10.5005/jp-journals-10006-1248
REVIEW ARTICLE

Pruritus in Pregnancy

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ABSTRACT

Itching is a common complaint in pregnancy, occurring in up to 14 to 23% of women. Pruritus may be so severe that it affects sleep and quality of life. It has a prevalence of 0.7 to 5% in different populations.[1] Prevalence is influenced by genetic and environmental factors and varies between populations worldwide. In Chile, 2.4% of all pregnancies are affected with a 5% prevalence in women of Araucanian-Indian origin.[1]

Obstetric cholestasis (OC) (also referred to as intrahepatic cholestasis of pregnancy) is a multifactorial condition of pregnancy characterized by pruritus in the absence of a skin rash with abnormal liver function tests (LFTs), neither of which has an alternative cause and both of which resolve after delivery.[2] Investigations to exclude other causes of pruritus and of abnormal LFTs should be performed.

Obstetric cholestasis has a potential for fetal risks, which may include spontaneous preterm birth, iatrogenic preterm birth and fetal death. Intense pruritus causes. Maternal morbidity and sleep deprivation. An interdisciplinary management of intrahepatic cholestasis of pregnancy by dermatologists, hepatologists, gynecologists and pediatricians is absolutely mandatory.

Keywords: Intrahepatic cholestasis, Ursodeoxycholic acid, Pregnancy.

How to cite this article: Malhotra J, Agrawal P, Garg R, Malhotra N. Pruritus in Pregnancy. J South Asian Feder Obst Gynae 2013;5(3):142-146.

Source of support: Nil

Conflict of interest: None declared

INTRODUCTION

Itching is a common complaint in pregnancy, occurring in up to 14 to 23 of women. Pruritus may be so severe that it affects sleep and quality of life. It has a prevalence of 0.7 to 5% in different populations.[1] Genetic and environmental factors and varies between populations worldwide.

OBSTETRIC CHOLESTASIS (OC) [INTRAHEPATIC CHOLESTASIS (IC) OF PREGNANCY]

Pathogenesis

The pathogenesis of ICP is multifactorial. ICP is caused by a defect in the excretion of bile salts leading to increase in bile acids. Potential contributors include a genetic predisposition interacting with the effects of estrogen and progesterone metabolites on bile secretory mechanisms as well as environmental factor.

- Genetic
- Hormonal
- Environmental
- Selenium deficiency

Genetic

Mutations in genes encoding proteins necessary for bile excretion (e.g. the ABCB4 [MDR 3] gene) have been identified. With normal hormone levels, this defect has no clinical implications; it only becomes evident with high hormone levels in late pregnancy and/or with hormonal contraception. Estrogen and progesterone metabolites are cholestatic themselves.

Dietary Factors Like Decreased Serum Selenium Levels

- Risk factors
- Personal or family history of obstetric cholestasis
- Multiple pregnancy
- Carriage of hepatitis C and
- Gallstones

Otherwise unexplained abnormalities in transaminases, gamma-glutamyl transferase and/or bile salts are considered sufficient to support the diagnosis of obstetric cholestasis.

The increase in alkaline phosphatase in pregnancy is usually placental in origin and so does not normally reflect liver disease. A thorough history and examination should be carried out, including a drug history, before abnormal LFTs are determined to be otherwise unexplained. Bilirubin is raised only infrequently and most women will have increased levels of one or more of the remaining LFTs.

The upper limit of pregnancy-specific ranges LFT should be applied. The upper limit of normal pregnancy transaminases, gamma-glutamyl transferase and bilirubin throughout pregnancy is 20% lower than the nonpregnant range.[4] Rise significantly after a meal, so while fasting might give lower values and help the diagnosis to be avoided in a few women with otherwise normal LFT, in the majority of studies and in clinical practice random levels are generally used. Pruritus may develop days or weeks before the development of abnormal liver function. If persistent unexplained pruritus with normal biochemistry is present, LFTs should be measured every 1 to 2 weeks. Isolated elevation of bile salts may occur but this is uncommon; normal levels of bile salts do not exclude the diagnosis. This may include carrying out a viral screen for hepatitis A, B and C, Epstein-Barr and cytomegalovirus, a liver autoimmune screen for chronic active hepatitis and primary biliary cirrhosis (for example, antismooth muscle and antimitochondrial antibodies).

Obstetric cholestasis has a tendency to recur in subsequent pregnancies (45-70%).

