Int J Physiol Pathophysiol Pharmacol 2022;14(1):16-23
www.ijppp.org /ISSN:1944-8171/IJPPP0138991

Review Article

Unfolding newer concepts in placental pathology of obstetric cholestasis-a cause for prematurity

Anusha Devalla[1], Kriti Srivastava[2]

[1]Obgyn Practitioner, Gayathri Hospital, Ramanthapur, Hyderabad, Telangana, India; [2]Assistant Professor, Department of Obstetrics and Gynecology, Chirayu Medical College, Bhopal, Madhya Pradesh, India

Received September 8, 2021; Accepted January 30, 2022; Epub February 15, 2022; Published February 28, 2022

Abstract: Intrahepatic cholestasis of pregnancy (ICP) has an increased predisposition to occur in the third trimester of pregnancy and has a varied population incidence rates due to genetic influences. Owing to the adverse and unpredictable fetal outcomes, it poses a serious therapeutic challenge to the clinician. A rise in the incidence of iatrogenic prematurity has been observed, raising concerns over the perinatal outcomes. Excess bile acids and altered placental transport mechanisms have been strongly implicated in the pathogenesis of ICP and its complications. The exact etiology is not known; yet major underlying risk factors that are thought to contribute to the disease process include genetic, environmental, hormonal, and immunological. Newer molecular processes acting at the placental level, apart from specific histopathological changes, have assumed significance in recent times. In this review, we attempt to highlight the recent understanding of the mechanisms that operate in the placenta in patients with obstetric cholestasis that lead to poor fetal outcomes, through various studies published in the literature. Despite these additions to the existing knowledge on the etiopathogenesis of obstetric cholestasis and its possible placental origin, further studies are needed to validate the newer concepts.

Keywords: Bile acids and salts, intrahepatic cholestasis of pregnancy, placenta, pregnancy, trimester, third, premature birth

Introduction

Intrahepatic cholestasis of pregnancy (ICP) or Obstetric cholestasis is a disorder that primarily affects pregnant women in their third trimester. It is characterized by maternal pruritus and reversible liver dysfunction with unfavourable fetal outcomes such as premature birth, fetal distress, and intrauterine fetal death [1-3]. Prematurity with a prevalence of 5% to 18% is a leading cause of neonatal mortality and its prevention needs to be addressed through vigilant antenatal care [4].

Incidence of ICP varies among different populations, probably due to genetic influences with the incidence as high as 27% in Chile (particularly of native Indian descent) [5]. A range of factors may be responsible for the pathogenesis of ICP viz. genetic, hormonal, immunologic, and/or environmental interacting in a manner as shown in the **Figure 1** [6].

Figure 2 shows the mechanism through which high serum bile acid levels (above 40 millimoles/L) can significantly increase fetal distress as observed by Echo-Doppler detection of fetal blood flow [7].

This review aims at describing the principal molecular processes acting at the placental level causing the pathophysiological changes affecting the patients with obstetric cholestasis, one of the main causes for prematurity.

Literature review

Bile acids are produced by the fetal liver from 12 weeks gestation. Normally in a healthy pregnancy, they are transferred, owing to poor utilization, to the maternal circulation through a steep transplacental gradient mediated by ATP-dependent mechanisms. Whereas in women with ICP, the excessive rise in the maternal serum bile acid levels reverses the transplacental gradient and causes bile acids to accumulate in the fetal circulation [8]. It has been also documented that a positive linear correlation between serum bile acid levels and preterm

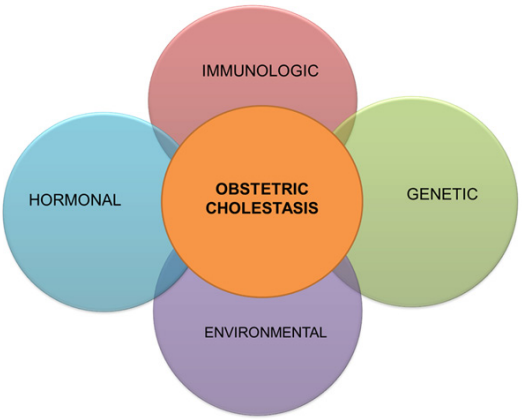

Figure 1. Factors responsible for intra-hepatic cholestasis of pregnancy.

delivery exists with every 1-2 millimoles/L rise in the levels and causes adverse perinatal outcomes [9]. A Meta-analysis by Ovadia C et al. performed on the women with ICP had higher Odd Ratios of preterm birth (OR 3.54 [95% CI 2.72-4.62]); but significant heterogeneity was observed between studies, particularly for iatrogenic preterm birth [3].

