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Clinical and Pathophysiological Aspects of Intrahepatic Cholestasis of Pregnancy

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ABSTRACT

Objective: The pathogenesis of intrahepatic cholestasis of pregnancy (ICP) involves impaired bile acid and estrogen/progesterone metabolism and excretion based on genetic and environmental factors. In this thesis we evaluated different pathophysiological and clinical aspects of ICP, i.e., serum levels of vitamin D, the morphology of ICP placentas, maternal and fetal outcomes in ICP at a time of active management, and ICP-associated pregnancy conditions.

Methods: In Paper I, we performed an observational study and compared the levels of active vitamin D (1,25-dihydroxy vitamin D3) in women with ICP and normal pregnancies. In Paper II we examined in a prospective case-control study morphological differences of placentas from untreated and ursodeoxycholic acid (UDCA) treated ICP, respectively, and normal pregnancies, by using stereology and systematic random sampling. In paper III, we estimated in a nationwide cohort study of more than 1.2 million singleton births in Sweden between 1997 and 2009 the actual prevalence of ICP and its association with adverse pregnancy and fetal outcomes, using data of the Swedish Medical Birth Registry (MBR). In Paper IV, we assessed in a hospital based retrospective cohort study the risk of emergency cesarean section (CS) and fetal asphyxia in ICP women with spontaneous and induced onset of labor at gestational weeks 37-39, by linkage of the MBR and a local obstetrical database.

Results: We report for the first time that women with ICP have lower levels of active vitamin D. We also show that ICP substantially affects the morphology of the placenta, with increased surface capillary area and syncytial knots. These changes were not observed in UDCA-treated ICP. In our nationwide population based study, we found a previously unknown strong association of ICP with gestational diabetes, preeclampsia and large for gestational age, and that ICP bears an increased risk of moderate prematurity but not of stillbirth at a time of active management. We found that induction of labor in women with ICP in gestational weeks 37-39 in a tertiary Swedish hospital did not increase the risks of emergency CS or fetal asphyxia.

Conclusions: Decreased levels of active vitamin D may contribute to the pathogenesis of ICP. ICP causes morphological changes in the placenta that might be improved by treatment with UDCA. Induction of labor in ICP does not increase the rate of emergency CS. The low risk of stillbirths at a time of modern management of ICP is reassuring but the strong association of ICP with gestational diabetes and preeclampsia needs consideration, e.g., by oral glucose tolerance testing and proper management of possibly coexisting conditions.

Keys words: Intrahepatic cholestasis of pregnancy, bile acids, vitamin D, placenta, stereology, labor induction, cesarean section, preeclampsia, gestational diabetes