Clinical Presentation

Obstetric cholestasis typically presents with sudden onset of severe pruritus that may start on palms and soles but quickly becomes generalized. It persists throughout pregnancy and may be worse at night. To start with the skin usually is completely unaffected; later-on scratching leads to, secondary skin lesions ranging from slight excoriations to severe prurigo nodules. The skin should be inspected and dermatographia artefacta (skin trauma from intense scratching), which may be seen in OC should be differentiated from other common skin conditions such as eczema or atopic eruption of pregnancy (previously referred to as eczema of pregnancy, prurigo and pruritic folliculitis) should be done. If a rash is present, polymorphic eruption of pregnancy or pemphigoid gestations (blisters) should be considered.

Skin lesions usually involve the extensor surfaces of the extremities, but may also affect other sites of the body such as buttocks and the abdomen. Pale stools and dark urine should be looked for. Jaundice, due to concomitant extrahepatic cholestasis, occurs in about 10% of patients, usually after 2 to 4 weeks, complicating the most severe and prolonged episodes. Steatorrhea may lead to the development of cholelithiasis.

Diagnostic Tests

Histopathology is nonspecific; direct and indirect immunofluorescence are negative.

The most sensitive indicator for the diagnosis of intrahepatic cholestasis of pregnancy is a rise of serum bile acid levels while routine liver function tests (including transaminases) may be normal in up to 30%. Normal non-pregnant levels of total serum bile acid are 0 to 6 μmol/l. In healthy pregnancies, total serum bile acid levels are slightly higher than in nonpregnant women and levels up to 11.0 μmol/l are accepted as normal in late gestation.

Hyperbilirubinemia is noted in only 10 to 20%; it should always lead to close surveillance of prothrombin time and an ultrasound of the liver may be necessary to exclude cholelithiasis in such cases.

Prognosis

The prognosis for the mother is generally good. After delivery, pruritus disappears spontaneously within days to weeks but may recur with subsequent pregnancies and oral contraception.

Vitamin K Deficiency

Malabsorption of fat-soluble vitamins including vitamin K may occur. It may lead to an increased risk for intra- and postpartum hemorrhage in both mother and child. However, the key consideration in this disease is not maternal pruritus but the significantly impaired fetal prognosis.

IC is associated with an increased risk for prematurity (19-60%), intrapartal fetal distress (22-33%) and stillbirths (1-2%) which correlates with higher bile acid levels, particularly if exceeding 40 μmol/l. Therefore, prompt diagnosis, specific therapy, and close obstetric monitoring as well as maternal counseling, particularly recurrence in subsequent pregnancies, is a must.

Differential Diagnosis

Pregnancy-specific causes of abnormal LFTs:

- Pre-eclampsia and
- Acute fatty liver of pregnancy.

Dermatologic Causes of Pruritus

Irrespective of the etiology exacerbating factors are skin inflammation, dry or hot surroundings, skin vasodilation and stress.

XEROSIS

The itch of dry skin is common during the winter in Northern climates.

Patients with xerosis experience an intense pruritus, usually involving the anterolateral lower legs. Other commonly involved areas include the back, flank, abdomen and waist.

ATOPIC DERMATITIS

Atopic dermatitis often persists into adulthood and may be exacerbated during pregnancy. Such patients usually have a family history of asthma and allergic rhinitis.

Classically histamine (released by mast cells) in urticaria and other allergic reactions, is associated with pruritus. With the exception of allergic conditions, histamine is only one of the several chemical mediators of itch.

Atopic dermatitis of the hands, upper eyelids and anogenital region. There is immune-mediated release of cytokines and other proinflammatory agents along with distorted touch sensation. Mild mechanical stimulation as touch is perceived as pruritus.

ALLERGIC CONTACT DERMATITIS

It may be caused by exposure nickel, latex, cosmetics, poison ivy, and topical medications, such as benzocaine and neomycin.

SCABIES OR LICE

Pruritus may be the chief complaint. Pathognomonic burrows within the hand web spaces, axillae and genitalia, nonspecific pruritic papules may be the only sign of scabies.

Serotonin appears to be a key component of the pruritus in polycythemia vera, uremia, cholestasis and lymphoma and narcotic associated pruritus. Serotonin inhibitors such as cyproheptadine, paroxetine and ondansetron are effective in treating these pruritic conditions.

