Departments of Obstetrics and Gynecology, and Medical Genetics, Helsinki University Central Hospital, University of Helsinki, Finland

INTRAHEPATIC CHOLESTASIS OF PREGNANCY-
Genetic background, epidemiology and hepatobiliary consequences

Anne Ropponen

Academic Dissertation

To be presented by permission of the Medical Faculty of the University of Helsinki for public discussion in the Auditorium of the Department of Obstetrics and Gynecology, Helsinki University Central Hospital, Haartmanninkatu 2, Helsinki, on May 19th, 2006,
at 12 o'clock noon.

ABSTRACT

Intrahepatic cholestasis of pregnancy (ICP) is the most common cholestatic liver disease during pregnancy. The reported incidence varies from 0.4 to 15% of full-term pregnancies. The etiology is heterogeneous but familial clustering is known to occur. Here we have studied the genetic background, epidemiology, and long-term hepatobiliary consequences of ICP.

In a register-based nation-wide study (n=1 080 310) the incidence of ICP was 0.94% during 1987-2004. A slightly higher incidence, 1.3%, was found in a hospital-based series (n=5304) among women attending the University Hospital of Helsinki in 1992-1993. Of these 16% (11/69) were familial and showed a higher (92%) recurrence rate than the sporadic (40%) cases. In the register-based epidemiological study, advanced maternal age and, to a lesser degree, parity were identified as new risk factors for ICP. The risk was 3-fold higher in women >39 years of age compared to women <30 years. Multiple pregnancy also associated with an elevated risk. In a genetic study we found no association of ICP with the genes regulating bile salt transport (*ABCB4, ABCB11* and *ATP8B1*).

The livers of postmenopausal women with a history of ICP tolerated well the short-term exposure to oral and transdermal estradiol, although the doses used were higher than those in routine clinical use. The response of serum levels of sex hormone-binding globulin (SHBG) to oral estradiol was slightly reduced in the ICP group. Transdermal estradiol had no effect on C-reactive protein (CRP) or SHBG. A number of liver and biliary diseases were found to be associated with ICP. Women with a history of ICP showed elevated risks for non-alcoholic liver cirrhosis (8.2 CI 1.9-36), cholelithiasis and cholecystitis (3.7 CI 3.2-4.2), hepatitis C (3.5 CI 1.6-7.6) and non-alcoholic pancreatitis (3.2 CI 1.7-5.7).

In conclusion, ICP complicates around 1% of all full-term pregnancies in Finland and its incidence has remained unchanged since 1987. It is familial in 16% of cases with a higher recurrence rate. Although the cause remains unknown, several risk factors, namely advanced maternal age, parity and multiple pregnancies, can be identified. Both oral and transdermal regimens of postmenopausal hormone therapy (HT) are safe for women with a history of ICP when liver function is considered. Some ICP patients are at risk of other liver and biliary diseases and, contrary to what has been thought, a follow-up is warranted.