Intrahepatic cholestasis of pregnancy

Akademisk avhandling

Som för avläggande av medicine doktorsexamen kommer att offentligen försvaras i aulan,
Kvinnokliniken, Sahlgrenska Universitetssjukhuset / Östra, Göteborg
Fredagen 24 mars, 2006, kl 09.00

av

Anna Glantz

Avhandlingen baseras på följande delarbeten:


IV. Intrahepatic cholestasis of pregnancy: serum bile acid composition and urinary disulphated progesterone metabolites during treatment with dexamethasone or ursodeoxycholic acid. Glantz A, Bentin L, Lammert F, Mattsson LA, Marschall HU. Manuscript

Fakultetsoppfunget: Docent Göran Berg
Avd. för Obstetrik och Gynekologi
Linköpings Universitet

Handledare: Professor Lars-Åke Mattsson
Docent Hanns-Ulrich Marschall
Intrahepatic cholestasis of pregnancy
Anna Glantz
Department of Obstetrics and Gynecology, The Institute of Clinical Sciences, Sahlgrenska Academy, Göteborg University, Göteborg, Sweden

Intrahepatic cholestasis of pregnancy (ICP) is a condition that has been reported to be associated with an increased fetal risk. A prospective study of ICP was conducted in the Västra Götaland region of Sweden between February 1, 1999 and January 31, 2002.

Objectives were to study:
I) The incidence of pruritus in pregnancy and ICP (defined as serum bile acid levels >10 µmol/L), the complications associated with ICP and whether complication rates correlate with serum bile acid levels, in an observational study with 690 subjects.
II) Whether fetal complication rates, laboratory parameters of cholestasis and pruritus could be reduced by treatment with ursodeoxycholic acid (UDCA) or dexamethasone in a randomised, placebo-controlled intervention trial with 130 participants.
III) If common haplotypes of the ABCB4-gene and the ABCB11-gene were associated with severe ICP. Fifty-two women with bile acid levels ≥40 µmol/L were included and compared to fifty-two healthy controls.
IV) If serum bile acid composition is dominated by cholic acid, if sulphated progesterone metabolites are found in urine and if serum bile acid composition and the relative amounts of sulphated progesterone metabolites would change during treatment with UDCA, dexamethasone or placebo in women with ICP. This study had 39 participants, who were also included in the intervention trial.

Results: Of 45,485 pregnancies leading to delivery in the region during the study period, 2.1% were complicated by pruritus of pregnancy and ICP was diagnosed in 1.5%. Of all women with ICP, 81% had the mild form with bile acid levels <40 µmol/L: no increase in fetal risk was found in these cases. Severe ICP (≥40 µmol/L) was diagnosed in 19%; fetal risk (spontaneous preterm delivery, asphyxial events and meconium-staining of amniotic fluid, placenta and membranes) was increased in these pregnancies. No reduction in fetal complications were found in the intervention study. Intention-to-treat-analysis showed reduction of alanine transferase (ALT) and bilirubin levels in the UDCA group. Sub-analysis of women with severe ICP showed reduction of serum bile acids in the UDCA and dexamethasone groups (greater reduction in the UDCA group) but reduction of pruritus was only associated with UDCA treatment. The genetic study showed that common haplotypes of the ABCB4-gene, but not of the ABCB11-gene, are associated with severe ICP. The metabolic study demonstrated ICP is characterised by a dominance (>50%) of cholic acid in the bile acid pool and that sulphated progesterone metabolites are found in ICP patients’ urine. Treatment with UDCA, but not dexamethasone, reduced relative amounts of sulphated progesterone metabolites in urine.

Conclusions: ICP occured in 1.5% of the pregnancies. Increased fetal risk was only associated with the severe form (serum bile acids ≥40 µmol/L), found in 19% of the cases. Treatment with UDCA reduced ALT and bilirubin levels regardless of the severity of ICP. In women with severe ICP, UDCA treatment alleviated pruritus and was more effective than dexamethasone in reducing serum bile acid levels. Common haplotypes of the ABCB4-gene were found to be associated with severe ICP. Women with ICP have increased relative amounts of cholic acid in serum and sulphated progesterone metabolite levels in urine, the latter of which was reduced by UDCA.

Key words: Intrahepatic cholestasis of pregnancy (ICP), pruritus, fetal risk, ursodeoxycholic acid, dexamethasone, ABCB4-gene, ABCB11-gene, haplotypes, sulphated progesterone metabolites.

ISBN 91-628-6754-7