Pruritus may be precipitated in many patients receiving intraspinal injections of narcotics. Intravenous and intradermal opioid injections also may induce itching. Narcotic antagonists have been used with success to relieve pruritus in patients with cholestasis.

The pruritus of herpes zoster prodrome is due to a neuropathic cause. Peripheral neuropathy may also cause pruritus. Brachioradial pruritus is an uncommon condition that presents as lateral arm pruritus and has been associated with spinal disease. Similarly, notalgia paresthetica is thought to be of neuropathic origin, with pruritus restricted to the middle of the back. Severe pruritus also has been observed in patients with spinal tumors and multiple sclerosis.

Systemic Causes of Pruritus

Pruritus can be an important dermatologic clue to the presence of significant underlying pathology in 10 to 50 % of adults. Systemic causes must be considered, in whom pruritus is persistent and refractory to management.

- Systemic causes of pruritus
- Uremia
- Cholestasis
- Polycythemia vera
- Hodgkin's lymphoma
- Hyperthyroidism chronic renal failure
- Cutaneous T-cell lymphoma
- Human immunodeficiency virus (HIV) infection
- Herpes zoster prodrome.

Evaluation

A thorough history and a complete physical examination are the key to the evaluation of pruritus. Other evidence of cholestasis like pale stool, dark urine and jaundice should be looked for:

- Complete blood count
- Thyroid-stimulating hormone
- Serum bilirubin, alkaline phosphatase
- Serum creatinine, blood urea nitrogen levels
- Chest radiography
- A coagulation screen—prothombin time (PT)
- Hepatitis A, B and C, Epstein-Barr and cytomegalovirus may be done. A liver autoimmune screen chronic active hepatitis and primary biliary cirrhosis (antismooth muscle and antimitochondrial antibodies) An ultrasound of upper abdomen for liver.[3]

Postnatal resolution of pruritus and of LFTs is required to secure the diagnosis.[4]

An increased incidence of meconium stained liquor, premature delivery, fetal distress has been found.

Cesarean section rate is high. The evidence comes from many case-control studies. In a study of 1621 pregnancies, which have reported outcome in OC pregnancies since 1965 meconium is more common in preterm OC pregnancies than in term obstetric cholestasis pregnancies (25% compared with 12%) and preterm controls (18% compared with 3%), although not all studies show this. Another study concluded that meconium stained liquor may be more common in those with severe cholestasis (defined as bile acids over 40 μm/l, 49 women) compared with mild cholestasis (bile acids under 20 μm/l, 34 women) (10% compared with 0%, $p = 0.02$).

Daily fetal movement count is a simple, inexpensive test for women but its role in monitoring pregnancy complicated by obstetric cholestasis has not been assessed.

Fetal death is usually sudden. There is no evidence of placental insufficiency. OC does not cause fetal growth[6] restriction and oligohydramnios and umbilical artery.

Doppler assessments are not different from other pregnancies. Stillbirth cannot be predicted.

Consensus

Twice weekly NST with or without Doppler testing.

Treatment

Close obstetric surveillance is required and includes weekly fetal cardiotocographic (CTG) starting from 34 weeks gestation. Obstetric cholestasis requires an interdisciplinary management by dermatologists, hepatologists, gynecologists and pediatricians.

When to deliver?

Induction of labor and delivery as soon as lung maturity is achieved after 37 + 0 weeks of gestation. Continuous fetal monitoring should be done in women in labor.

According to a study OC started at a mean ± SD of 30 ± 4 weeks' gestation, with pruritus as the leading symptom. Total serum bile acid levels were markedly elevated in all patients and correlated with impaired fetal prognosis. Only 10 cases (77%) had other liver function test result abnormalities. Fetal distress occurred in 3 pregnancies (23%). In the 10 cases treated with UDCA, 3 (30%) involved preterm deliveries compared with a 100% preterm delivery rate in the cases not treated with UDCA.[7]

Treatment

Nonspecific Therapy for Pruritus

Liberal use of skin lubricants like petrolatum or lubricant cream at bedtime is soothing. Alcohol-free lotions may be applied many times during the day. Bathing should restricted to brief exposure to tepid water; after bathing, briefly pat skin dry and immediately apply skin lubricant. Use mild, unscented, hypoallergenic soap two to three times per week; limit daily use of soap to groin and axillae (spare legs, arms and torso). Humidify dry indoor environment, especially in winter. Choose clothing of cotton or silk. Avoid synthetic fabrics. In general vasodilators like caffeine, alcohol, spices, hot water should be avoided. Excessive sweating should be avoided. Fingernails should be kept short and clean to prevent complications of scratching, and by rubbing skin with the palms of the hands if urge to scratch is irresistible.