Placental transporters include OATPs (Organic Aniontransporting polypeptides), mainly OATP1B1 and OATP1B3. Further, they are transported from the placenta to maternal blood either conjugated or unmodified by MRPs (multidrug resistance-associated proteins) such as MRP1, MRP2 and MRP3. Other transporter proteins like BCRP (Breast cancer resistance protein) may also be involved. In a healthy pregnancy, the canalicular membrane of the maternal hepatocytes takes part in the uptake via MRP2 and BSEP (Bile salt export pump). The above mechanisms that are illustrated in the **Figure 3**, may get interrupted at several levels to cause accumulation of the toxic bile acids in the maternal liver and hence fetal circulation inducing oxidative stress and apoptosis having detrimental effects on the fetus [5]. Other pathways include ATP-binding cassettes (ABC proteins-ABCC, ABCD4, ABCD11); Placental Lectin-like LDL-receptor-1, Sodium Taurocholate transporters (NTCP) have also been described [10, 11].

Locatelli et al. in 2004, examined placentas from 111 patients with ICP treated with Ursodeoxycholic acid (UDCA), S-Adenosyl Methionine (SAMe) or cholestyramine and found that gestational age at delivery and birth weight were inversely correlated with the presence of placental vascular lesions. However, they found no associations of placental pathology with the cholestasis-related serum markers and clinical symptoms [12].

An Austrian study in 2007 derived a conclusion upon reviewing 13 patients with signs and symptoms of ICP that fetal distress occurred in 3 pregnancies (23%). Out of the cases treated with UDCA, 30% had preterm birth when compared to 100% in the cases not treated [13].

Understanding pathogenesis of ICP: pathological mechanisms and possible etiological factors

Genetic and epi-genetic causes: mutations in bile-acid transport: The *MDR3* gene, localized on 7q21.1 region of the chromosome, was first reported to be involved in progressive familial ICP by de Vree et al. [14]. *ATP8B1* variants have been found in less than 10% of the ICP cases according to a study from Finland [15]. In the recent studies, the importance of genetic variations in *ABCB4* and *ABCA11*, coding for *BSEP* have been postulated to be causing at least 10-15% of the cases [16].

A study by Liu X et al. in 2021 suggested a total of 2953 mutations in 44 genes coding for ABC family transporter genes causing ICP, 42 of which were novel. Seven unique pathogenic mutations were identified including *ABCB4* (Trp708Ter, Gly527Glu and Lys386Glu), *ABCB11* (Gln1194Ter, Gln605Pro and Leu589Met) and *ABCC2* (Ser1342Tyr), in the damaging group [17].

OATP1A2, OATP1B1 and OATP1B3 are among the few bile acid transporters in the placenta, usually detected by immunohistochemistry, have been found to be altered in the placentas from ICP women [9].

It has been observed that *CXCL6*, *CXCL14* and *IL-7R genes* were seen in cases with mild ICP while *CCL3* and *CCL25* were up-regulated only in cases with severe ICP as observed by Du Q et al. [8].

Understanding the pathogenesis of ICP has been aided by genetic studies; however, several biases have been found in association-

