INTRAHEPATIC CHOLESTASIS OF PREGNANCY – A REVIEW

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A 32-year-old lady presented to the delivery suite at 36 weeks gestation with severe generalised pruritis. The itching was widespread, over her whole body, but especially noticeable on the palms of her hands and soles of her feet. The midwife performed a fetal heart trace (cardiotocogram (CTG)), which was normal, and also took some blood for liver enzymes and bile acids. Chlorpheniramine was prescribed for the itching and an appointment made to attend the antenatal clinic four days later to see the consultant.

The liver function tests showed a very high alanine transaminase (ALT) which was 557 iu/l, and raised bile acids of 52 micromols/l. Further CTG monitoring was organised and an ultrasound scan for fetal growth and wellbeing prior to the clinic appointment. Unfortunately, when the patient attended the hospital four days later for the scan an intrauterine death was confirmed. She had noticed decreased fetal movements for 24 hours prior to the visit. The stillbirth was attributed to 'obstetric cholestasis' and all other investigations were normal. The liver function reverted to normal after delivery.

INTRODUCTION

Obstetric cholestasis (OC) still remains widely disregarded as an important clinical problem, unique to pregnancy. Many consider its main symptom, pruritus, a natural association to pregnancy. There are numerous clinical studies that have confirmed the risks and complications of OC in both mother and baby. It can lead to intrauterine death in up to 2% of patients and preterm labour in up to 60%[1]. In the light of extensive evidence, intrahepatic cholestasis needs to be taken seriously and managed adequately. A document for guidance on OC is currently under preparation by the Royal College of Obstetrics and Gynaecology (RCOG).

The original description of generalised pruritus, mild jaundice and intrahepatic cholestasis in the third trimester has been attributed to Thorling[2], but was described 100 years before.

There is a remarkable geographical variation in the incidence of OC. It is reported in 0.1-1.5% of the European population, whereas it is considerably higher in South American countries such as Chile, where the incidence in the native Araucanian population reaches 28%[3]. In England, it affects 0.7% of pregnancies in the multi-ethnic population and 1.2-1.5% of women of Indian Asian or Pakistani Asian origin.

PATHOPHYSIOLOGY

Aetiology is multifactorial, with genetic, familial (possible dominant inheritance), environmental and hormonal factors playing important roles.

Bile acids are derived from cholesterol. Cholic acid and lithocholic acid are the hydrophobic type of bile acids and are toxic. The major bile acid in blood and urine of these patients is cholic acid instead of chenodeoxycholic acid present in normal pregnancies, which is considered mainly responsible for OC[4].

Mutations in genes that code for bile acid transporter proteins may impair maternal excretion and influence transplacental passage of bile acids. It is hypothesised that the surge in pregnancy steroid hormones may result in genetically predisposed women developing cholestasis[5]. One study proposes that patients with OC have a selective defect in the secretion of sulfated progesterone metabolites into bile and speculate that this may be caused by genetic polymorphism of canalicular transporter(s) for steroid sulfates or their regulation[4]. Interaction with oestrogen metabolites and/or some exogenous compounds may further enhance the process, triggering OC in genetically predisposed individuals[4].

More research is needed to improve the molecular and genetic understanding of the disease.

MATERNAL/FETAL RISKS

Sudden unexplained intrauterine fetal demise is the major concern for those involved in the management of OC. Intrauterine death (IUD) in singleton pregnancies complicated with OC mainly occurs after 37 weeks of gestation[6].

There have been studies which suggest that raised serum bile acid (SBA) levels can impair fetal cardiomyocyte function and may result in the development of dysrhythmia and sudden IUD[7].

Other risks associated with OC are spontaneous prematurity, iatrogenic prematurity, meconium stained liquor and fetal distress.

Maternal morbidity includes problems from scatching due to the intense pruritus, increased risk of postpartum haemorrhage due to vitamin K deficiency (malabsorption of fat-soluble vitamins) and an increased risk of Caesarean section.

CLINICAL PRESENTATION

There is absence of agreed diagnostic criteria for OC. In general, however, intense pruritus in absence of skin rash plus abnormal liver function tests (LFTs), neither of which have an alternative cause and both of which remit after delivery, is considered to diagnose OC.

Severe pruritus affecting limbs and trunk, particularly palms and soles, developing in the second half of pregnancy is the main clinical feature. Pruritus may precede abnormal

LFTs[8]. Gestation of onset of pruritus may help predict spontaneous preterm labour. Earlier onset of pruritus is more likely to go into preterm labour[6].

There may be associated dark urine, anorexia and malabsorption of fat with steatorrhoea.

