Tampere University

SUVI-TUULIA HÄMÄLÄINEN

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ACADEMIC DISSERTATION
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Responsible supervisor and Custos	Associate professor Markku Sumanen Tampere University Finland

Pre-examiners	Professor Juha Auvinen University of Oulu Finland	Docent Veli-Matti Ulander University of Helsinki Finland
Opponent	Professor Päivi Korhonen University of Turku Finland	

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Tampere 2019

To my family

&

in memory of my father

ABSTRACT

Intrahepatic cholestasis of pregnancy (ICP) is a liver disorder during pregnancy, and it occurs in 1% of pregnancies in Finland. In recent years, attention has been paid to the long-term effects of ICP. However, there is little information on the long-term health of women with a history of ICP. ICP has been found to be associated with an increased risk of liver, pancreatic and biliary disorders. One study found an association between ICP and liver and biliary tree cancer, autoimmune diseases, and cardiovascular diseases. In a questionnaire study, women reported higher frequencies of hypothyroidism and breast cancer. However, there are no previous studies on mortality and causes of death associated with previous ICP.

To investigate the long-term aspects of ICP, a cohort was collected for a period of 20 years. The cohort comprised all ICP pregnancies at Tampere University Hospital, Finland, between 1969 and 1988. For every ICP labour, previous and subsequent deliveries were obtained to form a control group. Altogether, the cohort comprised 571 women with ICP and 1,333 women as a reference.

The aim was to examine the health of Finnish women with a history of ICP using registries. To study the association between ICP and co-morbidity, the cohort's hospital discharge diagnoses were examined. The diagnoses were obtained from the Finnish Hospital Discharge Register, and the registry data included in this study contain all hospital discharge diagnoses in Finland from 1969 up to the end of 2013 as well as diagnoses from specialized outpatient care from 1998 to 2013. Women in the ICP group were diagnosed more with hypothyroidism and diseases of the digestive system, and the risk for hepatobiliary diseases and diseases of the pancreas in particular was increased. Arterial diseases were less common in the ICP group compared to the control group. Regarding other diseases, there were no differences in morbidity between the ICP and control groups.

The study included all reported cancers between 1953 and 1960 and all registered cancers – including the location and malignancy – between 1961 and 2013 for the cohort. The data were collected from the Finnish Cancer Registry. No significant differences between the ICP and control groups were found.

To study the association between ICP and mortality and survival, the cohort's deaths and causes of death were accessed for 1971–2015. The data were obtained

from Statistics Finland. Women with a history of ICP do not appear to have an increased overall mortality. However, deaths from gastrointestinal diseases were overrepresented among women with a history of ICP. In terms of survival from birth or ICP delivery, no differences were found between the ICP and control groups.

To investigate what kind of guidelines have been given to the physicians who treat women with ICP, a literature review was performed. This review was published in a Finnish medical journal.

A postal questionnaire was carried out to study the subjective health of the sons of mothers in the ICP group. There were no remarkable differences in terms of health between the sons of the ICP group and the sons of the control group.

This thesis confirms the results of previous studies and also brings new insights to the long-term aspects of ICP. Intrahepatic cholestasis of pregnancy seems to be associated with gastrointestinal diseases and hypothyroidism. Based on the literature and this study, the risk for hepatobiliary diseases and diseases of the pancreas is especially increased. It is no doubt a relief for women with a history of ICP that based on the registries, no associations were found between ICP and breast cancer. Based on this study, the risk for hepatobiliary cancer was not found to be increased among women who had experienced ICP. Nevertheless, a gastrointestinal disease was more often the cause of death among women with a history of ICP than it was among the controls.

It is commonly noted that autoimmune pathogenesis has a remarkable effect on hypothyroidism. There might also be an autoimmune aspect in the pathogenesis of ICP. Mutations in gene ABCB4 in ICP and cholelithiasis might be an example of the shared risk factors that may influence the pathogenesis of ICP and other diseases of the digestive system.

In primary health care, attention should be paid to certain illnesses when encountering women with a history of ICP later in their life. This study does not investigate whether women with a history of ICP should be screened for gastrointestinal diseases or hypothyroidism. However, it confirms the importance of anamnesis in guiding the conclusions of the clinician.

In the future, even longer follow-up studies are required to study the association between ICP and mortality and co-morbidity. New guidelines for clinicians should be considered, as there is growing evidence of the long-term effects of ICP.

TIIVISTELMÄ

Raskaushepatoosi on raskauden aikainen sapen salpaus, johon sairastuu noin 1 % suomalaisista synnyttäjistä. Siihen liittyy monia sikiön riskejä ja vasta viime vuosina on huomiota kiinnitetty raskaushepatoosin pitkäaikaisvaikutuksiin.

Raskaushepatoosin pitkäaikaisvaikutuksia naisen terveyteen on tutkittu vasta hyvin vähän. Raskaushepatoosiin on havaittu liittyvän suurentunut riski maksa-, sappi- ja haimasairauksille. Yhdessä tutkimuksessa havaittiin raskaushepatoosin sairastaneilla naisilla lisääntynyt riski maksa- ja sappisyövälle sekä autoimmuuni- ja sydän- sekä verisuonitaudeille. Suomalaisessa kyselytutkimuksessa raskaushepatoosin sairastaneet naiset ilmoittivat enemmän rintasyöpää ja kilpirauhasen vajaatoimintaa kuin verrokit. Raskaushepatoosin sairastaneiden naisten pitkäaikaista kuolleisuutta ja kuolinsyitä ei ole aiemmin tutkittu.

Väitöskirjatyössä tutkitaan raskaushepatoosin pitkäaikaisvaikutuksia 20 vuoden ajalta kerätyn tutkimusjoukon avulla. Tutkimusjoukkoon kerättiin kaikki Tampereen yliopistollisessa sairaalassa raskaushepatoosin sairastaneet naiset vuosien 1969 ja 1988 väliltä. Jokaiselle naiselle otettiin verrokki edeltävästä ja seuraavasta synnytyksestä. Siten tutkimusjoukossa oli 571 raskaushepatoosin sairastanutta naista ja 1333 verrokkia.

Tutkimuksen tarkoituksena oli tutkia raskaushepatoosin sairastaneiden naisten terveyttä rekistereitä käyttäen. Raskaushepatoosin ja sairastavuuden yhteyden tutkimiseksi tutkimusjoukolta kerättiin tiedot hoitoilmoitusrekisteristä. Tämän rekisterin avulla tutkimusjoukolta kerättiin tieto kaikista sairaaloiden hoidonpäättödiagnooseista vuosilta 1969–2013 ja erikoissairaanhoidon poliklinikkakäyntien diagnoosit vuosilta 1998–2013. Raskaushepatoosin sairastaneet naiset näyttävät kuitenkin sairastavan muuta väestöä enemmän kilpirauhasen vajaatoimintaa ja ruuansulatuselinten sairauksia, erityisesti riski maksa- ja sappisairauksille sekä haiman sairauksille on suurentunut. Valtimotauteja raskaushepatoosin sairastaneet naiset sairastavat vähemmän kuin verrokit. Suurimmassa osassa diagnoosiryhmiä ei raskaushepatoosin sairastaneiden ja verrokkien välillä ollut eroa.

Väitöskirjatyöhön sisältyy kaikki tutkimusjoukon syöpärekisteriin ilmoitetut syövät vuosien 1953 ja 1960 väliltä ja kaikki syövät vuosilta 1961–2013. Todetuista syö-

vistä selvitettiin sijainti ja pahanlaatuisuus. Merkittäviä eroja syöpäsairastavuudessa ei raskaushepatoosin sairastaneiden ja verrokkien välillä havaittu.

Kuolleisuuden ja elossa olon tutkimiseksi kerättiin tutkimusjoukolta tieto kaikista kuolemista Tilastokeskukselta. Kuolinsyyt ja -päivät kerättiin vuosien 1971 ja 2015 väliltä. Raskaushepatoosin sairastaneilla naisilla ei ole kohonnutta kokonaiskuolleisuutta verrokkeihin nähden. Kuitenkin ruuansulatuselinsairauksien osuus oli kuolinsyissä suurempi raskaushepatoosin sairastaneilla naisilla kuin verrokeilla. Elossa olossa ei ryhmien välillä ollut eroa tarkastellen joko iän tai raskaushepatoosisynnytyksen suhteen.

Hoitosuosituksien kartoittamiseksi kirjoitettiin katsaus raskaushepatoosista Suomen Lääkärilehteen. Yhtenä väitöskirjan osatyönä suoritettiin postikysely raskaushepatoosin sairastaneiden naisten ja verrokkien poikalapsille. Näiden miesten terveydessä ei vaikuta olevan eroa.

Väitöskirjatyö vahvistaa aiempaa tutkimustietoa, mutta tuo myös uusia näkökulmia raskaushepatoosin pitkäaikaisvaikutuksiin. Raskaushepatoosi näyttää olevan yhteydessä ruuansulatuselinten sairauksiin ja kilpirauhasen vajaatoimintaan. Tutkimuksen ja kirjallisuuden perusteella erityisesti riski maksa-, sappi- ja haimasairauksille on suurentunut. Raskaushepatoosin sairastaneet naiset kuolevat useammin ruuansulatuselinten sairauksiin kuin muu väestö. Tutkimus ei vahvista aiempaa havaintoa raskaushepatoosin ja rintasyövän yhteydestä. Tutkimuksessa ei havaittu yhteyttä maksa- tai sappiteiden syövälle ja raskaushepatoosille.

Autoimmuniteetin merkitystä pidetään selvänä kilpirauhasen vajaatoiminnan kehittymisessä. Myös raskaushepatoosin kehittymisessä sillä saattaa olla vaikutusta. ABCB4-geenin mutaatiot raskaushepatoosissa ja sappikivitaudissa ovat esimerkki mahdollisesta jaetusta riskitekijästä, joka voi vaikuttaa sekä raskaushepatoosin että muiden ruuansulatuselinten sairauksien riskiin.

Perusterveydenhuollossa tulee kiinnittää huomiota raskaushepatoosin sairastaneeseen naiseen. Erityistä huomiota tarvitaan tutkimuksessa havaittuihin lisääntyneisiin riskeihin ja lisäsairastavuuteen naisen myöhemmän elämän aikana. Tässä tutkimuksessa ei selvitetty hepatoosin sairastaneiden naisten seulontaa. Tutkimus vahvistaa käsitystä anamneesin tärkeydestä ohjaamassa kliinikon päätelmiä.

Tulevaisuudessa vieläkin pidempiä seurantatutkimuksia tarvitaan, jotta voidaan vahvistaa raskaushepatoosin ja sairastavuuden sekä kuolleisuuden yhteyksiä. Uusia hoitosuosituksia tulisi pohtia, kun lisääntyvästi saadaan tietoa raskaushepatoosin pitkäaikaisvaikutuksista terveyteen.

CONTENTS

ABBREVIATIONS

AFOS = alkaline phosphatase
ALAT = alanine aminotransferase
ASAT = aspartate aminotransferase
BA = bile acids
FHDR = Finnish Hospital Discharge Register
FXR = farsenoid X receptor
GLP-1 = glucagon-like peptide-1
GLUT-4 = glucose transporter type 4
GSTA = Glutathione S-transferase alpha
HDL = high-density lipoprotein
ICP = intrahepatic cholestasis of pregnancy
LDL = low-density lipoprotein
LGA = large for gestational age
SAMe = S-adenosylmethionine
TBA = total bile acids
TGR5 = M-BAR = GP-BAR1 = membrane-bile acid receptor
TUH = Tampere University Hospital
UDCA = ursodeoxycholic acid

LIST OF ORIGINAL PUBLICATIONS

The thesis is based on the following publications. These publications are referred to as Studies I–VI in the text. The articles are included with the permission of the copyright owners.

I Hämäläinen ST, Turunen K, Mattila K, Uotila J, Sumanen M. 2016. Raskaushepatoosi – hankala, mutta ohimenevä vaiva. SLL 15:1059-1063.

II Hämäläinen ST, Turunen K, Mattila KJ, Kosunen E, Sumanen M. 2019. Intrahepatic cholestasis of pregnancy and co-morbidity: A 44-year follow-up study. Acta Obstet Gynecol Scand 00:1-6.

III Hämäläinen ST, Turunen K, Mattila KJ, Kosunen E, Sumanen M. 2017. Intrahepatic Cholestasis of Pregnancy and Cancer: A Cohort Study. Fam Med Med Sci Res 6:216.

IV Hämäläinen ST, Turunen K, Mattila KJ, Kosunen E, Sumanen M. 2019. Long-term survival after intrahepatic cholestasis of pregnancy: A follow-up of 571 mothers. EJOG 240:109-112.

V Hämäläinen ST, Turunen, K, Mattila KJ, Sumanen, M. 2018. Intrahepatic cholestasis of pregnancy and associated causes of death: A cohort study with follow-up of 27-46 years. BMC Womens Health 18:98.

