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REVIEW ARTICLE

Intrahepatic Cholestasis of Pregnancy (ICP): A Patho-Physiological Review

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ABSTRACT

Intrahepatic cholestasis is a pregnancy-specific liver disorder characterized by maternal pruritus in the third trimester, raised serum bile acids and increased rates of adverse fetal outcomes, generally faced by the genetically predisposed women up to moderate to severe stage that cause skin itching and make the life debilitating but not fatal during the time of pregnancy often after second trimester rarely before that,alleviation of this difficulty is achieved by using pharamcological measures. The etiology of ICP and its molecular mechanism is complex and not fully understood, but it is likely to result from the cholestatic effects of reproductive hormones and their metabolites. Equally unclear are the mechanisms by which the fetal complications occur. This article reviews the probable mechanism of pruritus and future therapeutic target for the alleviation of maternal pruritus and fetal outcome.

Key words: Intrahepatic cholestasis, bile acids, pruritus, fetal outcome.

INTRODUCTION

Intrahepatic Cholestasis of pregnancy (Obstretics cholestasis) is a a reversible type of hormonally influenced decrease in bile flow in which the normal flow of bile in the gallbladder is affected by the high amounts of pregnancy hormone at their peak in the last trimester, bile acid and phospholipid accompany cholesterol secretion, but it usually goes away within a few days after delivery [1]. P-glycoprotein which regulates a Cl-channel in a manner analogous to that of CFTR, influences bile flow [2], that is essential for movement of water and solutes across liver canalicular membranes, bile acid is transported across by an ATP binding cassette transporter (ABC) super family, known as sister of P-glycoprotein (Spgp) or bile salt export pump (Bsep, ABCB11), mutations in the BSEP gene are associated with a very low level of bile acid secretion and severe cholestasis.

However, in general it is prevented due to presence of "alternative transport system" known as multidrug resistance Mdr1 gene encoded P-glycoprotein. An alternative pathway to transport bile acids and protects hepatocytes from bile acid-induced cholestasis, though with a 5-fold lower affinity compared to Spgp(sister P glycoprotein) that is insufficient to prevent mild cholestasis.(3) Hepatocellular cholestas during pregnancy is induced by high ethynylestradiol that represses FXR(farnesoid X receptor) receptor which stimulate hepatic bile export (bile salt export pump BSEP) in an estradiol-dependent manner linked with increased P-glycoprotein biliary excretion and decreased hepatic content through alternative transport system [4,5].

Pathophysiology

Intrahepatic cholestasis of pregnancy (ICP) is defect involving the excretion of bile salts which leads to increased bile acids in serum that is deposited within the skin causing intense pruritus characterized by generalized itching, often commencing with pruritus of the palms and soles of the feet, with no other skin manifestations, a multifactorial disorder with environmental, hormonal, and genetic contributions, frequently develops in late pregnancy in individuals with genetic predisposition [6,7]. Up to 15% of ICP cases are associated with the adenosine triphosphate binding cassette, subfamily B, member 4 (*ABCB4/abcb4*) gene also known as multidrug resistant protein 3 (MDR3),and ATP-binding cassette, subfamily B, member 11 (ABCB11) gene encodes the transporter for phospholipids and bile salt export pump respectively ,which is exclusively expressed at the canalicular membrane of hepatocyte that get

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inhibited by sex hormone (estrogen, progesterone, and corticosteroids) of which level are 1,000-fold increased during pregnancy at term compared with the nonpregnant state [7-9].

Specific bile acid transporters expressed in the liver, play a critical role in driving bile acids in the circulation maintaining bile acid homeostasis. In the hepatocytes, the vectorial transport of bile acids from blood to bile is ensured by Na+ taurocholate co-transporting peptide (NTCP) and organic anion transport polypeptides (OATPs). After binding to a cytosolic bile acid binding protein, are secreted into the canaliculus via ATP-dependent bile salt excretory pump (BSEP) and multi drug resistant proteins (MRPs) [10].

Mutations of this results into malfunctioning of hepatic bile acid transporters and is implicated in the pathophysiology of cholestatic liver disease and the depletion of circulating pool of bile acids ,.thus genetic disruption or dysregulation of their function. Therefore, raise bile acid levels [11-13] and increases sensitivity to estrogen [14]. Individuals with a sensitivity to estrogen should be monitored closely during pregnancy for signs and symptoms of ICP, especially in the third trimester when estrogen levels are at their highest [15].

Recent studies have implemented 2 bile acids, taurocholic and taurodeoxycholic aids, as being the specific ones elevated in ICP. Interestingly, these are also the bile acids significantly decreased by ursodeoxycholic acid (UCDA), which is currently the main pharmacological treatment. The significance of these findings remains to be fully elucidated [16.17].

