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SHORT COMMENTARY

Early Onset Intrahepatic Cholestasis of Pregnancy: Is Progesterone Supplementation to be Blamed For?

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Abstract Progesterone supplementation is a routine practice after intrauterine insemination and IVF-ET procedures. Progesterone is indicated in patients of PCOS and cervical incompetence. It also helps in prevention of recurrent unexplained miscarriages. Effect of a high dose of progesterone supplementation in causing earlier onset of Intrahepatic cholestasis of pregnancy (ICP) merits further focussed investigation.

Keywords Intrahepatic cholestasis of pregnancy (ICP) · Ursodeoxycholic acid (UDCA) · 3β-Sulfated progesterone metabolites

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Intrahepatic cholestasis of pregnancy (ICP) is characterized by intense pruritus in the absence of a skin rash with abnormal liver function test (LFTs) neither of which have an alternative cause and both of which remit following delivery. It classically appears in third trimester and is diagnosed by raised serum bile acid $\geq$ 10 micromol/L. Incidence of ICP is 0.02–2.4% of all pregnancies [1]. Though maternal complications are rare, ICP can cause serious risks to the fetus.

The etiopathogenesis of ICP is multifactorial. Hormonal factors play a significant role along with genetic and exogenous factors. The levels of progesterone metabolites especially the 3β-sulfated progesterone metabolite epiallopregnanolone sulfate is supraphysiologically raised in the serum of ICP patients. The molecular interaction between ICP associated levels of the 3β-sulfated progesterone metabolite epiallopregnanolone sulfate and the farnesoid X receptor (FXR) results in the aberrant expression of bile acid homeostasis. These along with 17β-oestradiol influence the metabolism of bile acids at various levels [2].

Exogenous progesterone supplementation early in pregnancy can cause increase in levels of progesterone metabolites and lead to ICP at earlier gestation. Several other exogenous factors are also associated with the development of ICP. One of the factors associated with development of ICP is lowered selenium levels and the other is the leaky gut, which increases absorption of bacterial endotoxins influencing the enterohepatic circulation of cholestatic metabolites of steroids and bile acids [1]. Bile acids play a significant role in pathophysiology of ICP and increase the risks of premature birth, meconium-stained amniotic fluid, respiratory distress syndrome and sudden fetal death [3].

PCOS is a complex disease associated with higher levels of androgens and estrogens in the circulating blood. Due to anovulation, progesterone levels are typically low. These low levels persist in first trimester and early second trimester till placental function takes over. Progesterone modulates the immune response of the mother to prevent rejection of the embryo and enhances uterine quiescence. Wang et al. did a retrospective analysis of 178 patients with cervical incompetence. Of these, 80 cases (44.9%) exhibited PCOS comorbidity. Compared with the non-PCOS group, the PCOS group exhibited worse pregnancy outcomes (31.1% miscarriage, 43.8% preterm birth and 25% term birth). The outcomes were even worse for patients with additional comorbidity of insulin resistance which was statistically significant ($p = 0.03$). They concluded that treatment of cervical incompetence in PCOS requires both obstetric and endocrine inputs [4]. Such patients need progesterone supplementation and are more likely to develop ICP at earlier gestational age.

Progesterone can be administered by three routes: oral, vaginal and intramuscular. The last ensures optimal blood levels but is painful and vaginal route does not give optimal levels. Oral route depends on patient compliance. The dose of natural micronized progesterone which can be given is 400–800 mg per day and the dose of 17-α-hydroxyprogesterone caproate (17-OHPC) that can be given is 250–500 mg per week. Saccone et al. [5] did a systematic review and meta-analysis of randomized controlled trials on progesterone supplementation for unexplained recurrent miscarriage. They concluded that supplementation with progestogens may reduce the incidence of unexplained recurrent miscarriages.

The addition of ursodeoxycholic acid (UDCA) improves the symptoms of ICP. It is postulated that UDCA works by displacing hydrophobic endogenous bile salts from the bile acid pool and protects hepatocytes from their toxic effects and enhances bile acid clearance across placenta from the fetus. Timely diagnosis and treatment is urged in order to prevent fetal complications and an early delivery between 37 and 38 weeks should be contemplated in severe cases, especially once fetal lung maturity is attained [1].

With the increasing incidence of PCOS, more and more patients need IUI and IVF-ET. Progesterone supplementation is advisable but the ideal route and dose is still debatable. The development of early onset ICP can be due to high-dose progesterone supplementation in early pregnancy; hence, lowest possible dose of progesterone should be used and should be withdrawn at the earliest.

Compliance with Ethical Standards

Conflict of interest The authors report no conflict of interest.

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