VI Hämäläinen ST, Turunen K, Kosunen E, Mattila KJ, Sumanen M. 2016. Men's Health Is Not Affected by Their Mothers' Intrahepatic Cholestasis of Pregnancy. Am J Mens Health 10:71-77.

1 INTRODUCTION

Intrahepatic cholestasis of pregnancy (ICP) is a liver disorder during pregnancy in which bile flow is diminished. It usually manifests during the third trimester of gestation. Pruritus, especially on the palms and soles, is the leading symptom. Additionally, liver transaminases and/or bile acids are elevated.

In recent years, there has been a growing interest in the long-term health of women who have experienced ICP. Nevertheless, there is a need for reassess the findings, as little is known about the mortality or survival of women with a history of ICP.

This study investigates the long-term health women with a history of ICP using an objective methodology: registries. In addition, a questionnaire study for the sons of such women was carried out to investigate their long-term health. Furthermore, knowledge about intrahepatic cholestasis of pregnancy was spread to Finnish doctors via a review in a national medical journal.

2 REVIEW OF THE LITERATURE

2.1 Terminology of intrahepatic cholestasis of pregnancy

In 1883, F. Ahlfeld described intrahepatic cholestasis of pregnancy as recurrent jaundice in pregnancy that resolved following delivery (Geenes and Williamson 2009). In the 1950s, case reports mentioned pruritus with or without jaundice completely resolving after delivery and noted high recurrence rates in following pregnancies (Svanborg 1954, Thorling 1955).

Earlier ICP has been addressed as jaundice in pregnancy, recurrent jaundice in pregnancy, idiopathic jaundice of pregnancy, obstetric hepatosis, hepatosis gestationalis and obstetric cholestasis (Geenes and Williamson 2009). Nowadays, obstetric cholestasis is used to describe ICP.

2.2 Epidemiology

The incidence of ICP varies extensively based on ethnicity and geographic location. In the 1970s, the overall prevalence was 10% in Chile and as high as 28% among Araucanian Indians (Reyes et al. 1978). Thereafter, the prevalence of ICP in Chile has decreased to 1.5–4% of all pregnancies (Reyes 2008). In parts of Europe, the incidence is 0.1–0.2%, but a higher prevalence has been reported in the Scandinavian countries (Lammert et al. 2000, Ozkan et al. 2015). In Finland, the ICP incidence is approximately 1.0–1.5% (Ropponen 2006).

The risk for obstetric cholestasis seems to depend on age and parity. The risk has been shown to be three-fold higher in women over 39 years old compared to women under 30 years old (Ropponen 2006). Another study found an increased risk for ICP among women over 35 years (Heinonen and Kirkinen 1999). By comparison, teenage pregnancy was not associated with ICP in a large population-based study (Raatikainen et al. 2006). Nulliparous women were found to have an increased incidence of ICP, at 1.24%, compared to the incidence of multiparous women, at 0.80% (Ropponen 2006). Maternal age and parity were consequently found to interact with multiple pregnancy to increase the risk for ICP (Ropponen 2006).

However, multiple pregnancy has been found to act independently and elevate the risk for ICP (Ropponen 2006). The incidence has been found to be nearly 17% in the first multiple pregnancy of women over 39 years (Ropponen 2006). Additionally, in vitro fertilization seems to increase the risk for ICP nearly four-fold (Koivurova et al. 2002), and serum bile acid levels have been found to be higher in IVF than in spontaneous pregnancies with ICP (Bolukbas et al. 2017). ICP has been found to recur in 40–70% of subsequent pregnancies (Reyes 1997, Hay 2008).

2.3 Aetiology and pathogenesis

The aetiology of intrahepatic cholestasis of pregnancy is multifactorial. Aetio-pathology is influenced by environmental factors, hormonal factors and genetics. Estimates are that 10–15% of ICP cases can be explained by known genetic variation (Geenes et al. 2016).

Environmental factors seem to interact in the pathogenesis of cholestasis of pregnancy. Selenium deficiency and reduced glutathione peroxidase activity are associated with its aetio-pathogenesis (Kauppila et al. 1987, Reyes et al. 2000). This may be due to their effects on bile formation and secretion, as bile enzymes need selenium to work properly. In winter, the incidence of ICP has been shown to be increased (Berg et al. 1986), and women with a history of ICP have been shown to have a lower vitamin D status at mid-gestation or delivery compared with controls (Dror 2011). A major indicator of foetal distress, meconium staining, is inversely correlated with lower 1,25-D3 levels in ICP (Wikström, Shemer and Marschall 2010). Two hours after breakfast and supper, greater glucose concentrations in serum samples were reported among women with ICP when compared with healthy controls (Wojcicka-Jagodzinska et al. 1989).

Metabolic markers are related in the pathogenesis of obstetric cholestasis. Postprandial plasma glucose levels have been found to be higher in women with ICP than in controls when using a continuous glucose monitoring system at home (Martineau et al. 2015). The same study revealed a 30% incidence of gestational diabetes after the ICP diagnosis. The association between ICP and gestational diabetes has also been observed before (Baliutaviciene et al. 2011, Martineau et al. 2014, Wikström Shemer et al. 2013). Elevated serum levels of triglycerides and total and LDL cholesterol, as well as a decrease in HDL cholesterol, have been associated with the disease (Martineau et al. 2015, Dann et al. 2006, Nikkilä et al. 1996, Johnson 1973). Lipoprotein lipase expression has been shown to be increased limitedly in

maternal plasma, and disturbances in lipid profiles were reported among women with ICP (Hao et al. 2016).

The association between cholestasis of pregnancy and changes in lipid and glucose metabolism may be augmented by a decline in the activity of the bile acid receptors FXR and TGR5, which are associated with lipid and glucose metabolism (Fiorucci et al. 2009, Sharma et al. 2011). A rise in sulphated progesterone metabolites is associated with ICP pregnancies (Glantz et al. 2008). The rise includes the 3β-sulphated progesterone metabolite epiallopregnanolone sulphate, which has been shown to antagonize FXR (Abu-Hayyeh et al. 2013). Gluconeogenesis has been shown to be weakened by the bile acid activation of FXR (Ma et al. 2006, Y. Zhang et al. 2006, Yamagata et al. 2004) and to induce the insulin-regulated glucose transporter GLUT-4 (Shen et al. 2008). Thus, the rise in blood glucose levels observed in ICP may be explained by disruption in these homeostatic pathways. Glucose and bile acids have been reported to act synergistically to stimulate insulin release through FXR-mediated pathways (Renga et al. 2010, Seyer et al. 2013, Dufer et al. 2012). TGR5 is promoted by enteric bile acids and results in GLP-1 release and the promotion of pancreatic β-cell function (Thomas et al. 2009, Parker et al. 2012, Jansen 2010). In the condition, the insulinotropic effect of prandial bile acid release might be both directly and indirectly attenuated due to disruption of the enterohepatic circulation. Postprandial concentration of GLP-1 has been reported to be lower among women with ICP (Martineau et al. 2015). The possibly reproductive hormone-related antagonism of FXR is a result of a fall in the levels of HDL cholesterol and apolipoprotein A1 in pregnant women with ICP (Dann et al. 2006).

The inheritance of ICP is under considerable research. It is assumed to run dominantly in an autosomal or X-chromosome-linked fashion (Holzbach et al. 1983, Hirvioja and Kivinen 1993). Several genes or their mutations have been proposed to be associated with the condition. For Finnish patients, a mutation of chromosome region 2p13 is reported to indicate maternal susceptibility (Heinonen et al. 2001).

The association of canalicular transporter ABCB4 with ICP has been studied. Firstly, homozygous mutations of this gene were identified in progressive familial intrahepatic cholestasis (de Vree et al. 1998). Secondly, an ICP pedigree with a segregating mutation in the absence of progressive familial intrahepatic cholestasis was identified (Jacquemin et al. 1999). Thirdly, the first sporadic case of ICP caused by a heterozygous mutation was identified (Dixon et al. 2000). Thereafter, several studies have investigated the range of mutant alleles in this gene associated with ICP.

In recent studies, a vital role for common variation around the ABCB4 and ABCB11 loci has been noted (Dixon et al. 2014, Anzivino et al. 2013, Dixon et al. 2009).

Mutations in transporter ABCB11 have been noted to play a role in ICP. Both novel and recurrent mutations have been recognized in ICP cohorts (Pauli-Magnus et al. 2004). In addition, many other canalicular transporters affect bile formation and membrane stability in hepatocytes. ATP8B1 mutations have been suggested to play a possible role in some cases (Painter et al. 2005, Müllenbach et al. 2005). In a South American cohort, ABCC2 was suggested to affect ICP (Sookoian et al. 2008), although the finding could not be replicated in a larger European cohort (Dixon et al. 2014).

The aetiology seems to be related to the cholestatic effect of reproductive hormones in genetically sensitive women (Williamson and Geenes 2014). Progesterone and oestrogen have been shown to be associated with the pathogenesis of ICP. ICP typically manifests in the third trimester of pregnancy when oestrogen levels are at their maximum (Ozkan et al. 2015). This finding suggests that oestrogen takes part in ICP's pathogenesis. Higher level of oestrogen is associated with multiple pregnancy, and the risk for a multiple pregnancy is 2.5- to five-fold higher with ICP (Gonzalez et al. 1989, Turunen et al. 2010). Orally administered progesterone used to prevent preterm labour was associated with pruritus or jaundice and elevated fasting serum levels of total bile acids (Bacq et al. 1997). This indicates that progesterone plays a role in the pathogenesis of obstetric cholestasis. Further supporting the hypothesis, some women with a history of ICP have had a recurrence of symptoms and biochemical abnormalities with oral contraceptives (Williamson et al. 2004). Additionally, the role of prolactin is under study (Bulaeva et al. 2017).

There have been studies suggesting an association between cholestatic liver disease and inflammatory processes (Kosters and Karpen 2010, Allen et al. 2011). There has also been a study suggesting that dendritic cells participate in damaging maternal-foetal immune tolerance, and this might be associated with the differentiation of T helper 17 and regulatory T cells, causing ICP (Kong et al. 2018).

2.4 Diagnosis

The diagnosis of intrahepatic cholestasis of pregnancy is based on maternal pruritus and raised levels of liver enzymes and/or serum bile acids. To diagnose ICP, other possible reasons for pruritus and biochemical abnormalities must be excluded.

Pruritus itself is common in pregnancy, as it occurs in nearly one in four pregnancies (Kenyon et al. 2010).

Approximately 80% of ICP cases present after 30 weeks of gestation (Kenyon et al. 2002, Geenes et al. 2014). However, the onset of ICP has been reported even at 8 weeks of gestation (Berg et al. 1986). Thirty-four weeks is suggested to be the cut-off time for the diagnosis of early-onset ICP (Lin et al. 2017).

2.4.1 Symptoms

Pruritus is the key symptom in the diagnosis of ICP. It is presented typically on the palms and soles, but it can be generalized (Bacq and Sentilhes 2014, Ozkan et al. 2015, Williamson and Geenes 2014). In one study, 86% of women with ICP had generalized pruritus (Sharma et al. 2016). Many women experience worsening symptoms at night, and thereafter sleep is disturbed (Geenes et al. 2016, Ahmed et al. 2013). As liver function may deteriorate, pruritus often worsens as the pregnancy advances (Geenes et al. 2016). ICP is characterized by the pruritus of otherwise healthy skin. However, secondary excoriation marks, pigmented lesions, friction blisters and abrasions may be present (Geenes et al. 2016).

Symptoms of cholestasis may occur. Dark urine, pale stools and right upper quadrant pain may be present (Geenes et al. 2016). In addition, steatorrhea, mal-absorption of fat-soluble vitamins and weight loss may occur (Ahmed et al. 2013). However, less than 10% of women with ICP have jaundice (Geenes et al. 2016).

2.4.2 Biochemical abnormalities

Normal pregnancy seems to be mildly cholestatic (Castano et al. 2006, Pascual et al. 2002). Bile acids are toxic, so their homeostasis needs to be strictly regulated (Geenes et al. 2016). In clinical practice, it is important to remember that pruritus may precede biochemical abnormalities (Kenyon et al. 2001). If the unexplained pruritus continues, laboratory markers should be taken repeatedly every one or two weeks.

Usually, alanine aminotransferase (ALAT) and bile acids are used in the diagnostics. It has been suggested that the upper limit of the normal reference range for ALAT should be reduced 20% during pregnancy (Girling et al. 1997). During ICP, ALAT levels may rise two- to ten-fold (Geenes and Williamson 2009), and it is considered a sensitive test for ICP (Bacq et al. 1997). Increase in total bile acids (TBA) is a highly sensitive marker of the disease (Heikkinen et al. 1981, Shaw et al.

1982, Bacq et al. 1997, Lunzer et al. 1986). The generally accepted upper limit of normal TBA in the serum is 10 μmol/L. Some studies also use the limit of ≥6 the threshold value of bile acids (Joutsiniemi et al. 2014). TBA may rise to 100 times the upper limit of normal (Sjövall and Sjövall 1966, Heikkinen et al. 1981). Taurocholate is the main bile acid to increase in ICP (Pataia et al. 2017).

