5, 6, 7], fetal distress[5, 6, 7], meconium staining[5, 6], spontaneous intrauterine death[5, 6, 7].

Fasting serum bile acid (SBA) concentrations ≥ 10µmol/L is the most commonly used diagnostic tool.[3, 6, 9, 10] Prospective studies indicate that fetal complications are associated with SBA concentrations above 40µmol/L[3, 6, 9, 11], however individual cases have described fetal deaths at lower levels.[6, 12]

The condition typically resolves within 48 hours of women giving birth, with biochemical markers predominantly becoming normal within 2-4 weeks postnatally.[5] In subsequent pregnancies risk of reoccurrence is 40-60%.[6]

DIAGNOSIS

Diagnosis of cholestasis in pregnancy is confirmed by:
- clinical features
- exclusion of other forms of liver disease or cholestasis
- laboratory findings

CLINICAL FEATURES

- Pruritis without a rash – itching is classically on the palms and soles of the feet although it may be more widespread. The pruritis is worst at night[7], and women may exhibit skin excoriations from scratching.[7, 9]
- malaise[9]
- steatorrhea with fat malabsorption[9]
- Jaundice - uncommon[9], but can occur in 10-15% of cases[7]

EXCLUDE OF OTHER CAUSES

- Autoimmune hepatitis[2, 7, 9]
- Hepatitis A,B, C[2, 9] or E[7]
- Epstein Barr[2, 7]
- Cytomegalovirus[2, 7]
- Gall bladder disease[9]
- Liver disease e.g. cirrhosis, acute fatty liver[2, 7]
- Early HELLP syndrome or preeclampsia[7]
- Skin conditions e.g. eczema, pruritic eruption of pregnancy[2], scabies[7]

LABORATORY TESTS

- Bile Acids – levels greater than 10µmol/L are a common diagnostic marker[10]
- Liver Function Tests (LFTs):
    - Aminiotransferase (ALT, AST) activity can be raised by up to 20 times the normal level[3]
    - Gamma-glutamyl transferase activity is unusual but indicative of MDR3 gene mutation leading to increased bile acids, or of underlying liver disease.[3]
    - It is uncommon to have a raised serum bilirubin[2]

ANTENATAL MANAGEMENT

LABORATORY TESTS

1. Serum Bile Acids – to make the diagnosis
2. LFTs –**weekly** if normal, or **bi-weekly** if abnormal[2], if serum bile acids are increasing, or are ≥ 40µmol/L.
3. Full blood picture
4. Coagulation studies – may be ordered by the obstetric team if abnormal LFTs. Prolonged prothrombin times may reflect Vitamin K deficiency.[7]

FETAL SURVEILLANCE

Ultrasound

- Perform a baseline ultrasound
- Thereafter perform ultrasound assessment 3 weekly for growth and wellbeing
- More frequent ultrasound surveillance may be requested by the obstetric team on an individual basis depending on the clinical situation.

Ultrasound is not a reliable tool for prediction of fetal death in obstetric cholestasis.[2]

Cardiotocograph monitoring (CTG)

- Perform CTG monitoring **weekly** from 30 to 34 weeks gestation. The interval may be adjusted depending on the clinical situation.
- Perform CTG monitoring **bi-weekly** from 34 weeks gestation.
- The decision of CTG monitoring < 30 weeks gestation is at the discretion of the Team Consultant.

Fetal monitoring has not been shown to be predictive of fetal death.[2, 6, 13]

FREQUENCY OF ANTENATAL VISITS

Antenatal visits should be arranged 2nd weekly.

TIMING OF DELIVERY

Aim to delivery the woman between 37weeks [1, 5, 7, 9] and 38 weeks gestation, or earlier is there is sufficient risk for maternal morbidity or fetal compromise detected. Consider administration of corticosteroids if induction of labour is anticipated prior to 34 weeks gestation.

TREATMENT OF MATERNAL PRURITIS

1. The use of topical emollients e.g. calamine lotion may provide temporary relief of itching.[2]
2. Offer advice to decrease skin irritation - wear cool loose cotton clothing, keep skin moisturised, cool baths/showers for comfort, use of cotton material where possible (e.g. bed linen).[4]
3. Encourage a low fat diet, and advise women to increase their water intake.[4]
4. Offer anti-histamines at night (beneficial for their sedative effect).[2, 13]
5. Offer Ursodeoxycholic acid (UDCA or URAO). Dosage required to attain effect on maternal pruritis and serum bile acids is from 10 to 15 mg/kg/day.[3, 6] Relief usually occurs in one to two weeks.[6]

Ursodeoxycholic acid (UDCA)

It has been postulated that UDCA works by:

- Displacing hydrophobic endogenous bile salts from the bile acid pool, and protects hepatocytes from their toxic effects[2]
- Enhances bile acid clearance across the placenta from the fetus[2]
- Protects cardiomyocytes from damage by bile salts (in vitro rat cardiomyosites)[2]

UDCA may be useful in symptomatic women as it has been associated in some studies with improvement of the itch and LFTs. However, results of randomised controlled trials with a small number of patients did not show that it was superior to placebo for relief of symptoms or improvement of LFTs.[2, 14] Use of UDCA have not been shown to be harmful to the woman or fetus, therefore the decision of use should be individualised between the woman and her doctor.[14]

VITAMIN K SUPPLEMENTATION

Obstetric cholestasis can lead to a reduction of circulating enerohepatic bile acids causing reduced absorption of fat-soluble vitamins. Vitamin K is a fat-soluble vitamin required for coagulation.[2]

Recommend daily supplementation of water soluble 10mg of Vitamin K orally to reduce the risk of post-partum haemorrhage (PPH).

NUTRITIONAL SUPPLEMENTATION

Steatorrhea and fat malabsorption may lead to nutritional deficiency.[7]

Consider multivitamin supplementation. Consider referral to the dietician for information regarding a low fat diet.

PAEDIATRIC CONSULTATION

Arrange a paediatric consult if risk of pre term birth is anticipated.

LABOUR AND BIRTH MANAGEMENT

MATERNAL MANAGEMENT

1. Arrange a blood group and hold, full blood picture, and LFTs on admission.
2. If LFTs are abnormal order a coagulation profile.

INTRAPARTUM CTG

1. Monitor the fetal heart rate continuously with a CTG.
2. Anticipate the risk of meconium liquor and request a paediatrician at delivery as necessary.
   Increased incidence of meconium liquor at delivery has been linked with obstetric cholestasis, and is more common in preterm than term pregnancies (25% versus 12%).[2]

POSTNATAL MANAGEMENT

COUNSELLING PRIOR TO DISCHARGE

Counselling prior to discharge should include the following:

- risk of reoccurrence in a subsequent pregnancy is 40-60%[6]
- reassurance about the lack of long term sequelae for mother and baby
- pruritis normally resolves within 48 hours of giving birth[2], however in some women it may last 4-8 weeks[7]
- women who have had a familial severe form of obstetric cholestasis are at risk for chronic liver disease and should have long term follow-up[6]
- female family members may have an increased chance of developing obstetric cholestasis
- the use of combined oral contraceptive pill postpartum should be avoided.[8] Low dose estrogens or progesterone –only pills are recommended.[7]

GP REFERRAL

- Ensure the GP is apprised of the woman's condition prior to discharge and a follow-up plan is in place.
- Arrange review by the GP in 2-4 weeks to check resolution of the woman's condition. Liver function tests are expected to normalise within a month of delivery.[13]
- Follow-up monitoring of LFTs should be deferred for at least 10 days after birth. In normal pregnancy the LFTs can normally increase in the postpartum period.[2]

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