Cholestatic Pruritus and its molecular mechanism

Pruritus is disturbing sensation that evokes the urge to scratch and is associated with dermatological features other than excoriation mark, distressing for patients and can lead to a marked decrease in quality of life due to impaired sleep and depression, in rare cases, pruritus can be so debilitating that this symptom alone can justify a patient's listing for liver transplantation., specifically affects the palms of the hands and soles of the feet but can be generalized or affect other areas of the body, worsening at night leading to sleeplessness and fatigue [18], that can be alleviated by the use of cholestyramine, silymarin, or epomediol more specific is ursodeoxycholic acid shown to be beneficial in pruritus and in liver function tests [19]. Clinical icterus is rare, and if it does tends to be mild with bilirubin levels rarely exceeding 100 μmol/L affecting approximately 10%-15% of pregnant women with ICP, Unlike the pruritus, it does not typically deteriorate with advancing gestation [20].

The molecular mechanism of pruritus signal transduction is largely unsettled but it is hypothesised that potential pruritogens accumulate in the circulation of cholestatic patients and compounds which accumulate in the circulation during cholestasis act as direct or indirect pruritogens by affecting signaling in itch fibers. Therefore, initially itching in IPC is commonly believed to be caused by retention of bile acids as bile acid transport system in IPC has impaired and elevates serum cholic acid 10 fold and chenodeoxycholic acid 5 fold with their sequestration in the skin. However absolute concentrations of bile acids in the skin do not correlate well with the sensation of itch [21], different reports demonstrate that skin levels of bile acids in patients with cholestasis is not directly related to bile acid retention thus correlate poorly with pruritus [22,23].

A study showed plasma samples from itchy cholestatic patients caused a significantly higher activation of neuroblastoma cells than non-itchy cholestatic patients and healthy controls [24],purification revealed lysophosphatidic acid (LPA) as the active compound, generated form lysophosphatidylcholine into LPA by the elevated levels of serum enzyme autotaxin (ATX),an cholestatic inducible enzyme that increases local formation of LPA a very potent signalling phospholipid near unmyelinated nerve endings of itch fibers, LPA then activates these neurons through one of the LPA receptors**,** increases neuronal [Ca(2+)](i) as a major [Ca(2+)](i) agonist which in turn potentiates action potentials along itch fibers [25,26].

Current management of pruritus in liver disease

LPA and autotaxin play a critical role in cholestatic pruritus and may serve as potential targets for future therapeutic interventions. Pruritus in cholestasis of pregnancy and hereditary cholestatic syndromes is common accompanying almost any other liver disease. Increased concentrations of bile salts, histamine, progesterone metabolites or endogenous opioids are considered to be potential pruritogens in cholestasis in the past, recent finding unraveled lysophosphatidic acid (LPA), a potent neuronal activator, as a potential pruritogen in pruritus of

cholestasis [27]. A meta-analysis revealed, UDCA is effective in reducing pruritus but does not provide relief from pruritus from primary biliary cirrhosis , provides pruritus relief in patients with intrahepatic cholestasis of pregnancy improving liver function test and beneficial to fetal outcomes in patients with ICP [28] however different medication are used in managing pruritus in patients with cholestatic liver disease among them cholestyramine is considered as a first-line therapy ,second-, third-, and fourth-line therapies include rifampicin, opiate antagonists (such as naloxone and naltrexone), and the serotonin reuptake inhibitor sertraline, respectively. For patients with intrahepatic cholestasis of pregnancy, treatment with UDCA improves both pruritus and liver function.(29) Of which efficacy rates below 50% are common for most of the drugs used to treat pruritus with mild to moderate gastrointestinal side effects and withdrawal like symptoms that includes nausea, bloating and constipation ,sertaline is usually tolerated but sometime can cause dry mouth, anxiety, drowsiness, tolerance is generally present in the patient if drugs provided is from very low to progressively increasing dose, other option for treatment is nasobilliary drainage which temporarily drops autotoxin activity and decrease intensity of pruritus,(30) therefore now the current therapeutic target for the treatment is to drop the autotoxin activity and to modulate LPA receptors.

Ursodeoxycholic acid and cholestatic pruritus

Intrahepatic cholestasis of pregnancy (ICP) is a reversible cholestatic liver disease with chief complaint is pruritus during the second or third trimester of pregnancy and resolves rapidly after delivery. The serum liver tests reveal moderate cholestasis with increased levels of bile salts (> or = 10 micromol/l) and aminotransferases. Which could be due to the effects of estrogen and progesterone metabolites on bile secretory mechanisms, as well as dietary factors like as selenium active part of GSH-Px, reduction in seleneium content in diet decreases glutathione peroxidase activity reduces antioxidative defence that may lead to the formation of free radicals, which could damage the structure and function of hepatocytes and result in ICP(31,32)causing fetal distress, with stillbirths or premature deliveries, leading to increased perinatal morbidity and mortality [33].