Other liver function tests may also be used. Glutathione S-transferase alpha (GSTA) is reported to be a more sensitive and specific marker of hepatic damage than other liver function tests (Knapen et al. 2000, Hayes et al. 1988, Beckett and Hayes 1993). GSTA has been reported to rise in cases of ICP, and it has been proposed to be used for the early diagnosis of cholestasis of pregnancy (Joutsiniemi et al. 2008, Dann et al. 2004).

Not all liver function tests can be used to diagnose ICP. Alkaline phosphatase (AFOS) typically rises during pregnancy (Bacq et al. 1996). The rise is usually of placental origin, so AFOS cannot be used for the diagnosis of ICP (Geenes and Williamson 2009). Bilirubin is not used for diagnostic purposes because it is at a normal level in the majority of ICP cases. If abnormally high levels of bilirubin are detected, it is conjugated hyperbilirubinemia (Heikkinen 1983).

In the future, some new biochemical markers might become useful in the grading and early diagnosis of ICP. Increased white blood cell counts, mean platelet volume, the platelet-to-lymphocyte ratio and decreased red blood cell distribution have been associated with ICP (Yayla Abide et al. 2017). Mean platelet volume was found to increase with the severity of ICP, but clinical use for predicting the severity of ICP needs further research (Yayla Abide et al. 2017). High red cell distribution width has been associated with the incidence of meconium staining in women with ICP (Vural Yilmaz et al. 2017). This is a potential novel laboratory test marker, which indicates a meconium staining risk in labour. Matrix metalloproteinase-2 and -9 might become useful in diagnosing and grading ICP (Chen et al. 2017).

2.4.3 Differential diagnostics

Other reasons for cholestasis should be sought out. The most important ones are hepatitis and cholelithiasis. In patients who have a high increase in ALAT levels, current viral hepatitis should be ruled out (Bacq et al. 1997). The incidence of cholelithiasis is suggested to be 0.5–2% among pregnant women (Ko et al. 2005, Ko 2006), and pregnancy is considered a risk factor for it (Jorge et al. 2015).

Other diseases may cause an increase in liver function tests, but the following diseases do not typically cause pruritus. Pre-eclampsia and acute fatty liver of pregnancy may rarely be associated with ICP, as they all occur during the last trimester of pregnancy (Bacq 2011). Additionally, hyperemesis gravidarum may result in an abnormal liver function test, but this normalizes as the pregnancy continues (Williamson and Geenes 2014).

Moreover, cytomegalovirus, Epstein–Barr infection and drug-induced liver injury may cause challenges in differential diagnostics (Bacq and Sentilhes 2014, Royal College of Obstetricians & Gynaecologists 2011). Cholestasis can also be caused by a urinary tract infection, and it may associate with ICP (Bacq and Sentilhes 2014). During pregnancy, existing chronic liver disease may worsen (Bacq and Sentilhes 2014) and be unmasked (Pataia et al. 2017). Examples of this include primary biliary cirrhosis and primary sclerosing cholangitis (Williamson and Geenes 2014).

There are pregnancy-specific causes of pruritus. One similar presentation of pruritus other than ICP is pruritus gravidarum, although there are no biochemical abnormalities (Williamson and Geenes 2014). Furthermore, pruritus may be caused by atopic eruption of pregnancy, polymorphic eruption of pregnancy or pemphigoid gestationis (Williamson and Geenes 2014). Prurigo of pregnancy and pruritic folliculitis of pregnancy are also possible causes of pruritus (Williamson and Geenes 2014).

2.5 Risks of ICP for the mother and foetus at the time of delivery

In a recent study, maternal deaths were investigated during hepatic dysfunction in pregnancy. In the study, there were no maternal deaths after delivery (Suresh et al. 2017). Postpartum blood loss was no different compared to controls in the women with ICP who were treated with ursodeoxycholic acid (UDCA) and women who had a planned delivery (Furrer et al. 2016).

In a meta-analysis, elevated maternal bile acids were significantly associated with increased risks of overall adverse perinatal outcomes, preterm birth, meconium-stained amniotic fluid, asphyxia or respiratory distress syndrome (Cui et al. 2017). ICP has been linked to 2–4% of foetal deaths (Fisk and Storey 1988, Alsulyman et al. 1996), although not all studies confirm such a high foetal mortality (Turunen et al. 2010, Sharma et al. 2016, Wikström Shemer et al. 2013).

Maternal serum bile acid levels could be used as a predictor for the risk of adverse perinatal outcomes (Cui et al. 2017). When maternal bile acid concentrations are ≥40 μmol/l, the risk for adverse foetal outcome has been found to be increased (Geenes et al. 2014, Glantz et al. 2004). Recently, the increased risk of stillbirth was shown to be higher in singleton ICP pregnancies at bile acids concentrations ≥100 μmol/l. The risk of stillbirth in ICP pregnancies with bile acids <100 μmol/l seems to be similar to the risk of the general population (Ovadia et al. 2019). The risks for the foetus seem to be caused by increased bile acids in the foetus. Normally in pregnancy, the bile acid (BA) gradient ensures that BAs are transported from the foetus to the mother. In intrahepatic cholestasis of pregnancy, the gradient has been shown to be reversed (Geenes et al. 2014).

The underlying mechanisms of foetal complications are not fully known. High BA levels seem to have a harmful effect on cardiomyocytes, causing arrhythmia (Gorelik et al. 2004, Gorelik et al. 2002, Williamson et al. 2001). The increased incidence in stillbirths could possibly be explained by this phenomenon if these potentially lethal arrhythmias also occur in the foetus. Regarding adult electrocardiographs, the PR interval is reported to be a potential marker of arrhythmia development, such as atrial fibrillation, heart block and tachyarrhythmias (Schnabel et al. 2009, Simpson et al. 1982). During the second and third trimester, foetal supraventricular tachycardia and atrial fibrillation has been shown to occur in ICP (Shand et al. 2008, Al Inizi et al. 2006). The foetuses of mothers with ICP have been reported to have a higher PR interval (Strehlow et al. 2010), which might be linked to foetal arrhythmias.

Placental chorionic veins are reported to be influenced by the vasoconstrictive effect of bile acids (Sepulveda et al. 1991), which may explain foetal distress, asphyxia and mortality. Additionally, oxytocin receptor expression and sensitivity in the human myometrium is reported to increase because of BA (Germain et al. 2003, Israel et al. 1986). This may be the mechanism of spontaneous preterm delivery in ICP. Maternal cholestasis may also have an impact on neonatal lung surfactant and cause atelectasis for the foetus in women with ICP affected by a genetic mutation (Zhang et al. 2015).

Studies investigating the association between foetus size and intrahepatic cholestasis of pregnancy have been performed. An association between the incidence of infants being large for gestational age (LGA) and ICP was found even after excluding women with gestational diabetes (Wikström Shemer et al. 2013). Independently of glucose levels, elevated serum triglycerides have been suggested to promote foetal growth (Herrera and Ortega-Senovilla 2010), which gives a possible

explanation for the increase in foetal growth in ICP. On the contrary, a meta-analysis found ICP to be associated with a lower birth weight compared to controls (Li et al. 2017). Compared to controls, the risk for a lower infant birth weight in mothers with ICP was increased in a Finnish study (Turunen et al. 2010).

The onset of cholestasis of pregnancy is linked to pregnancy outcome. Early-onset ICP is associated with a higher incidence of preterm labour, foetal distress and foetal low birth weight compared to late-onset ICP (Lin et al. 2017, Li et al. 2017, Estiu et al. 2017). Women with ICP and dichorionic diamniotic twin pregnancies have been associated with adverse perinatal outcomes when the onset is before 30 weeks of gestation, TBA is >40 μml/l, aspartate aminotransferase (ASAT) is >200 U/l and AFOS is >400 U/l (Mei et al. 2017).

2.6 Management and treatment of ICP

2.6.1 Management and care of pregnancy

When a suspicion of intrahepatic cholestasis of pregnancy arises, the pregnant mother is referred to an obstetric clinic. The management and follow-up are individual and based on case series and/or consensus. It is recommended that liver function tests are measured weekly during pregnancy (Royal College of Obstetricians & Gynaecologists 2011). Cardiotocography and ultrasound are monitored according to individual assessment.

2.6.2 Medication

2.6.2.1 Ursodeoxycholic acid

Ursodeoxycholic acid (UDCA) is the most common treatment for ICP (Pataia et al. 2017). It can be considered the first-line treatment (Bacq et al. 2017). UDCA is considered a safe treatment during pregnancy (Parizek et al. 2016). The treatment is quite well tolerated, and the most common side effects are nausea, vomiting and loose stools (Chappell et al. 2012).

UDCA is a relatively hydrophilic bile acid, and it comprises 1–3% of human BAs (Pataia et al. 2017). The mechanism of UDCA treatment is suggested to have three

main aspects. Firstly, it stimulates BA transporter synthesis, targeting and insertion into the hepatocyte membrane, and thus promotes BA secretion from the hepatocytes. Secondly, UDCA prevents the apoptotic effects of more hydrophobic BAs on mitochondria. Thirdly, it affects micelle formation, buffers BA toxicity and decreases bile hydrophobicity (Beuers 2006).

UDCA has been reported to ameliorate pruritus (Glantz et al. 2008). The relief of the symptoms was not correlated with a reduction in serum bile acid levels, but with changes in decreased progesterone disulphate excretion in the urine (Glantz et al. 2008). According to a meta-analysis that compared UDCA to placebo, UDCA was reported to improve pruritus and liver function tests and reduce bile acid levels (Kong et al. 2016). A double-blind randomized placebo-controlled trial was recently published that is five times larger than the largest previous trial. UDCA had no clinically meaningful effect on maternal itching symptoms nor did it reduce bile acid levels (Chappell et al. 2019).

UDCA is shown partially to reverse the GLP-1 deficit (Martineau et al. 2015). After initiation of UDCA therapy, increased GLP-1 release and a decrease in plasma glucose levels have been reported (Murakami et al. 2013).

The evidence suggests that the effect of foetal well-being is aggregative. An *in vitro* rat model involving UDCA found the treatment to have a protective antiarrhythmic role for the foetal heart (Miragoli et al. 2011). Additionally, an *in vitro* model of the human foetal heart showed the protective effect of UDCA via a reduction in fibroblast differentiation into myofibroblasts and the hyperpolarization of myofibroblasts (Schultz et al. 2016). In addition, UDCA restores T-type calcium in the foetuses of mothers with ICP and prevents ventricular conduction slowing and arrhythmia (Adeyemi et al. 2017). UDCA has been reported to protect neonatal rat cardiomyocytes from the arrhythmogenic effects of bile acid taurocholate (Gorelik et al. 2003). Studies report UDCA reducing bile acids in amniotic fluid and colostrum (Brites et al. 1997, Brites and Rodrigues 1998, Brites et al. 1998) and improving placental morphology and function (Serrano et al. 1998, Geenes et al. 2011).

A recent large double-blind randomized placebo-controlled trial showed that UDCA does not reduce adverse perinatal outcomes (Chappell et al. 2019). As there is new evidence of UDCA's effect on maternal and perinatal outcomes, the treatment should be carefully reconsidered.

2.6.2.2 Other treatments

UDCA is the most commonly used treatment for ICP, but not all women respond to it. The second-line treatment is rifampicin, which is an antibiotic with cholestatic properties. It can ameliorate pruritus and lower serum BA, especially when combined with UDCA (Geenes et al. 2015).

Cholestyramine is an anion exchange resin. One study suggests that it is effective in ameliorating pruritus, but biochemical abnormalities do not improve (Kondrackiene et al. 2005). It may affect intestinal absorption of UDCA or fat-soluble vitamins, and thereafter raise the risk of intrapartum or postpartum haemorrhage (Williamson and Geenes 2014). Thus, cholestyramine is not a first-line treatment.

In a meta-analysis, UDCA decreased pruritus, TBA, ALAT levels and preterm delivery more effectively than S-adenosylmethionine (SAMe) (Zhang et al. 2016). SAMe is not recommended as a treatment because there is no evidence of it controlling maternal symptoms or improving foetal outcome (Royal College of Obstetricians & Gynaecologists 2011). SAMe should be given twice a day intravenously, which also makes it a less attractive treatment (Williamson and Geenes 2014).

Dexamethasone has been reported to have a beneficial effect (Hirvioja et al. 1992). With a small study population, Asian and South American women in particular were more likely to respond to the treatment compared to Caucasians (Diac et al. 2006). In a randomized controlled trial, ursodeoxycholic acid was more effective in improving biochemical abnormalities and symptoms compared to dexamethasone (Glantz et al. 2005). Based on a rodent study, dexamethasone may have an antiarrhytmogenic effect (Gorelik et al. 2003). Nevertheless, dexamethasone treatment has been associated with lower birth weight (Bloom et al. 2001). Repeated antenatal glucocorticoid treatment is also associated with measurable differences in brain maturation (Modi et al. 2001). Due to these side-effects, dexamethasone is not recommended as a first-line treatment for cholestasis of pregnancy.