INVESTIGATIONS

Given that the generalised itching is a classic sign of liver disease, LFTs should be carried out. The LFTs that are most commonly abnormal in women with OC are the transaminases, alanine (ALT) and aspartate (AST) aminotransferase and alkaline phosphatase (ALP). High values should prompt further investigations as well as regular monitoring of the baby. An elevated gamma-glutamyl transpeptidase (GGT) occurs in less than one third of patients with OC in the United Kingdom (UK) and, when present, is associated with greater impairment of LFT, but no difference in gestational age at onset[9].

Total SBA is an important investigation in any pregnant woman with itching but no rash. Raised LFTs usually accompany or follow the findings of raised bile acids. However, bile acids are sensitive but not specific[10].

Deficiency of the fat-soluble vitamin K may cause excessive bleeding in mother and baby if untreated. Vitamin K deficiency prolongs the blood's clotting and can be measured as a prothrombin time (PT).

DIAGNOSIS

Diagnosis is by exclusion; there is no diagnostic test. Differential diagnosis includes viral hepatitis, cholelithiasis, autoimmune conditions and acute fatty liver of pregnancy. Anti-smooth muscle and antimitochondrial antibodies, hepatitis A, B, C, Epstein Barr and cytomegalovirus serology and liver ultrasound are the investigations that should be considered in order to exclude other causes of pruritus and abnormal LFTs[11].

MANAGEMENT

Current data is insufficient to confirm or refute any correlation between levels of liver enzymes and maternal symptoms and fetal risks. It is not advisable at present to base management decisions on the degree of biochemical abnormality.

Drugs

Topical emollients, such as calamine lotion, seem safe and may provide temporary relief of pruritus to some women. Antihistamines, such as chlorpheniramine, may provide with sedation at night, but do not have a significant impact on itching.

Ursodeoxycholic acid (UDCA) is the most widely used agent in management of OC in the UK. UDCA is a naturally occurring bile acid. With the administration of UDCA to patients with OC, pruritus and serum LFTs values improve, the concentration of bile acids in blood diminishes and the proportion of their conjugated metabolites returns near normal. Simultaneously, the concentration of sulphated progesterone metabolites in blood and their urinary excretion are reduced[4]. Treatment with UDCA appears to be safe and significantly improves LFT in patients with OC, with the exception of SBA in the high GGT group[9].

Dexamethasone: the studies concerning dexamethasone have been on small numbers but have shown improvement in pruritus and decrease in bile salts and LFTs. There is general concern regarding adverse fetal and neonatal neurological effects of dexamethasone administered antenatally. It should not be used as a first line drug and should not be used without thorough consultation with the woman.

S adenosyl methionine is another agent used in management of OC. There is insufficient evidence to support its use and it requires intravenous administration, which makes its use unacceptable.

There are good physiological reasons to support the use of vitamin K in women with OC. And the case is even stronger in women with steatorrhoea or prolonged prothrombin time. Failure of excretion of bile salts into gastrointestinal tract reduces the absorption of dietary fats and fat-soluble vitamins including vitamin K, which is required for manufacture of coagulation factors II, VII, IX and X. This can increase the risk of postpartum haemorrhage and fetal/neonatal bleeding. Usually 10mgs of water-soluble vitamin K daily is prescribed from the diagnosis.

Surveillance

Monitoring of fetal wellbeing and regular LFTs and bile acids assessment is the mainstay of management until delivery.

Since the cause of sudden fetal demise is unclear, prevention is challenging. Various techniques have been used for fetal wellbeing, including CTGs at varying time intervals, ultrasound scans and maternal assessment of fetal movements. There have been no studies to support or refute any of these. However, maternal detection of fetal movements is simple, non-invasive and inexpensive, hence it seems reasonable to encourage the same.

Delivery

It is now a widely adopted practice to offer delivery at 37 weeks of gestation with the aim of reducing stillbirth. However, there have been no direct comparisons of early delivery and no intervention.

COUNSELLING

It is important that the woman understands the implications of OC, including reassurance about lack of long term sequelae for mother and baby, high risk of recurrence and increased incidence of OC in the family.

PRACTICE POINTS

- pathophysiology of OC still remains unclear
- pruritus without rash in pregnancy should be investigated
- raised transaminases is the most usual abnormality
- bile acids are sensitive but not specific
- diagnosis is by exclusion of other causes of raised LFTs and itching
- there is significant risk to the fetus, which is not predictable
- mainstay of management includes relief of maternal symptoms, close fetal monitoring and early delivery
- high risk of recurrence
- advice to avoid oestrogen-containing contraceptives

Postnatal resolution of symptoms and biochemical abnormalities is essential as a part of confirmation of diagnosis. Hence it is important to ensure LFTs have returned to normal, pruritus has resolved and that all the investigations done during pregnancy have been reviewed.

Advice regarding avoiding oestrogen-containing contraceptives and discussion of contraceptive choices must be offered.

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