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Invited Editorial

Intra-hepatic cholestasis of pregnancy: Management challenges

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Intra-hepatic cholestasis of pregnancy (ICP), also known as obstetric cholestasis, is a pregnancy-specific liver disorder which classically presents in the third trimester as a persistent itch (particularly of the hands and feet) without a rash, together with elevated serum bile acid concentrations of 19 micromol/L or more, with resolution after delivery [1]. Other symptoms at presentation may include dark urine and pale stools. Jaundice is rare and should prompt a search for an alternative diagnosis [1]. In most cases of ICP, formal investigation to exclude other hepatic disorders is unnecessary.

Genetic susceptibility and reproductive hormones, especially oestrogen, are thought to be the principal contributing factors to the development of ICP, with environmental factors also thought to play a role in aetiology. The incidence of ICP therefore varies geographically and among different ethnic groups. In the United Kingdom, for instance, ICP affects 0.7% of pregnancies [1] but the incidence is higher in countries such as Sweden, Finland, and Chile, particularly in the winter [2]. Elevated bile acids are thought to play a significant role in maternal symptoms and adverse pregnancy outcomes, including fetal distress and stillbirth [1]. The mechanism by which elevated bile acids cause fetal demise is uncertain; however, elevated bile acids can affect the electrical conduction system of the heart, potentially leading to myocardial conduction defects in the fetus and arrhythmias [3].

In most pregnancies complicated by ICP, the management is straightforward and consists of symptomatic treatment of maternal itching, and regular monitoring of serum bile acids and hepatic transaminases, with delivery timed to minimise iatrogenic prematurity while reducing the risk of stillbirth. Aqueous creams with menthol, topical emollients, and antihistamines are commonly used to relieve maternal itching; however, there is a lack of high-quality evidence regarding their efficacy [1]. Ursodeoxycholic acid has been used to treat symptoms but available data indicates that its use does not result in a clinically significant reduction in maternal itching [4]. There is limited data to support the use of rifampicin plus ursodeoxycholic acid to treat ICP that has not responded to ursodeoxycholic acid alone and a randomised controlled trial to establish the safety and efficacy is ongoing [1]. To minimise the risk of stillbirth, early delivery is recommended, at 38–39 weeks in cases of bile acids $\geq$40 micromol/L (moderate ICP), and at 35–36 weeks in cases of bile acids $\geq$100 micromol/L (severe ICP) [1]. In cases of mild ICP, with bile acids 19–39 micromol/L, the risk of stillbirth is similar to the background population risk until 40 weeks of gestation [1].

The management of ICP can be challenging if it has a very early onset, is rapidly progressive, and when it coexists with pre-existing medical disorders or pregnancy-related conditions like pre-eclampsia. Early-onset ICP refers to the development of the condition in the first or second trimester of pregnancy, with cases reported as early as five weeks of gestation [5]. In multiple pregnancy or in vitro fertilisation pregnancy complicated by ovarian hyperstimulation syndrome, oestrogen levels can be markedly elevated in early pregnancy, and this is thought to contribute to the development of early-onset ICP [6]. Early-onset ICP is rare; however, crucially, it has been associated with higher risk of preterm birth, meconium-stained amniotic fluid, which may indicate fetal distress especially in preterm infants, and low birth weight [7].

Diagnosing ICP in the first or second trimester should involve careful assessment to exclude pre-existing or new-onset medical conditions which may also cause liver dysfunction, particularly in cases associated with markedly elevated hepatic transaminases, rapidly deterioration in hepatic function or liver failure. Conditions to consider include viral hepatitis, autoimmune hepatitis, gallstones, fatty liver disease, drug-induced liver injury, primary biliary cholangitis, and primary sclerosing cholangitis [8]. A comprehensive work-up is fundamental for accurate diagnosis, including a detailed clinical history and examination, imaging studies such as liver ultrasound or magnetic resonance imaging (MRI), and viral liver serology or liver autoantibody tests, depending on risk factors [1]. Such cases should be managed by a multidisciplinary team that includes a hepatologist.

In cases of ICP associated with rapid deterioration of hepatic

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function, pregnancy-specific conditions like, pre-eclampsia, HELLP (haemolysis, elevated liver enzymes, low platelets) syndrome, and acute fatty liver of pregnancy (AFLP) should be excluded [8]. While these conditions share some common features, they have specific key features that can allow differentiation. Pre-eclampsia is characterised by hypertension and proteinuria, which may, in atypical cases, only manifest in the post-partum period [9]. The introduction of sensitive and specific screening tests such as the sFlt-1:PLGF ratio may support the diagnosis of pre-eclampsia [10]. HELLP syndrome is a severe variant of pre-eclampsia with evidence of haemolysis and thrombocytopenia together with elevated liver enzymes [8]. While gestational thrombocytopenia may coexist with ICP, a diagnosis of ICP should be made with extreme caution in the presence of a low or falling platelet count. AFLP is a rare but life-threatening obstetric emergency which in some cases has been linked to a deficiency of the enzyme long-chain-3-hydroxyacyl coenzyme A dehydrogenase in the fetus [8]. AFLP typically presents in the third trimester of pregnancy with nausea and vomiting, abdominal pain, jaundice, and profound liver dysfunction [8]. Given a high maternal and fetal mortality rate associated with AFLP, early recognition and prompt diagnosis are of particular importance for initiating timely and appropriate interventions [8].

When pre-eclampsia coexists with ICP, abdominal pain and deteriorating liver function should be ascribed to severe pre-eclampsia rather than ICP and may necessitate delivery before 37 weeks of gestation to prevent maternal and fetal complications [10]. In multiple pregnancies complicated by ICP, delivery should be at an earlier gestational age than for singleton pregnancies with the same degree of hepatic dysfunction. Detailed parental counselling is essential when delivery is contemplated before 34 weeks of gestation. In rare circumstances where delivery is being contemplated at peri-viable gestational age for maternal well-being, consideration should be given to fetal reduction as this may permit pregnancy to progress to a gestational age with more favourable perinatal outcomes [11]. Again, detailed multidisciplinary parental counselling is essential.

ICP is expected to resolve spontaneously within six weeks of birth, with resolution of itching occurring typically within days; otherwise, an alternative diagnosis should be considered and the woman should be referred to a hepatologist [1]. Women with a history of ICP should be informed that there is a high risk of recurrence in a subsequent pregnancy [1].

In summary, the management of ICP is straightforward in most cases with bile acid concentrations used to time delivery. The management of maternal symptoms can be challenging and further research is needed to develop effective treatments. ICP may coexist or be misdiagnosed when women have other common pregnancy complications like pre-eclampsia, or rare but serious complications like HELLP syndrome. Clinicians should remain alert to this possibility when diagnosing atypical ICP or early-onset or ICP with rapidly deteriorating liver function. The possibility of pre-existing or new-onset liver disorders should also be considered including idiosyncratic drug reactions. When delivery of a multiple pregnancy is being considered at a peri-viable gestational age because of severe ICP, fetal reduction should be considered with the necessary parental counselling.

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