Antihistamines may be used to reduce the sensation of pruritus, although they do not influence biochemical abnormalities (Williamson and Geenes 2014). This treatment may help insomnia in addition to the itching by causing drowsiness (Williamson and Geenes 2014).

Some clinicians recommend women with ICP use vitamin K. The recommendation is more based on physiological than evidence-based reasons (Royal College of Obstetricians & Gynaecologists 2011). However, because of the risk for

neonatal haemolytic anaemia, hyperbilirubinemia and kernicterus (British Medical Association, Pharmaceutical Society of Great Britain 2010) the usage of vitamin K is recommended only after individual assessment.

Treatment of cholestasis of pregnancy is under continuous research. In a recent study, epigallocatechin-3-gallate was shown to improve ICP symptoms by inhibiting matrix metalloproteinase-2 and matrix metalloproteinase-9 (Zhang and Xu 2017). Likewise, a case report suggested a possible role of metformin in the management of ICP (Elfituri et al. 2016).

Additionally, a low-fat diet and menthol may be used to relieve pruritus (Royal College of Obstetricians & Gynaecologists 2011).

2.6.3 Timing and management of delivery

It is widely accepted that cholestasis of pregnancy is associated with unpredictable stillbirths that occur after 37 weeks (Williamson et al. 2004). The fear of stillbirth is the main reason for iatrogenic preterm delivery. Preterm delivery may also have adverse effects, so the timing of the delivery must be balanced with the foetus' risk from ICP. The timing of the delivery should be evaluated individually (Henderson et al. 2014). It has been suggested that gestation should be prolonged up to 37 weeks before selecting iatrogenic birth (Lin et al. 2017). Compared to controls, women with ICP have been found to have a seven-fold risk of delivery at less than 37 weeks of pregnancy (Turunen et al. 2010). In a review, no evidence was found to support the active management of ICP (Henderson et al. 2014).

The induction of labour has been reported to be more common among women with ICP than among controls (Wikström Shemer et al. 2013, Turunen et al. 2010). Moreover, spontaneous and iatrogenic preterm labour have been shown to more likely occur in ICP pregnancies than in control pregnancies (Wikström Shemer et al. 2013).

2.6.4 Pregnancy outcome

There is controversial evidence on the risk of stillbirths. Early reports have been interpreted to suggest that ICP is associated with an increased risk of stillbirth (Laatikainen and Ikonen 1975, Fisk and Storey 1988). Nevertheless, an increased risk of stillbirth was not reported in a large population-based Swedish study (Wikström Shemer et al. 2013). Furthermore, a Finnish cohort study did not find an association

between stillbirths and ICP (Turunen et al. 2010). The low rate of stillbirths is sometimes explained by the active management of ICP, although there are some critical views on the matter. In one review, stillbirth rates in early reports were found to be similar to the respective national stillbirth rate in those countries where the studies were performed (Henderson et al. 2014). Nowadays, the prevalence of stillbirths is 1–2%, and this may be due to the induction and active management of labour, not because of ICP (Bacq and Sentilhes 2014, Lee et al. 2008, Bacq et al. 2012).

Preterm delivery may be iatrogenic or spontaneous in ICP pregnancies. Preterm delivery causes adverse effects on the newborn. In addition, meconium staining of the amniotic fluid and foetal hypoxia has been connected to intrahepatic cholestasis of pregnancy (Geenes et al. 2014). Meconium staining correlates with the severity of the ICP (Glantz et al. 2004, Lee et al. 2008). In the Finnish population at least, ICP is not associated with low Apgar scores (Turunen et al. 2010).

2.6.5 Postpartum follow-up

Some international publications suggest that liver function tests should be performed after delivery (Bacq and Sentilhes 2014, Wikström Shemer et al. 2015). It has been the case in Finland that if the clinical picture is clear and symptoms resolve after delivery, liver function tests are not routinely checked.

2.6.6 The path in the Finnish maternity health care system

In Finland, the pregnant woman is referred to an obstetrician if there is a suspicion of intrahepatic cholestasis of pregnancy in primary care. After delivery, there is no routine check-up if the woman feels well and the symptoms resolve.

2.7 Long-term aspects of intrahepatic cholestasis of pregnancy

2.7.1 Health behaviour

Only a few studies have examined health behaviour after intrahepatic cholestasis of pregnancy. Women with a history of ICP reported smoking less frequently compared

to controls. They also reported maintaining a gallbladder diet more often compared to controls (Turunen et al. 2013a).

Oral contraceptives and hormone replacement therapy can be used safely by women with a history of ICP. Nevertheless, women should be informed about the possibility of pruritus. It is recommended that liver tests are carried out three and six months after initiating hormonal contraceptives (Bacq and Sentilhes 2014) because the history of ICP may predict an increased risk of developing cholestasis, especially with combined contraceptives (World Health Organization 2015). Progestogen-only contraceptives can be used safely (World Health Organization 2015). Nevertheless, women with a history of ICP have reported using oral contraceptives less commonly and they reported limiting their number of children for health reasons more often compared to controls (Mölsä et al. 2012).

Among women with a history of ICP, oral or transdermal hormone therapy does not seem to affect the levels of bile acids or liver transaminases (Tuomikoski et al. 2008, Ropponen et al. 2005). In a questionnaire study, women with a history of ICP reported the same amount of hormone replacement therapy compared to the reference group (Turunen et al. 2013b).

2.7.2 Heredity

ICP is reported to be hereditary in 16% of cases (Savander et al. 2003). First-degree relatives seem to have a 6% risk of ICP delivery (Eloranta et al. 2001). Moreover, the first-degree relatives' risk for liver dysfunction during pregnancy has been shown to be five-fold (Eloranta et al. 2001). Compared to controls, the risk of women with a history of ICP having mothers who also had ICP is nine-fold, and the risk is five-fold for both sisters and daughters (Turunen et al. 2013c). In familial cases, the recurrence of ICP is reported to be 92% (Savander et al. 2003).

2.7.3 Morbidity

Co-morbidity with cholestasis of pregnancy has been under research in recent years, although there are only a few studies concerning this topic; they are introduced below. Higher rates of gestational diabetes and pre-eclampsia are associated with ICP (Wikström Shemer et al. 2013, Marathe et al. 2017, Martineau et al. 2014). On the other hand, previous gestational diabetes is associated with an increased risk of type 2 diabetes, hypertension and ischemic heart disease (Daly et al. 2018). In

addition, an increased risk of cardiovascular diseases is associated with pre-eclampsia (Brown et al. 2013). Perhaps due to combined morbidity or because of a separate pathway, a small increased risk of later cardiovascular disease has been found (Wikström Shemer et al. 2015). P-wave duration and P-wave dispersion in electrocardiographs were shown to be lower in women with ICP, so they can be used to screen for women with an increased cardiovascular risk in order to target lifestyle counselling (Biberoglu et al. 2015). However, women with a history of ICP have reported less diagnosed hypertension or high cholesterol requiring medication as well as less cardiac arrhythmia compared to controls (Turunen et al. 2012), which does not confirm the increased risk of cardiovascular diseases among women with a history of ICP.

Alcohol consumption might affect morbidity and mortality. However, based on a questionnaire study, alcohol consumption was not remarkably different in mothers with a history of ICP compared to controls (Turunen et al. 2013a). Alcoholic cirrhosis has been noted to be less likely diagnosed in women with a history of ICP than in controls (Marschall et al. 2013). Nevertheless, women with a history of ICP have been shown to have an increased risk for liver fibrosis and cirrhosis (Marschall et al. 2013, Ropponen et al. 2006). Additionally, the risk for non-alcoholic pancreatitis has been reported to be increased among women with a history of ICP (Ropponen et al. 2006).

ICP has been associated with hepatitis C (Locatelli et al. 1999, Paternoster et al. 2002) before and after experiencing ICP (Marschall et al. 2013). Therefore, hepatitis serology testing is recommended for the diagnosis of ICP (Bacq and Sentilhes 2014). Pregnant women who have ICP and hepatitis C seem to have a higher hepatitis C viral load than those who do not have ICP (Belay et al. 2015).

The first studies to report the association between ICP and a higher frequency of gallstones were published in the late 1990s (Glasinovic et al. 1996). A shared risk factor, mutations in the ABCB4 gene, may explain the positive association between ICP and hepatobiliary diseases (Jacquemin et al. 1999, Marschall et al. 2010, Wasmuth et al. 2007). The risk for cholelithiasis and cholecystitis has been reported to be three-fold among women who have experienced ICP compared to the controls (Ropponen et al. 2006, Marschall et al. 2013). Hepatobiliary disorders were more often reported by women with a history of ICP than by controls (Turunen et al. 2012).

One population-based study has been conducted to investigate the association between ICP and autoimmune diseases. These autoimmune diseases – such as diabetes mellitus, thyroid disease, psoriasis, inflammatory polyarthropathies, and

Crohn's disease – were found to be more common among ICP patients than among the controls (Wikström Shemer et al. 2015). Previously, women with a history of ICP have reported more hypothyroidism compared to controls (Turunen et al. 2012).

In a questionnaire, women with a history of ICP reported more breast cancer compared to the reference group (Turunen et al. 2012). In a registry-based study, this association could not be confirmed (Wikström Shemer et al. 2015). Instead, an association between ICP and liver and biliary tree cancer was found (Wikström Shemer et al. 2015).

2.7.4 Mortality

After delivery, the risk of death is low among women with ICP (Suresh et al. 2017). Nevertheless, there are no studies investigating long-term mortality among women with a history of intrahepatic cholestasis of pregnancy.

2.7.5 Health of the offspring after ICP

It is well accepted that there are consequences of programming. Permanent or harmful effects on the structure, physiology or metabolism of the offspring may be caused by a stimulus or insult at a sensitive period of early life (Gluckman et al. 2009).

Only a few studies have been conducted concerning the health of the children of women with ICP. It has been reported that the 16-year-old offspring of mothers with a history of ICP have altered lipid profiles. In this study, the males had an increased BMI and the females increased waist and hip girth compared to controls (Papacleovoulou et al. 2013). In a questionnaire study, daughters of women with a history of ICP reported more epilepsy than the reference group, but generally the mother's ICP does not seem to have an effect on the health of the daughter (Vimpeli et al. 2013).

2.8 Summary of literature

Intrahepatic cholestasis of pregnancy is a pregnancy-related liver disorder characterized by pruritus on the soles and palms. In Finland, it manifests in approximately 1% of pregnancies. ICP typically occurs after 30 gestational weeks.

For the diagnosis of ICP, pruritus and a rise in liver function parameters, typically ALAT and/or bile acids, is required.

The aetiology and pathogenesis of ICP is complex. Genetic factors are undoubtably associated with ICP. Mutations in canalicular transporter ABCB4 in particular have been found. In addition to genetic susceptibility, the hormonal component during pregnancy and environmental factors have also been suggested. The risk of ICP has been shown to be increased among first-degree relatives.

An increased risk of adverse pregnancy outcomes is associated with obstetric cholestasis. When maternal bile acid concentrations are ≥40 μmol/l, the risk for adverse foetal outcome has been shown to increase. Stillbirths are feared, but recent studies do not support a link between ICP and increased rates of stillbirth. The most common treatment for cholestasis of pregnancy is ursodeoxycholic acid, but the benefits of the treatment are controversial and deficient.

Only a few studies concerning the long-term aspects of ICP have been published. Higher rates of gestational diabetes and pre-eclampsia are associated with ICP. Additionally, a small increased risk of later cardiovascular disease has been found. Nevertheless, women with a history of ICP have reported less diagnosed hypertension or high cholesterol requiring medication as well as less cardiac arrhythmia compared to controls.

Women with a history of ICP have been found to have an increased risk for some gastrointestinal diseases. An increased risk for liver fibrosis and cirrhosis has been found to be linked to ICP. Additionally, the risk for non-alcoholic pancreatitis has been found to be increased among women with a history of ICP. Intrahepatic cholestasis of pregnancy has been associated with hepatitis C before and after experiencing ICP. Therefore, hepatitis serology testing is recommended for the diagnosis of ICP.

An increased risk for autoimmune diseases has been linked to ICP. One questionnaire study and one registry-based study have studied the association of ICP with cancers. In the questionnaire, women with a history of ICP announced more breast cancer compared to the reference group. This association was not confirmed in the registry-based study. Instead, an association between ICP and liver and biliary tree cancer was found.

There are no studies investigating long-term mortality among women with a history of intrahepatic cholestasis of pregnancy. Moreover, little is known about the health of the offspring of mothers with a history of ICP. It has been reported that the 16-year-old offspring of mothers with a history of ICP have altered lipid profiles. In a questionnaire study, the daughters of mothers with a history of ICP reported

more epilepsy than the reference group, but generally the mother's ICP does not seem to affect the health of the daughter.

As ICP is the most common liver disease during pregnancy, it is important to study the long-term effects of the disease. There are only a few studies concerning women's health after an ICP pregnancy, so there is a need to investigate this phenomenon.