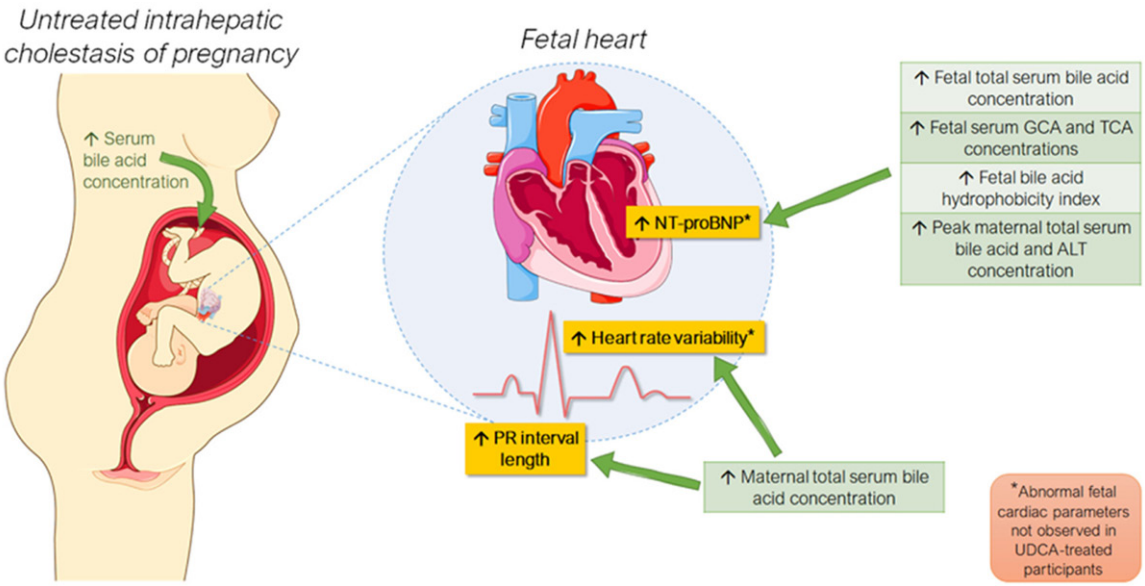

Figure 2. Pathogenesis of fetal heart dysfunction by increased fetal serum bile acid levels. (NT-pro BNP = N-terminal pro- Brain Natriuretic peptide). Reused with permissions. The original version of this article is available at Journal of Hepatology 2021 741087-1096. Copyright © 2021 European Association for the Study of the Liver [35].