Ursodeoxycholic is superior in the efficacy and safety for management of the intrahepatic cholestatic pruritus, (66.6% P < .005) taken 8-10 mg/kg body weight daily with no adverse effects reported till date and total resolution of pruritus, associated with normalization of serum levels of alanine aminotransferase,with reducing serum levels of bile acids, reduced fetal distress and beneficial for fetal outcomes [34,35]. UDCA stabilizes plasma membranes, halts apoptosis by preventing the formation of mitochondrial pores, induce changes in the expression of metabolizing enzymes and transporters that reduce bile acid cytotoxicity and improve renal excretion,. Positively modulate ductular bile flow that preserves the integrity of bile ducts. Prevents the endocytic internalization of canalicular transporters, a common feature in cholestasis [36]. stimulates a CFTR-dependent apical ATP release in cholangiocytes that activates purinergic 2Y receptors, and, through $[Ca^{2+}]i$ increase and PKC activation stimulates Cl^- efflux and fluid secretion, a choleretic effect of UDCA [37].

Obstrectic cholestasis and pregnancy outcome

Most cases of stillbirth are associated with meconium passage, the rate of which is significantly higher before 37 weeks in obstetric cholestasis than in the general obstetric population [38]. Poor fetal outcomes, including asphyxial spontaneous preterm delivery, is associated with elevated maternal total serum bile acids (>40 micromol/L) in pregnancy [39].

Recent study of histopathology examination showed matured fetal pulmonary tissues with dilated and congested interstitial lung capillaries, thickened alveolar septum, mild focal inflammatory exudation and focal hemorrhage in alveolus. Furthermore, reduced microvilli, mitochondrion vacuolization, cytoplasm disintegration and increased lamellar body evacuation were observed in type II pneumonocytes in ICP group under light and electron microscopes. While fetal pulmonary tissues of the control group did not show any significant lesions [40].

Risk of adverse pregnancy outcomes increasing in intrahepatic cholestasis of pregnancy (ICP). Fetal distress in ICP is an acute process, and the abnormal expression of placental local vasodilatory factors play an essential role. Urocortin (UCN) exhibits a powerful concentration-dependent vasodilatation effect in the utero-placental-fetal unit. down-regulated UCN expression in the placenta and maternal serum during ICP may impair the blood flow

regulation of the utero-placental-fetal unit and contribute to fetal distress [41].

CRH in human pregnancy appears to be involved in placental bloodflow, placental prostaglandin production, myornetrial function, fetal pituitary and adrenal function and the maternal stress axis. Since fetal cortisol levels are associated with pulmonary development and maturity, placental CRH may have role in fetal development and in the regulation of gestational length and timing of placental clock. Therefore, CRH appears to link placental function, maternal well-being, fetal well-being and fetal development to the duration of gestation and the timing of parturition [42].

The CRH expression level in ICP placenta was significantly lower than those results in controls ($P < 0.01$). For CRH-R1, CRH mRNA and CRH-R1 mRNA expressions, no statistical differences were found between control and ICP groups (all $P > 0.05$). Serum CRH levels increased in both control and ICP groups, but the growth rate was limited in ICP group, especially in late pregnancy ($P < 0.05$) the down-regulation of CRH in ICP placentas and the limited growth rate of CRH in the maternal serum of ICP patients might impair the blood flow regulation of the utero-placental-fetal unit, which might result in poor fetoplacental vascular perfusion and adverse pregnancy outcomes [43].

CONCLUSION

Obstretic cholestasis is a relatively common cause of hepatic impairment in pregnancy. It has a complex transient abnormality caused by genetic,environmental and hormonal effects with postnatal resolution,. It causes maternal pruritus with no fatal impairement to liver function and raised serum bile acids,although affected women have increased rates of hepatobiliary disorders in later life.

ICP is associated with adverse fetal outcomes. The risk of meconium-stained liquor, fetal asphyxia and spontaneous preterm delivery is greater in pregnancies with more marked elevations in maternal serum bile acid levels. The most effective pharmacological therapy for improvement of maternal symptoms and biochemical abnormalities is UDCA, and this has also been shown to reduce placental abnormalities and to improve placental bile acid transport in *in vitro* studies. Fetal outcomes are improved with a active management procedure although the most effective intervention has not currently been established. A common practice is induction of labour at 37-38 wk of gestation with the aim of reducing the risk of uterine death. A future trial for the specific drugs of therapeutics is necessary to established to confront the fetal outcome in obstretic cholestasis.

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