3 AIMS OF THE STUDY

The aims of the study were:

1. to investigate what kind of guidelines have been given to the physicians who treat women with ICP;
2. to obtain information about the co-morbidity of women with a history of ICP;
3. to study whether there is an association between the occurrence of cancers and a history of ICP;
4. to explore the survival of women with ICP from their birth and from their ICP delivery;
5. to investigate the underlying causes of death among women with a history of ICP;
6. to investigate the health of the sons of women with a history of ICP.

4 MATERIAL AND METHODS

4.1 Study design

A long follow-up time is required to investigate the association between a disease suffered during pregnancy and co-morbidity, mortality and survival from birth and from ICP delivery later in life. Consequently, a study population was obtained for a 20-year period from Tampere University Hospital (TUH). The hospital discharge register contains diagnostic codes (ICD-8 for 1969–1986 and ICD-9 for 1987–1988), so the data were appropriate for the study.

To explore the association between cancer morbidity and ICP, all diagnosed cancers were obtained from the Finnish Cancer Registry. The study included all reported cancers in the cohort for 1953–1960, all registered cancers for 1961–2013, and the location and malignancy of the cancer.

To study the association between ICP and mortality and survival, causes of death were obtained from Statistics Finland. The cohort's causes and dates of death were obtained for 1971–2015.

In addition, to study the association between ICP and co-morbidity, the cohort's hospital discharge diagnoses were accessed. The diagnoses were obtained from the Finnish Hospital Discharge Register (FHDR), which contains every hospital discharge diagnosis in Finland. The data gathered for this study included all hospital discharge diagnoses from 1969 up to the end of 2013 as well as diagnoses from specialized outpatient care for 1998–2013. The diagnoses were extrapolated to ICD-10 as in a previous Swedish study (Wikström Shemer et al. 2015). More accurate analyses were made with diagnosis codes that had not been used in previous ICP studies. If the code in ICD-8 or -9 was less accurate than in ICD-10, the diagnostic classification was made by the superior code heading. The possibility of misdiagnosis can be considered low.

To increase Finnish doctors' knowledge about ICP, a review of the literature and a search of PubMed and Scopus was performed. In addition, a questionnaire was conducted to study the subjective health of the sons of mothers with a history of ICP.

The study was approved by the Regional Ethics Committee of Tampere University Hospital (R02149), the National Institute for Health and Welfare in Finland (THL/1051/5.05.00/2014) and Statistics Finland (TK53-740-15).

4.2 Study population

All ICP pregnancies at TUH from 1969 to 1988 were collected from the patient records. ICD-8 was used at TUH from 1969 to 1986. Because ICD-8 did not include a precise code for ICP, all the obstetric codes that might contain ICP were checked: 637.9 Toxicosis NUD, 639.00 Pruritus, 639.01 Icterus gravis, 639.09 Necrosis acuta et subacuta hepatis, and 639.98 Aliae definitae. The code was verified by analysing the written diagnosis, and if it involved ICP, the case was included. ICD-9 was used between 1987 and 1988, and it contained the appropriate codes 6467A Hepatosis gravidarum and 6467X Hepatopathia alia. Every case was established from the patient records. For an ICP diagnosis, itching was required along with at least one of the following laboratory test results: ASAT >35 U/l, ALAT >40 U/l, or bile acids ≥6 μmol/l.

Altogether, 687 ICP deliveries were obtained from the patient records. The control group comprised the previous and subsequent women from the maternity ward diary for each ICP case. In total, the control group consisted of 1,374 women. Because the cohort included some women with repeated ICP deliveries, every woman was studied only once. Thereby, the cohort contained 575 women with a history of ICP. Personal identity codes were missing for four women in the ICP group and 41 in the control group, hence they were excluded. The final cohort constituted 571 women with ICP and 1,333 women in the control group (Figure 1).

The details of the sons of the women in the ICP group (n=394) and the sons of women in the control group (n=705) were collected from TUH. The mothers of these sons were the same mothers used in the registry studies. Excluded from the cohort were 8 stillborn, 27 deceased, and 82 with missing addresses. Altogether, 982 questionnaires were sent. The men's postal addresses were accessed from the Finnish Population Register Centre and the postal survey was conducted in autumn 2010. Identical questionnaires were sent to both groups. The response rate was 37.8% (n=138) for the sons of the ICP group and 36.6% (n=226) for the sons of the control group.

The women in the ICP and the control groups were found to be comparable regarding age, educational level, and body mass index in a previous questionnaire

study where the response rate was good, at over 65% (Turunen et al. 2012). The cohort was comparable regarding age at labour, age at death, and age of those still alive at the end of 2015 (Table 1). Mothers with ICP delivered in earlier gestational weeks than the controls did (Turunen et al. 2010) and they more often had a single child compared to the controls (Mölsä et al. 2012).

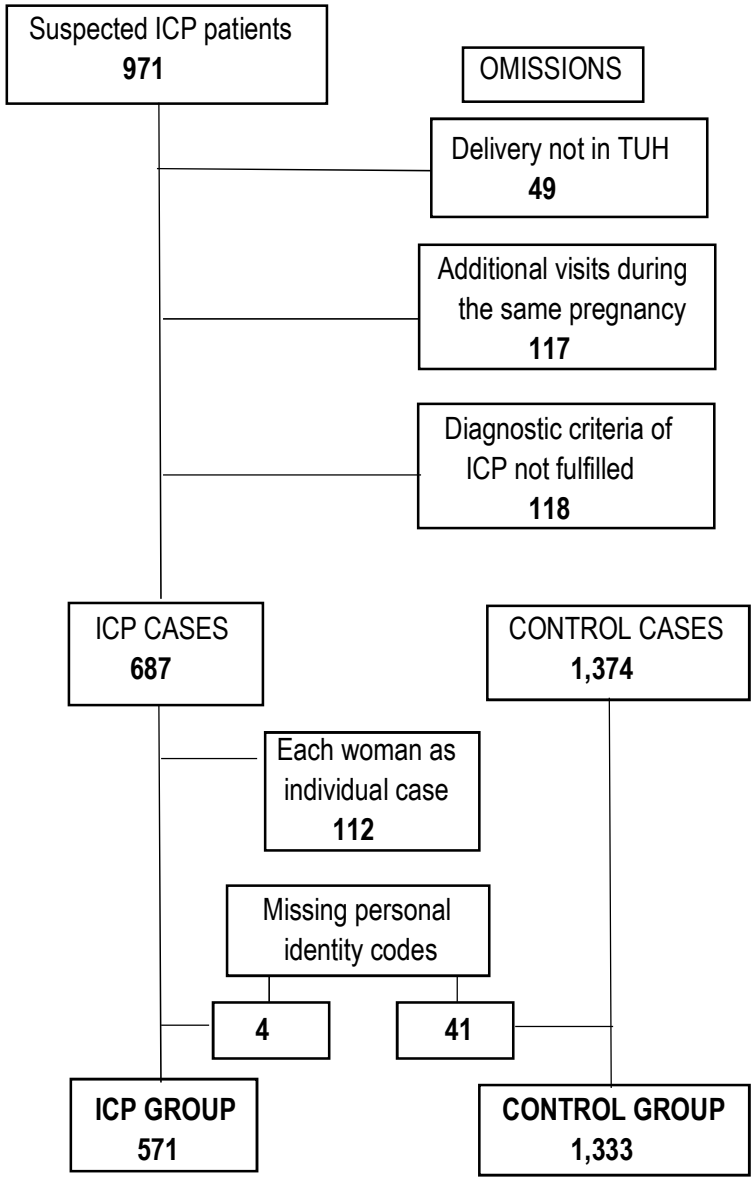

Figure 1. Flow chart of the ICP and control groups.

Table 1. Patients' median age at labour, age at death, and age when still alive at the end of 2015.

	Mothers with ICP			Control group		
	n	age	age range	n	age	age range
At labour	571	27.6	16.9 – 41.1	1,333	27.1	15.0 – 46.4
At death	39	56.7	34.1 – 78.5	111	55.9	28.1 – 83.8
Alive at the end of 2015	532	63.7	48.0 – 80.8	1,222	63.3	46.3 – 85.0

4.3 Questionnaire and measurements

For Study VI, a postal survey was conducted in autumn 2010 to study the health of the male offspring of women with a history of ICP and the controls. The men's mean age was 30 years (range: 21–40 years). The age of 30 years was set as a cut-off point to categorize the respondents' age. Education was classified as "high" for those who had finished high school and "low" for those who had not. The body mass index (BMI) of respondents was categorized, and a cut-off point was set at 25 kg/m^2. The groups were comparable regarding age and BMI. On the other hand, the groups were not comparable with respect to education. Sons of the ICP group were more often in the higher education group (63.0%) than the sons of the control group (46.2%) (p=0.002). Identical questionnaires were sent to both groups. The questionnaire comprised 39 items. The main aspects relevant to this study were present health, symptoms and complaints, diseases diagnosed by a doctor, use of medicines and mental health. Smoking and alcohol usage were also enquired.

The respondents were asked to assess their present health by choosing one of the following choices: good, fairly good, moderate, rather poor or poor. Questions concerning symptoms and complaints during the previous 12 months were included in the query. In addition, the questions addressed diseases diagnosed by a doctor, and there were further questions focusing on the gastrointestinal, endocrine and metabolic systems, the urinary tract, heart and circulatory systems; respiratory diseases; the musculoskeletal system and connective tissue disorders. Furthermore, respondents were requested to state whether they had been diagnosed with cancer, migraine, urticaria, epilepsy or some significant injury or disease. Questions concerning whether the respondents had undergone any major surgery or had ever suffered hip, wrist or vertebral fractures were also included.

The use of medicines, natural health drugs and vitamins during the previous year was enquired. Two mental health-related questions and the Depression Scale were used to evaluate mental health. The questions included whether the respondent had

suffered from or had undergone treatment for a mental health disorder. A validated Finnish test screening for the risk of present clinical depression, the Depression Scale, was included in the questionnaire (Salokangas, Poutanen, and Stengård 1995). The results of the Depression Scale vary from 0 to 30. The probability of depression is clinically relevant with a result of ≥9 and depression is quite probably diagnosed if the result is ≥12 points.

4.4 Statistical analysis

The SPSS System for Windows (Versions 22.0, 23.0 and 24.0) was used to analyse the data. Frequencies and percentages were used to present the results. The chi-squared test was used to evaluate statistical significance. Odds ratios (OR) and 95% confidence intervals (CI) were conducted with binary logistic regression analysis. "ICP or not" was the dependent variable. The T-test was carried out to investigate the age at the time of cancer diagnosis. The Kaplan-Meir method was used to explore the survival of the mothers in the ICP and control groups.

5 RESULTS

5.1 Review of the literature (Study I)

This study was conducted to increase Finnish doctors' knowledge about intrahepatic cholestasis of pregnancy and the route of these patients in the Finnish healthcare system. Information about the long-term aspects of ICP is accumulating. Women with a history of ICP should be encouraged to live normally after experiencing ICP.

5.2 Co-morbidity of women with a history of ICP (Study II)

In this 44-year follow-up study, the most common diseases group among the ICP and control groups were diseases of the genitourinary system, the nervous system and sense organs, and the musculoskeletal system and connective tissue. Diseases of the digestive system (ICP not included) were diagnosed in over a half of the ICP group, but in only a third of references ($p<0.001$).

At least one disease of the thyroid gland was diagnosed in 7.0% (n=40) of the ICP group and 4.6% (n=61) of the controls ($p=0.030$) (Table 2). Arterial diseases were diagnosed in 0.9% (n=5) of the ICP group and 2.3% (n=30) of the controls ($p=0.041$, OR=0.38, 95% CI 0.15−0.99).

When looking closer at the individual diagnoses from the ICD-10 classification groups, hypothyroidism was more common in the ICP group than in the controls. Some 3.5% (n=20) of the ICP group and 1.5% (n=20) of the controls were diagnosed with hypothyroidism (OR=2.38, 95% CI 1.27–4.46).

Hepatobiliary diseases (ICP not included, K00–K99) were found in 35.2% (n=201) of the ICP group and in 11.6% (n=155) of the controls ($p<0.001$). Diseases of the digestive system other than hepatobiliary diseases were found in 28.4% (n=162) of the ICP group and in 27.5% (n=366) of the controls ($p=0.683$). Cholecystitis and/or cholelithiasis (OR 2.88, 95% CI 2.17–3.84) and diseases of the pancreas (OR 2.26, 1.20–4.27) were found significantly more often in the ICP group than in the control group (Table 3). The results include all subjects who have at least

one diagnosis among certain disease groups, although some subjects might have had several diagnoses regarding the same ICD-10 disease groups.

Table 2. The occurrence (%) of neoplasms; disorders of the thyroid gland; and immune-mediated, cardiovascular and pregnancy-associated diseases in the ICP group and the references.