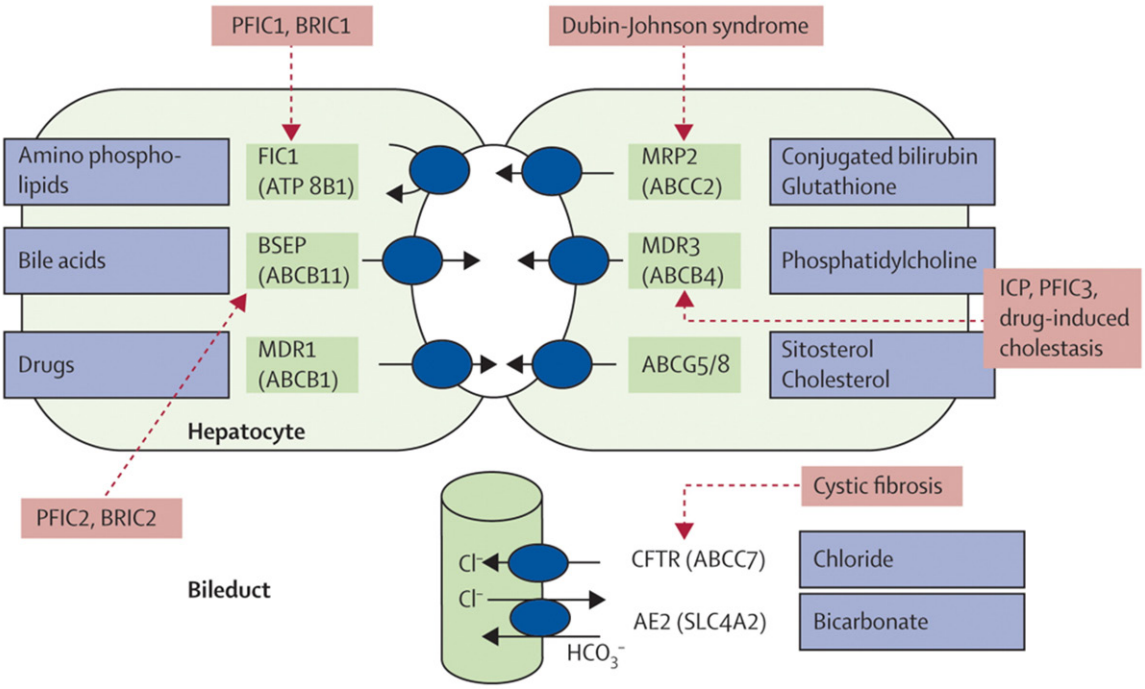

Figure 3. MDR3 translocates phosphatidylcholine across the canalicular membrane. There is formation of toxic monomeric bile salts in the bile ducts, due to the lack of this phospholipid, which ends up in cholangiocyte injury, pericholangitis, and periductal fibrosis. The phenotype expressed when a mutation occurs in the targeted transporter gene has been represented in the figure by a red dotted arrow. (PFIC1,2,3 = progressive familial intrahepatic cholestasis type 1,2,3 ABCG5/8 = ATP binding cassette transporters G5 and G8. AE2 = anion exchanger. BSEP = bile salt export pump. BRIC1 = benign recurrent intrahepatic cholestasis type 1. BRIC2 = benign intrahepatic cholestasis type 2. CFTR = cystic fibrosis transmembrane conductance regulator. FIC1 = familial intrahepatic cholestasis type 1. ICP = intrahepatic cholestasis of pregnancy. Cl^- = chloride ion. HCO_3^- = bicarbonate ion. MRP2 = multidrug resistance-associated protein 2. MDR1 = multidrug resistance protein 1. MDR3 = multidrug resistance protein). Reproduced with permission from the Lancet. *Copyright © 2010 Elsevier Ltd. All rights reserved* [36].

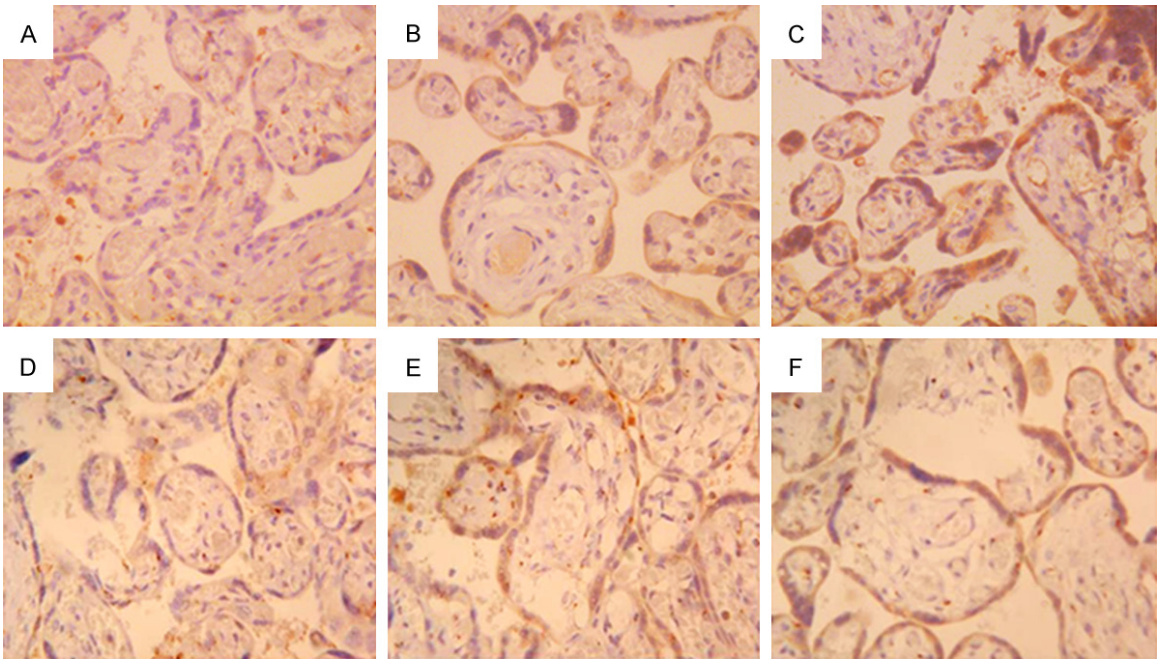

Figure 4. PPARγ and NF-κB staining were found in the membrane and cytoplasm of placental trophoblast cell. A-C. PPAR-γ protein expressed in placenta of control patients, mild ICP and severe ICP patients. D-F. NF-κB protein expressed in placenta of control patients, mild ICP and severe ICP patients. Reproduced with permissions from © 2014 Zhang et al. [23].

based studies, especially the sample size, the complex variability of phenotypes, the penetrance, environmental factors and the lack of independent replication in different populations.