Topical Emollients

These include calamine lotion and menthol containing creams. There are no data to support or refute their use. They are safe in pregnancy and provide slight temporary relief of pruritus.

Systemic Therapy

Cholestyramine (bile acid-chelating agent). It may improve pruritus in some women but there is fear of exacerbating vitamin K deficiency (which can cause fetal intracranial hemorrhage). There are no randomized trials and is not in clinical use.

Antihistamines chlorpheramine may provide sedation at night but do not have a significant impact on pruritus. Activated charcoal and guar gum do not relieve pruritus.

Ursodeoxycholic Acid

Aim of treatment is to reduce serum bile acid levels in order to prolong pregnancy and reduce both fetal risks and maternal symptoms.

Ursodeoxycholic acid (UDCA) is the only treatment that has been shown not only to reduce maternal pruritus but to also improve fetal prognosis. It is a naturally occurring, hydrophilic, nontoxic bile acid that has been successfully used in China for over 5,000 years for various liver diseases. Nowadays it has a vital-role in treating hepatobiliary disorders.

Dose of 15 mg/kg/day or, independent of body weight, 1 g/day is administered either as single dose or divided into 2 to 3 doses until delivery, when it usually can be stopped. Adverse effects- none except for occasional mild diarrhea. However, UDCA is not licensed for use in pregnancy and thus requires special patient information. UDCA is a very commonly prescribed agent in India for relief of pruritus in OC; but, its effect on fetal outcome remains yet to be determined. As the pathophysiology of OC and the mechanism of fetal death are not clear, the possible role of UDCA is unclear.[8] Further larger studies are required to determine this. The available evidence labels UDCA as the most effective therapy as UDCA improves pruritus and liver function in women with OC.[9] Lack of robust data concerning protection against stillbirth and safety to the fetus or neonate.

Proposed Mechanism of Action of UDCA

It enhances bile acid clearance across the placenta from the fetus.

Randomized controlled trials suggest that improvement in pruritus and bile acid concentrations were observed only in those with bile acids over 40 μm/l.

Dexamethasone

Dexamethasone should not be first-line therapy for treatment of OC. It is not recommended to be used outside of a randomized controlled trial without a thorough consultation with the woman.

The results of the use of dexamethasone (10 mg orally for 7 days and then stopping over 3 days) in 23 women are conflicting, with some improvement in symptoms and biochemistry in some women. The numbers of women recrited were small.

Repeated courses of dexamethasone (as used for fetal lung maturation) may cause adverse fetal and neonatal neurological effects and hence limits its use.

Vitamin K: should or should not be given?

Women with fat malabsorption — especially biliary obstruction or hepatic disease — may become deficient in vitamin K. For oral administration to prevent vitamin K deficiency in malabsorption syndromes, a water-soluble preparation (menadiol sodium phosphate) must be used with a daily dose of 10 mg.

This should be avoided in late pregnancy and labor because of a risk of neonatal hemolytic anemia, hyper-bilirubinemia and kernicterus.

Follow-up of Patients of Obstetric Cholestasis

Once the diagnosis of OC is made, LFTs should be measured weekly until delivery. Postnatally, LFTs should be deferred for at least 10 days.

Transaminases will range from just above the upper limit of normal to several hundreds. Regular LFTs, along with a general review, blood pressure measurement and urine examination, monitoring of the condition and exclusion of other diagnoses is a must. If LFTs return to normal, OC is not likely

to be the correct diagnosis. If LFTs escalate very rapidly, additional diagnoses need to be considered and the monitoring should be made more frequent: although this situation can be consistent with OC, it is not typical.

Patient should be reassured that there are no long-term implications for the mother and baby. Estrogen containing contraceptives should be avoided. LFTs should be repeated 6 weeks after delivery. A coagulation screen should be performed.

Postnatal resolution of symptoms and of biochemical abnormalities is required to secure the diagnosis.[5]

CONCLUSION

ICP is a diagnosis of exclusion. Close obstetric surveillance and prompt treatment with ursodeoxycholic acid are warranted. Early recognition and timely delivery are the key to successful perinatal outcome. In general maternal outcome are good but fetal outcome can be disasterous. Prevention and prediction of fetal death is still a challenge.

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