	ICD-10 code	ICP N=571		Controls N=1,333		Difference	
		n	%	n	%	%-units	p-value
Neoplasms							
Breast cancer	C50	36	6.3	66	5.0	1.3	0.30
Liver and biliary tree cancer	C22–C24	0	0.0	0	0.0	0.0	-
Malignant diseases other than the aforementioned	C00–D48	216	37.8	458	34.4	3.4	0.15
Diseases of the thyroid gland	E00–E07	40	7.0	61	4.6	2.4	**0.03**
Immune-mediated diseases							
Diabetes mellitus	E10–E14	34	6.0	97	7.3	-1.3	0.30
Sarcoidosis	D86	2	0.4	5	0.4	0.0	0.94
Crohn's	K50	3	0.5	5	0.4	0.1	0.64
Ulcerative colitis	K51	6	1.1	10	0.8	0.3	0.51
Coeliac disease	K90.0	6	1.1	13	1.0	0.1	0.88
Inflammatory polyarthropathies	M05–M09	20	3.5	46	3.5	0.0	0.96
Systemic connective tissue disorders	M32	1	0.2	3	0.2	0.0	0.83
Asthma	J45	28	4.9	72	5.4	-0.5	0.66
Psoriasis	L40	8	1.4	27	2.0	-0.6	0.35
Cardiovascular diseases							
Hypertensive disease	I10–I15	67	11.7	178	13.4	-1.7	0.33
Coronary heart disease	I21–I25	27	4.7	65	4.9	-0.2	0.89
Pulmonary heart disease	I26	8	1.4	18	1.4	0.0	0.93
Cerebrovascular disease	I27–I28 G45	22	3.9	56	4.2	-0.3	0.73
Arterial diseases	I70–I79	5	0.9	30	2.3	-1.4	**0.04**
Pregnancy-associated diseases							
Pre-eclampsia	O14.0–O14.2	23	4.0	72	5.4	-1.4	0.21
Gestational diabetes	O24.4	9	1.6	24	1.8	-.02	0.73

*The results include all subjects who have at least one of these diagnoses.

Table 3. Risk (OR with 95% CI) for at least one mentioned hepatobiliary disease or disease of the pancreas in the ICP and control groups.

Hepatobiliary disease	ICD-10		N	%	OR	95% CI
Cholecystitis and/or cholelithiasis	K80–K81	Controls	106	8.0	1	
		ICP	114	20.0	2.88	2.17–3.84
Diseases of the pancreas	K85–K86	Controls	20	1.5	1	
		ICP	19	3.3	2.26	1.20–4.27
Cirrhosis of the liver	K70.2, K76.1,K70.3,P78.8, K71.7,K74	Controls	8	0.6	1	
		ICP	7	1.2	2.06	0.74–5.70

5.3 Occurrence of cancers among women with a history of ICP (Study III)

This follow-up study considered cancers in a 50-year follow-up. At least one cancer was diagnosed in 16.8% (n=96) of the ICP group and in 13.9% (n=185) of the control group (p=0.098). A slightly higher risk for cancer (OR 1.26, 95% CI 0.96–1.64) was found in the ICP group than in the controls. Malignant cancers were the main form of cancer in both groups (nearly 90%) (p=0.758).

The most common cancer in both groups was breast cancer (Table 4). A slightly higher risk for breast cancer was found in the ICP group (OR 1.36, 95% CI 0.91–2.03) than in the control group, but the finding was not statistically significant. Regarding other neoplasms, there were no statistically significant differences between the groups. One mother in the ICP group had been diagnosed with hepatobiliary cancer, but this diagnosis was not found among the controls.

The mean age of mothers at the time of diagnosis was 53.0 years in the ICP group and 51.8 years in the control group (p=0.315). As of 31 December 2013, the mean age of those who had not been diagnosed with cancer was 61.5 years in the ICP group and 61.3 years in the control group.

Table 4. The occurrence of cancers in the ICP and control groups.

ICD-10 code	**Cancer**	**Mothers with ICP n=571**		**Controls mothers n=1,333**		**Difference**	
		n	%	n	%	%-units	p-value
C50	Breast	40	7.0	70	5.3	1.7	0.133
C73–C75	Thyroid and other endocrine glands	6	1.1	5	0.4	0.7	0.075
C64–C68	Urinary tract	4	0.7	3	0.2	0.5	0.116
C42	Haematopoietic and reticuloendothelial systems	2	0.4	2	0.2	0.2	0.382
C30–C39	Respiratory and intrathoracic organs	1	0.2	3	0.2	0.0	0.827
C40–C41	Bone and articular cartilage	1	0.2	3	0.2	0.0	0.827
C80	Unknown primary site	1	0.1	1	0.1	0.0	–
C00–C14	Lip, oral cavity and pharynx	0	0.0.	1	0.1	-0.1	0.513
C15–C26	Digestive organs	7	1.2	19	1.4	-0.1	0.731
C45–C49	Mesothelial and soft tissue	0	0.0	1	0.1	-0.1	0.513
C43–C44	Melanoma and other malignant neoplasms of skin	18	3.2	38	2.9	-0.1	0.721
C51–C58	Female genital organs	14	2.5	35	2.6	-0.1	0.826
C69–C72	Eye, brain and other parts of central nervous system	3	0.5	8	0.6	-0.1	0.844
C77	Lymph nodes	2	0.4	7	0.5	-0.1	0.610

5.4 Survival analysis (Study IV)

This study followed-up the cohort for 27–46 years. Nearly 7% (n=39) of the ICP group and 8% (n=111) of the control group had died by the end of 2015. The mean survival time from birth was 77.4 years in the ICP group and 79.2 years in the reference group (p=0.288) (Figure 2). The mean survival time after labour was 45.0 years in the ICP group and 44.8 years in the control group (p=0.259).

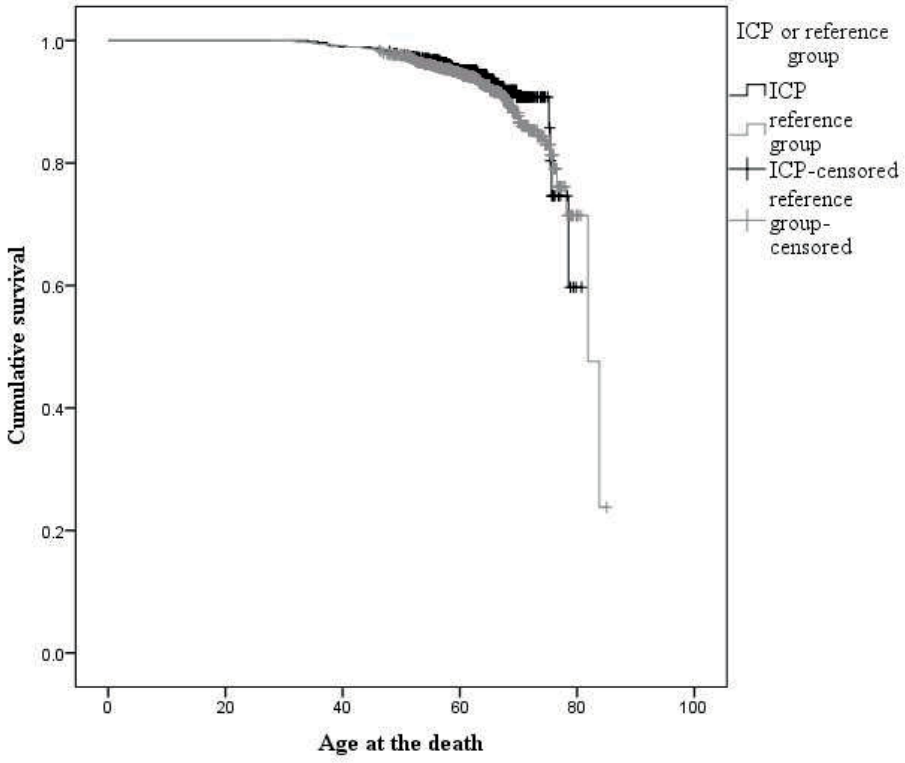

Figure 2. Survival in the ICP and reference groups in terms of age. The censored line indicates the subjects who are alive at the end of the follow-up time. (Reprinted with permission from Elsevier.)

5.5 Underlying causes of death in women with a history of ICP (Study V)

During this 44-year follow-up, the women of the cohort most commonly died of neoplasms – 46% (n=18) in the ICP group and 41% (n=46) in the control group (p=0.609) (Table 5). Statistically significant differences between the groups were not found concerning hepatobiliary neoplasms or malignant neoplasms of the digestive system as the underlying cause of death.

Diseases of the circulatory system were the second most common underlying cause of death among the controls. These underlying causes accounted for 13% (n=5) of deaths in the ICP group and 26% (n=29) of deaths in the control group (p=0.088).

Diseases of the digestive system were the second common underlying cause of death in the ICP group. These were more often the underlying cause of death in the ICP group than in the control group (15% (n=6) vs 4% (n=4), p=0.011). The risk of dying due to a gastrointestinal cause was nearly five-fold greater in the ICP group than in the control group (OR=4.85, 95% CI 1.29–18.18). Hepatobiliary diseases were the underlying cause of death in 67% (n=4) of those in the ICP group and 75% (n=3) of the controls (p=0.778) within the subset of gastrointestinal disease deaths. Alcoholic liver diseases were found in four mothers in the ICP group and in two mothers in the control group. Cirrhosis of the liver was found in one control. Diseases of the pancreas and alcohol-induced chronic pancreatitis were the underlying causes of death in two women in the ICP group. Gastro-oesophageal laceration-haemorrhage syndrome was the underlying cause of death in one control. In total, diseases of the digestive system and malignant neoplasms of the digestive system were the underlying causes of death in 28% (n=11) of the ICP group and 14% (n=16) of the controls (p=0.054). Diseases of the other organ systems were rare in both groups.

Table 5. Underlying causes of death among women with and without a history of ICP.

Underlying cause of death (ICD-10)	Mothers with ICP n=39		Controls n=111		Difference	
	n	%	n	%	% units	p-value
Neoplasms (C00–D48)	18	46	46	41	5	0.609
Diseases of the digestive system (K00–K93)	6	15	4	4	11	0.011
External causes of morbidity and mortality, injury, poisoning and certain consequences of external causes (V01–Y98, S00–T98)	5	13	17	15	-2	0.705
Diseases of the circulatory system (I00–I99)	5	13	29	26	-13	0.088
Endocrine, nutritional and metabolic diseases (E00–E90)	2	5	5	5	0	0.874
Diseases of the nervous system (G00–G99)	2	5	5	5	0	0.874
Diseases of the musculoskeletal system and connective tissue (M00–M99)	1	3	1	1	2	0.420
Diseases of the respiratory system (J00–J99)	0	0	4	4	-4	0.230

5.6 Health of the sons of women with a history of ICP (Study VI)

In a postal survey conducted in 2010, there were no differences between the sons of the ICP group and the sons of the control group in the majority of the aspects examined. There was no difference in self-evaluated current health status. Health was rated as good or fairly good by 89% of the sons of the ICP group and 88% of the sons of the control group.

Most commonly, backache, neck and shoulder pain, headache and coughing were reported in both groups. Coughing during the previous 12 months was reported by 27% of the sons of the ICP group and 38% of the sons of the control group (p=0.034). The groups did not differ with respect to other symptoms (Table 6).

Some 52% of the sons of the ICP group and 66% of the sons of the control group had smoked at least once in their lifetime (p=0.021). Current smoking was reported by 30% of the sons of the ICP group and 42% of the sons of the control group (p=0.023). Calculating smoking pack years, there were no significant differences between the groups. No differences were found in terms of the number

of doses of alcohol used or whether the respondent had ever considered reducing alcohol consumption.

Concerning diagnosed diseases, only minor differences between the groups were found. Acute hepatitis and cholelithiasis were diagnosed in 1% (n=2) of the sons of the ICP group but in none of the sons of the control group (p=0.070). Nearly 9% of the sons of the ICP group and 11% of the sons of the control group suffered from migraine, which was the most common disease among both groups. Urticaria was reported by 2% (n=3) of the sons of the ICP group, but by none of the sons of the control group (p=0.026). Diseases of the circulatory system were less common among the sons of the ICP group, although the findings were not statistically significant.

In the Depression Scale results, approximately 12% scored ≥9 points in both groups. Some 5% of the sons of the ICP group and 6% of the sons of the control group scored >12 points in the Depression Scale. There were no differences regarding mental health disorders. Wrist, back or hip fractures were reported by 10% of the sons of the ICP group and by 9% of the sons of the control group.

There were no statistically significant differences in the usage of medicines. The most commonly used medicines among the sons of the ICP group were painkillers (89%), vitamins or trace elements (62%), asthma and antiallergic medication (24%) and gastric acid inhibitors (23%).

Table 6. Symptoms and complaints during the previous 12 months among the sons of the ICP group and the sons of the control group.