Immunologic: One of the recent evidences by Du Q et al. suggest massive infiltration of CD45, CD3 and CD19 positive lymphocytes in severe ICP placentas as one of the mechanisms in the pathogenesis [8].

Another similar study performed using immunohistochemistry and TUNEL methods also demonstrated that the abnormal overexpression of p53 and *Bax* coupled with the underexpression of *Bcl-2* was responsible for placental apoptosis and dysfunction in patients with ICP [18].

VEGFC expression was up-regulated, compensating for hypoxia-induced by elevated concentrations of bile acids in ICP placentas [8, 19]. Interleukin-17 was found in a significantly higher number of iatrogenic preterm deliveries with severe ICP but not with mild cases (Pearson's negative correlation, r = 0.485, P = 0.049) [20]. IL-6 and TNF-α are important proinflammatory cytokines proved to be strongly associated with ICP pathology [21].

In a study reported from China, placentas from 37 ICP patients were processed through immunoblotting and Envision immunohistochemical methods to detect SOC3, TNF-α, and IL-10 protein levels in the trophoblasts. IL-10 expression was lower while SOCS3 protein and TNF-α expression were found to be higher in the ICP placentas than in the controls (P = 0.001) [22].

Peroxisome proliferator-activated receptor (PPAR-γ) and nuclear factor kappa-light-chain-enhancer of activated B (NF-κB) protein are also prominently expressed on the plasma membranes of the placental trophoblast cells of ICP placentas as shown in the **Figure 4** [23]. Apart from being intimately related to lipid metabolism, these markers have also been found to be associated with hepatocyte injury, fetal cholestasis and fetal complications associated with ICP [23]. UDCA competes with bile acids for binding with G-protein coupled bile acid receptor (Gpbar1) and thus inhibits bile acid-induced inflammatory response in trophoblasts and thereby improves fetal survival in pregnant rats with obstructive cholestasis [24].

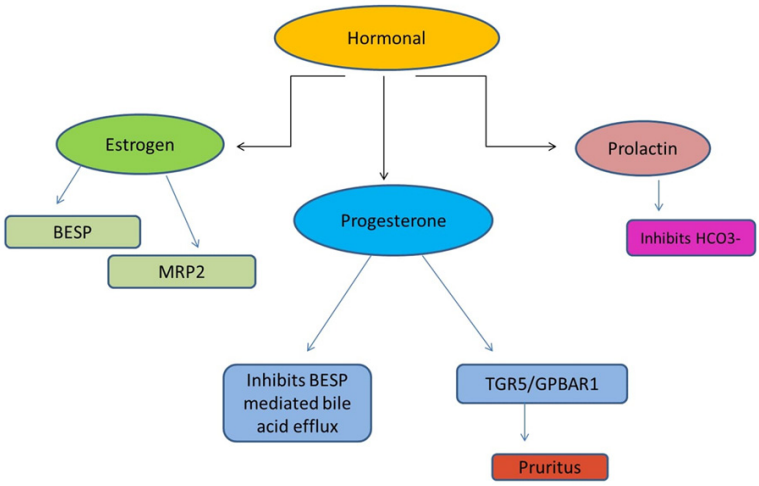

Figure 5. Role of Hormonal factors affecting the pathogenesis of ICP (BESP and MRP2 are the two proteins related to bile acid homeostasis regulated by oestrogen among which E2 inhibits interaction of BESP with Farsenoid X receptor. Metabolism of sulphated progesterone can activate GPBAR1/TGR5 and cause transinhibition of BSEP-mediated bile acid efflux.)-reproduced and modified with permission from Jianping Xiao et al. (Copyright © 2021) [37].

Environmental: Selenium, being an enzyme co-factor is involved in the oxidative metabolism in the liver but its exact role in the bile acid metabolism/transport is not yet completely understood. Interestingly, ICP has been associated with seasonal variations with more severe cases seen during the winter months [25].