Symptoms and complaints	Sons of the ICP group, n =138 (%)	Sons of the controls, n = 226 (%)	Difference in percentage points	Difference (p-value)
Heart palpitation	14.5	8.4	6.1	0.069
Blushing	10.1	4.9	5.2	0.053
Neck and shoulder pain	37.7	33.6	4.1	0.432
Dryness of the eyes and mouth	13.0	10.2	2.8	0.401
Insomnia	21.7	19.0	2.7	0.531
Rheumatic pains	5.1	2.7	2.4	0.228
Headache	31.9	29.6	2.3	0.653
Urinary problems	5.8	3.5	2.3	0.308
Nausea	7.2	6.2	1.0	0.695
Foot and/or leg swelling	3.6	3.1	0.5	0.785
Dyspnoea	8.7	8.4	0.3	0.924
Depression	13.0	12.8	0.2	0.953
Dizziness	10.1	10.2	-0.1	0.992
Chest pain	8.7	8.8	-0.1	0.960
Itching of the palms and soles	3.6	4.0	-0.4	0.863
General itching of the skin	14.5	17.3	-2.8	0.488
Backache	38.4	42.0	-3.6	0.494
Arthralgia, joint pain	14.5	19.0	-4.5	0.267
Nervousness	15.2	20.8	-5.6	0.185
Recurring stomach problems	9.4	15.0	-5.6	0.121
Sweating	14.5	20.4	-5.9	0.159
Coughing	26.8	37.6	-10.8	0.034

6 DISCUSSION

6.1 Main results of the study

Over a 44-year follow-up, diseases of the digestive system (ICP not included) were more common among mothers with a history of ICP when compared to the controls. Over a half of the ICP group were diagnosed with diseases of the digestive system, compared to only one third of the controls. Hepatobiliary diseases (ICP not included) were also more common in the ICP group compared to the control group. Over one third of the ICP group and one tenth of the controls were diagnosed with hepatobiliary diseases. The risk for cholecystitis and/or cholelithiasis was nearly three-fold and the risk for diseases of the pancreas was two-fold in the ICP group. Diseases of the thyroid gland were more common in the ICP group than in the control group. The risk for hypothyroidism was more than two-fold in the ICP group. However, arterial diseases were less common in the ICP group compared to the controls.

There were no statistically significant differences in the occurrence of cancer between the ICP group and the controls in the 50-year follow-up. In this study, the risk for cancer – especially breast cancer, the most common cancer in both groups – was not statistically significantly higher in the ICP group.

The mean survival time from birth and from labour did not differ significantly when comparing the ICP and control groups in the 27–46-year follow-up. During the 44-year follow-up, neoplasms were the most common underlying cause of death in both groups. Regarding hepatobiliary neoplasms, no significant differences were found between the ICP and control groups. Diseases of the circulatory system were the second most common underlying cause of death in the controls. The occurrence was two-fold in the controls when compared to the ICP group, but the finding was not statistically significant. In mothers with a history of ICP, the second most common underlying cause of death was diseases of the digestive system. These underlying causes of death were more common in the ICP group when compared to the control group. The risk of death from a gastrointestinal cause was nearly five-fold in ICP group when compared to the controls. Deaths due to diseases of the digestive system and malignant neoplasms of the digestive system were twice as

common in the ICP group when compared to the controls, the difference being close to statistically significant.

A postal questionnaire was conducted in 2010 to study the health of the male offspring of mothers with a history of ICP and mothers with no history of ICP. Generally, there were only minor differences between the groups in terms of health. The self-evaluated current health status was similar in the groups, and backache, neck and shoulder pain, headache and coughing were the most common symptoms in both groups. The sons of the ICP group reported less coughing during the previous 12 months compared to the sons of the controls. With respect to other symptoms, no significant differences between the sons of women with ICP and the sons of the controls were found. Sons of the ICP group had smoked at least once in their lifetime less frequently. Additionally, the sons of the ICP group reported currently smoking less frequently. Nevertheless, there were no differences between the groups in smoking pack years or alcohol usage. Migraine was the most common disease in both groups. Acute hepatitis and cholelithiasis were slightly more common in the sons of the ICP group compared to the sons of the controls, although the difference was not statistically significant. Urticaria was comparatively more common in the sons of the ICP group. The groups did not differ in terms of the Depression Scale score, nor were there differences in the occurrence of mental health disorders or wrist, back or hip fractures. The use of medicines was similar in both groups, with painkillers being the most commonly used drugs.

6.2 Reflections on the study setting, material and methods

The study population included all pregnancies complicated with intrahepatic cholestasis of pregnancy during a twenty-year period at Tampere University Hospital (TUH). The study population can be regarded as extensive. TUH is a university hospital in the "million range", and both normal and risky deliveries are carried out there. The prevalence of ICP was similar in the investigated period to the overall ICP prevalence in Finland (Turunen et al. 2010). There is a possibility that some controls may have had an ICP delivery in another hospital district. In addition, it is possible that some of the mothers may have had a delivery before 1969. The data collected from the cohort were based on personal identity codes, which makes the data more reliable. The cohort's follow-up time was long.

The ICP diagnoses were obtained and verified from the patient records: itching and laboratory test abnormalities were required as confirmation. The bile acid values

considered diagnostic for ICP were the standard for TUH at that time, but nowadays the diagnostic values for ICP are generally higher. The upper limit of normal bile acids can be reduced to between 6 and 10 μmol/l in fasted women, although many studies use an upper limit of normal between 10 and 14 μmol/l (Williamson and Geenes 2014). In our studies, the results can be considered similar, even though the diagnostic criterion for ICP was a bile acid concentration ≥6 μmol/l instead of ≥10 μmol/l. The diagnosis was made by an obstetrician, and the diagnosis was not questioned.

The controls were chosen to be the next and previous deliveries from the patient records. There were no power calculations made and that may be the reason why not all the differences were statistically significant. The aim was to obtain a large cohort and to follow it up for a long time. The follow-up time can be considered long. However, to investigate survival from birth and from ICP delivery and the underlying causes of death in more detail, the follow-up should be so long that everyone in the cohort has died.

A long follow-up is crucial to investigate long-term aspects. Despite the long follow-up time, the cohort represents those who have died or been diagnosed with a disease at a relatively young age. An even longer follow-up time would confirm the results, as a wider diagnosis range would be able to be analysed due to the increase in statistical power. Although the follow-up time is long, the power for analysing rare diseases is weak. For these reasons, the analysis of rare diseases was not successful in this study material.

The completeness and accuracy of the Finnish Hospital Discharge Register (FHDR) vary from satisfactory to very good (Sund 2012). A limitation of the FHDR is its inclusion of only those patients treated on an inpatient ward or in hospital. From 1998, information is available on outpatient visits to specialized healthcare. The prevalence of diseases typically treated in primary health care might have been greater if information had been available on diagnoses in primary health care. For instance, diabetes mellitus 2 and hypertension are typically treated in primary health care. Thus, these diagnoses are in the FHDR only if the condition is extraordinarily complicated or the patient is hospitalized for another reason. The ICD-8 and ICD-9 diagnoses were extrapolated to ICD-10, and this did not cause any significant problems. In Study II, the aim was to compare morbidity between women with a history of ICP and the controls, and an analysis of the time from ICP to the diagnosis of the certain diseases was not included.

The underlying causes and dates of death were obtained from Statistics Finland. The coverage of this information is practically 100% (Official Statistics of Finland

2013). The data for the deceased of the cohort can be considered reliable. However, one limitation of the study is the small number of death cases.

The completeness of the Finnish Cancer Registry has been shown to be over 99% (Teppo et al. 1994). The accuracy of the registry has been found to be high, but there is a delay in the collection of registry data (Korhonen et al. 2002). Nevertheless, this delay did not cause major problems.

The questionnaire for the sons of the cohort was sent via mail. Postal addresses were found for most of the sons, and the response rate was moderate. The response rate for the sons of the ICP group and the sons of the controls was 37.8% and 36.6%, respectively. The questionnaire was filled in at home. The respondents did not receive any payment for responding, but a prepaid return envelope was included with the questionnaire so there was no financial cost for answering. Had the questionnaire been online, the response rate might have been better. The response rate was lower for the sons of the cohort in comparison to a quite similar questionnaire sent to the daughters or mothers (Turunen et al. 2012, Vimpeli et al. 2013).

The questionnaire study had some limitations. Since the men were quite young, some of the diseases usually detected in later life would not yet have been diagnosed. The sample size could also have been even larger. Furthermore, questionnaire studies always include a risk of recall bias. There was no connection between the severity of the mother's ICP, the trimester of clinical presentation, peak bile acid levels (percentage of mothers with levels >40 μml/l), the presence of jaundice, average gestation at delivery, the percentage of males delivered before 37 weeks or the presence of other perinatal complications.

6.3 Discussion of the results

As intrahepatic cholestasis of pregnancy is hereditary in one in six cases (Savander et al. 2003) and the liver is crucial for maintaining the homeostasis of the human body, it was logical to investigate whether ICP has long-term effects. The registries used provided objective information on the long-term aspects of ICP. The health of the cohort's sons was evaluated by questionnaire.

6.3.1 Co-morbidity of women with a history of ICP

In the 44-year follow-up study, some differences were found in co-morbidity between the ICP group and the controls. Hepatobiliary diseases were overrepresented in the ICP group. Moreover, there was a higher occurrence of thyroid gland diseases in the ICP group, especially goitre and hypothyroidism. Cholelithiasis and/or cholecystitis and diseases of the pancreas were more common in the ICP group than in the control group. By contrast, the occurrence of arterial diseases was lower in the ICP group. In respect to other diseases, no differences were found between the ICP group and the controls.

Hepatobiliary diseases were more common among in the ICP group than in the reference group. Over half of the ICP group had been diagnosed with diseases of the digestive system. In addition, women in the ICP group had an increased risk for cholecystitis and cholelithiasis. The findings are congruent with previous studies (Turunen et al. 2012, Ropponen et al. 2006, Marschall et al. 2013). Diseases of the pancreas were overrepresented in the ICP group compared to the control group. Non-alcoholic pancreatitis was found to be more common among women with a history of ICP than among controls (Ropponen et al. 2006). Patients with pancreatitis may also have cholecystitis, and it is plausible that only one of the diagnoses had been noted down in the medical records. However, the records of women with ICP presumably have the same weakness as the records of the references.

A population-based study found an increased risk for later cardiovascular disease in women with a history of ICP, and the occurrence of cardiovascular diseases was lower than in our study (Wikström Shemer et al. 2015). In a previous questionnaire study, women who had experienced ICP reported less cardiac arrhythmia, high cholesterol and high blood pressure requiring medication compared to controls (Turunen et al. 2012). The difference might be explained by our cohort's older age at the end of the follow-up. In this study, arterial diseases were less common among mothers with a history of ICP compared to the references.

Hypothyroidism was more often found in the ICP group than in the control group. Congruent findings have been made regarding hypothyroidism in a questionnaire study (Turunen et al. 2012) and overall thyroid disease in a population-based study (Wikström Shemer et al. 2015). It is commonly noted that the autoimmune pathogenesis has a remarkable effect on hypothyroidism. There might also be an autoimmune aspect in the pathogenesis of ICP. Mutations in gene ABCB4 in ICP and cholelithiasis (Jacquemin et al. 1999, Marschall et al. 2010, Wasmuth et

al. 2007) might be an example of the shared risk factors possibly influencing the pathogenesis of ICP and other diseases of the digestive system.

6.3.2 Occurrence of cancers among women with a history of ICP

In the 50-year follow-up study, there were minor differences among the ICP and control groups regarding cancer occurrence. There was no statistically significant association between ICP and overall cancer. The finding is coherent with a previous study (Wikström Shemer et al. 2015). This same previous study found an association between ICP and hepatobiliary cancer. Nevertheless, the occurrence was small in the ICP group (0.1%), so the expectation of finding hepatobiliary cancers among our ICP group was low. However, one hepatobiliary cancer was found in the ICP group. The phenomenon could also be explained by the higher risk of chronic hepatitis, cholelithiasis and chronic cholangitis among women with a history of ICP (Ropponen et al. 2006, Marschall et al. 2013). The first may lead to liver cirrhosis and that may be complicated by hepatocellular cancer (Fattovich et al. 2004). Cholelithiasis and chronic cholangitis are associated with gallbladder and cholangiocellular cancer (Kim et al. 2015, Hundal and Shaffer 2014). Cholelithiasis has been associated with pooled gastrointestinal and right-side colon cancers (Shabanzadeh et al. 2017).

In a previous questionnaire study, women with a history of ICP reported more breast cancer compared to controls (Turunen et al. 2012). There was a need to investigate whether the reported information could be confirmed using objective data sources. A recent study found no association between ICP and breast cancer (Wikström Shemer et al. 2015). In the present study, no statistically significant increase in the risk for breast cancer was found in the ICP group compared to the controls. The occurrence of breast cancer was in accordance with the known breast cancer risk for Finnish women (Engholm et al. 2016). Delivery before 37 weeks of gestation seems to increase the mother's risk for breast cancer later in life (Hsieh et al. 1999). With the same cohort, ICP has been associated with premature delivery (Turunen et al. 2010), and thus this could increase the number of breast cancer cases among women with a history of ICP.

A multifactorial genetic base has been found to influence the pathogenesis of ICP, and ICP might be one expression of a larger group of genetic diseases. Furthermore, the same hormonal factors influencing ICP may have an impact on the pathogenesis of certain cancers.