Hormonal: This can be attributed to the fact that the incidence is relatively higher in multiple gestations than singletons owing to the greater oestrogen levels [2]. High doses of progesterone, particularly sulphated metabolites and prolonged use of oestrogen containing oral contraceptives can also trigger ICP by suppressing FXR (Farsenoid X receptor) activity. Few studies in rats also mention oestrogen to play a major role by inhibiting the major hepatic bile acid receptors [26]. Oestrogen may also inhibit the utilization of blood glucose that enhances the fat breakdown and free fatty acid release that can damage hepatocytes and cause cholestasis [27]. **Figure 5** highlights the important mechanisms through which the hormonal factors are known to affect the disease causation.

Newer insights into molecular biomarkers

11βHSD2: In placental cell lines from ICP patients and in parallel in-vitro studies using BeWo Choriocarcinoma cells, the expression of *11βHSD2* gene was seen to be reduced especially with raised chenodeoxycholic acid levels in ICP [28].

Irisin: A novel metabolic biomarker for ICP. Irisin is a potential "anti-oxidant" that acts by reducing the production of superoxide NADPH oxidase heme-binding subunit (gp91phox) and induced nitric oxide synthase (iNOS), and increase the production of antioxidant enzymes including glutathione peroxidase (GPX-1), catalase and superoxide dismutase [29].

Kirbas et al. in 2015 studied a possible link between Serum Irisin levels and ICP, through a logistic regression model. At serum Irisin levels of ≥908.875 pg/ml, the risk of ICP had increased 16.9-fold (OR = 16.972; 95% CI: 5.191-55.48; P<0.001) at which the sensitivity and specificity were 72.5% and 86.8%, respectively. Further studies are needed to clarify the significance of Irisin and elucidate its exact role in humans [30].

Chen J et al. evaluated the relationship between maternal serum, placental and umbilical Irisin in 108 women with ICP and found significantly lower levels in umbilical vein. Further, the serum Irisin of normal pregnant women (918.51±159.90 pg/ml) was significantly lower than that of pregnant women with mild ICP (1030.05±137.98 pg/ml) and pregnant women with severe ICP (1094.34±154.35 pg/ml). Also, the concentration of Irisin in umbilical vein of pregnant women with severe ICP (858.78±97.42 pg/ml) was significantly higher than that of normal pregnant women (595.33±162.70 pg/ml) and those with mild ICP (648.82±164.81 pg/ml) (*P*<.05) [29].

Observations made by Dabrowski et al. showed statistically significant differences in the concentration of Irisin between the time before starting treatment and the 8-week therapy. The Pearson correlation analysis showed two statistically significant relationships (*P*<.05) [31].

Constitutive androstane receptor (CAR protein): In the control group and mild ICP group, it showed light tan-coloured bands mainly in the cytoplasm, when stained on immunohistochemistry of syncytiotrophoblasts. In the severe ICP group, CAR was found mainly in the nucleolus, showed dark tan when stained suggesting a higher level. It is a potential marker that has much future implications to guide therapies [32].

A disintegrin and metalloproteinase with thrombospondin motifs (ADAMTS12): Popularly linked to pre-eclampsia and also have been related to the pathogenesis of ICP in rat models by modulating normal neutrophil apoptosis [33].

HDAC3 protein: Histone deacetylases act to silence genes in the nucleus of the placental trophoblasts. HDAC3 protein and mRNA expression were significantly lower in the ICP groups (both mild ICP and severe ICP groups) than in the control groups while no statistically significant difference was found between the mild ICP and severe ICP groups [34].

Conclusion

The above review highlights the mechanisms, in particular the newer insights, operating at the molecular level in the pathogenesis of ICP, through various studies published in the literature. Molecular biomarker proteins like Irisin, CAR, HDAC3 may also have a role in influencing therapeutic strategies in preventing the much avoidable iatrogenic prematurity in patients with obstetric cholestasis. However, these need further validation to prove their efficacy.

Acknowledgements

The authors would like to thank the publishers and the authors for providing permissions to reuse the images in this review article.

Disclosure of conflict of interest

None.

Address correspondence to: Dr. Anusha Devalla, HCL Nagar, Mallapur, Hyderabad, Telangana, India. E-mail: anushadevalla2@gmail.com

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