6.3.3 Survival analysis

The ICP and control groups did not significantly differ in terms of survival from birth or ICP delivery in the 27–46-year follow-up. ICP is associated with a certain genetic profile (Williamson and Geenes 2014, Ozkan et al. 2015), and the same profile may influence the survival of patients with ICP from birth. Indeed, ICP itself might not affect survival, but the specific genetic profile may do so. This research provides new insights on the long-term aspects of ICP by studying survival from birth and from ICP delivery over such a long follow-up time. No statistically significant differences in survival from the birth or from ICP delivery were found between the ICP group and the control group during the follow-up time. Based on this study, ICP does not seem to be associated with women's survival in middle age or in earlier life.

The known risk for certain diseases after ICP (Marschall et al. 2013, Ropponen et al. 2006, Turunen et al. 2012, Wikström Shemer et al. 2015) may have an impact on the survival of women with a history of ICP. Hepatobiliary cancer has been found to be more common among women with a history of ICP than among controls (Wikström Shemer et al. 2015). In a questionnaire study, women with a history of ICP reported more breast cancer compared to controls (Turunen et al. 2012), but this finding was not confirmed by a registry-based study (Wikström Shemer et al. 2015). The occurrence of cancer might have an effect on survival from birth. Furthermore, health behaviour has a crucial influence on survival. Women with a history of ICP reported less smoking compared to a control group, but no differences in recent alcohol consumption or physical activity were reported (Turunen et al. 2013a).

Hepatitis C is associated with an increased risk of the occurrence of coronary atherosclerosis (Olubamwo et al. 2016), and it is also associated with ICP (Locatelli et al. 1999, Marschall et al. 2013, Paternoster et al. 2002). There were no differences in our cohort in terms of hepatitis C incidence. Thus, it can be considered that hepatitis C has a similar effect on the survival of the groups.

6.3.4 Underlying causes of death among women with a history of ICP

In this study, the underlying causes of death were examined in a 44-year follow-up. Gastrointestinal diseases were overrepresented as an underlying cause of death among women with a history of cholestasis of pregnancy. On the other hand,

diseases of the circulatory system were more common in the controls than in the ICP group.

ICP has previously been associated with circulatory diseases (Wikström Shemer et al. 2015). However, women with a history of ICP reported less cardiac arrhythmia, high cholesterol and high blood pressure requiring medication compared to controls in a questionnaire study (Turunen et al. 2012). Among Finnish women over 15 years old, diseases of the circulatory system were the underlying cause in 38% of deaths (Official Statistics of Finland 2016). Over one of four underlying causes of death were diseases of the circulatory system in our control group. In the ICP group, diseases of the circulatory system accounted for only slightly more than one in ten deaths. ICP has been associated with gestational diabetes and pre-eclampsia (Wikström Shemer et al. 2013, Marathe et al. 2017). Gestational diabetes increases the risk of type 2 diabetes, hypertension and ischemic heart disease (Daly et al. 2018). An increased risk for cardiovascular diseases has been linked to pre-eclampsia (Brown et al. 2013). Nevertheless, in our study no association was found between ICP and an increased rate of diseases of the circulatory system as the underlying cause of death.

The increased occurrence of gastrointestinal diseases as the underlying cause of death may be considered clinically relevant. The increased occurrence of hepatobiliary disease (Ropponen et al. 2006, Marschall et al. 2013, Turunen et al. 2012) might increase the number of deaths from gastrointestinal diseases among women with a history of ICP. Hepatobiliary neoplasms were not underlying causes of death in either of the groups. An association between ICP and liver and biliary cancer has been reported, but the incidence was found to be rather low, at 0.1% (Wikström Shemer et al. 2015). The low incidence explains why none of these cancers were found in the cohort as an underlying cause of death.

Alcohol consumption may influence the underlying cause of death. In a questionnaire study, there was no difference between women who had experienced ICP and the controls regarding risky consumption of alcohol (Turunen et al. 2013a). Another study found that alcohol cirrhosis was less likely to be diagnosed in women with a history of ICP than in controls (Marschall et al. 2013). Additionally, the increased risk of liver fibrosis and cirrhosis (Ropponen et al. 2006, Marschall et al. 2013) among women with a history of ICP may explain the increased amount of hepatobiliary diseases among the underlying causes of death.

6.3.5 Health of the sons of mothers with a history of ICP

Only minor differences manifested for most of the aspects addressed in the questionnaire survey conducted in 2010. Compared to the controls' sons, the sons of the ICP group reported less coughing during the previous 12 months, and more had never smoked. The latter may have an impact on the former and partially explain the finding. The smoking habit may be influenced by the difference in the educational level of the two groups. The observation that mothers with a history of ICP tend to restrict their number of children (Mölsä et al. 2012) may have an impact on this. Hypothetically, parents in families with one child encourage their offspring to strive towards higher education.

The sons of the ICP group reported more urticaria compared to the sons of the controls. Because the frequencies were low, this finding can be considered clinically irrelevant. A higher education level may have an impact on health consciousness, and this could influence the number of appointments with a doctor.

Concerning epilepsy, there were no differences in the groups, although daughters of mothers with a history of ICP have reported more epilepsy. Instead, a trend was found of the sons of the ICP group having more physician-diagnosed acute hepatitis or cholelithiasis.

The reported frequencies of the diseases in our cohort were quite similar to those for the average population in Finland. Migraine was found among 11% of working-age men (Rantala et al. 2007), and asthma was reported in 8% of men in the Health 2011 survey (Koskinen et al. 2012). Respiratory diseases may affect the frequency of cough. Slightly more than 20% of 30–44-year-old men reported an infectious respiratory disease during the previous two months in the Health 2000 survey (Aromaa and Koskinen 2004). The Health 2000 survey also revealed that approximately 30% of men in the same age range as our sample reported backache during the previous month. Roughly 80% of men had had back pain at some time (Aromaa and Koskinen 2004). The results of the study can be considered congruent with previous findings.

7 CONCLUSIONS AND FUTURE IMPLICATIONS

This thesis includes the first Finnish registry studies with broad aspects investigating the health of women with a history of ICP. Some of these aspects were unique also from an international perspective.

Intrahepatic cholestasis of pregnancy is associated with a certain genetic profile. This same genetic background may also influence co-morbidity and survival. The explanation for the differences found between the ICP and the reference groups may stem from genetic predisposition rather than the history of ICP itself.

ICP was found to be associated with an increased risk for cholelithiasis and/or cholecystitis, diseases of the pancreas and hypothyroidism compared to the control group. Arterial diseases were less common in the ICP group compared to the control group. Extending the follow-up time might show whether co-morbidity converges as the cohort gets older. In further studies, the period from ICP to the diagnosis of various diseases might be of great interest. This was the first study to show the association between ICP and hypothyroidism based on registries.

In the present study, the incidence of breast cancer was not statistically significantly higher in women with ICP compared to the controls. This study could not reinforce the previously found association between ICP and liver and biliary cancer. There is no need to change treatment strategies or cancer screening due to a history of ICP.

Based on this study, intrahepatic cholestasis of pregnancy does not seem to influence survival from birth or from ICP delivery. Studying the survival of women with a history of ICP is unique. It is necessary to further extend the follow-up time of the cohort to verify these findings.

Compared to the controls, women who had experienced ICP died more often of gastrointestinal diseases. This study is the first to study the survival of such women from birth and from ICP delivery and their underlying causes of death. Consequently, the results can be regarded as unique.

In the future, an even larger cohort and longer follow-up time would confirm the results, as a wider diagnosis range might be analysed because of the increase in the statistical power. The follow-up time is long, but the power for analysing rare

diseases is weak. Thus, the analysis of rare diseases was not successful in this study material.

The sons of the ICP group did not have remarkable long-term health consequences as a result of their mother's pregnancy-related disorder. This finding can be considered a relief. From a public health perspective, there are numerous women with a history of ICP and the sons of such women, so it is meaningful to further study their health from a long-term perspective.

Women with a history of ICP require special attention from general practitioners to detect co-morbidity. In the future, it would be worthwhile to examine the association between ICP, hepatobiliary diseases and alcohol consumption. This could lead to special guidance for women with a history of ICP regarding alcohol consumption. Additionally, the survival of women who have experienced ICP from birth and from delivery needs to be studied further, as it might transpire to be meaningful in the clinical context.

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APPENDICES

Appendix 1 Information to the recipient
Translated from Finnish by Kristiina Helander, MA.

Appendix 2 Questionnaire
Translated from Finnish by Kristiina Helander, MA.

Appendix 1

INFORMED CONSENT

SURVEY ON THE LATER LIFE HEALTH OF THE MOTHERS WHO GAVE BIRTH AND THE CHILDREN BORN TO THEM IN THE TAMPERE UNIVERSITY HOSPITAL BETWEEN THE YEARS 1969 -1988

I have been asked to participate in the above mentioned scientific research and have received written information about the said research and an opportunity to present questions to the researcher.

I understand that this consent is voluntary and that I have the right to cancel my participation at any stage without giving any reason. I also understand that all information received will be kept confidential.

Place _____

Date ____/___2010

I hereby agree to participate in this research:

_____
participant's signature

_____
print name

_____
date of birth

_____
address

Receiver of the consent:

_____
researcher's signature

Kaisa Turunen

_____
print name

Appendix 2

PIRKANMAAN SAIRAANHOITOPIIRIN KUNTAYHTYMÄ

SURVEY 2010

BOYS

SURVEY ON THE LATER LIFE HEALTH OF THE MOTHERS WHO GAVE BIRTH AND THE CHILDREN BORN TO THEM IN THE TAMPERE UNIVERSITY HOSPITAL, BETWEEN THE YEARS 1969 - 1988

INSTRUCTIONS TO RESPONDENTS

Question-answering instructions are included before each set of questions. **Circle** the number or the letter of the appropriate answer alternative or tick it off. Use numerals to express size and measurements as well as years.

Some questions include sections where you need to write down, for example, names of your medications. In case your answer does not fit into the space provided, please continue on **page 14 of this questionnaire** and include the number of the question at the beginning.

Please answer the questions that are relevant to you, and feel free to skip the ones that do not apply to you. If you want to leave some questions blank or don't remember some detail, you can still return the questionnaire. All answers are valuable to our research.

BACKGROUND INFORMATION

1. Your current age:_____years old

2. What is your primary educational level?

1 primary school or secondary general school or less

2 middle school or comprehensive school

3 matriculation examination (equivalent to UK A-levels)

3. What kind of professional training do you have?

1 no professional training
2 a vocational course, short vocational training i.e. on-the-job-training
3 vocational school, trade school or equivalent
4 vocational college education
5 higher vocational school, higher vocational university degree or similar
6 university or other higher level degree
7 currently studying for a degree

4. How tall are you? _____ centimetres

5. What is your current weigh?_____ kilograms

6. What was your weight at 20? Approximately _____ kilograms

7. What is your highest weight ever?
Approximately _____ kilograms

8. Do you know your birthweight? ☐ no ☐ yes _____ grams

9. How important is sex to you?

Tick the box that best reflects your own situation. If you, for example, are of the opinion that sex is not at all important to you, then tick off the box next to number 1.

not at all important	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5	☐ 6	☐ 7	very important

10. How satisfied are you with your sex life?

very dissatisfied	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5	☐ 6	☐ 7	very satisfied

11. How satisfied are you with your current domestic partnership / marriage/ relationship?
If you don't have a spouse or partner at the moment, leave this question unanswered.

very dissatisfied	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5	☐ 6	☐ 7	very satisfied

CHILDREN

12. Do you have any biological children?

☐ no ☐ yes How many of them is alive:_____

13. Have any of your biological children died?

☐ no ☐ yes How many of them have died:_____

CURRENT HEALTH AND PHYSICAL CONDITION

14. How would you evaluate your current health status (regardless of whether you have any diseases), which of the following best describes you current health status? *Please circle only one alternative.*

1 good

2 fairly good

3 moderate

4 fairly poor

5 poor

15. Do you become breathless or do you experience difficulty in breathing when you walk uphill, climb the stairs or walk briskly on flat land?

1 no

2 yes

Do you become breathless or do you experience difficulty in breathing when you walk at normal space on flat land with people who are the same age as you are?

1 no

2 yes

Do you need to stop to rest due to being out of breath when you walk 150 metres at your own space on flat land?

1 no

2 yes

Do you become breathless even while at rest, for example, when washing yourself or dressing up?

1 no

2 yes

SYMPTOMS AND COMPLAINTS

16. In the past 12 months, have you been **bothered** by any of the following symptoms or complaints? Please mark the replies even when answering "no".

		no	yes			no	yes
1	dizziness	☐	☐	12	general itching of skin	☐	☐
2	coughing	☐	☐	13	dryness of eyes and mouth	☐	☐
3	shortness of breath	☐	☐	14	rheumatic pains	☐	☐
4	chest pain	☐	☐	15	joint pain, joint ache	☐	☐
5	sweating	☐	☐	16	back pain, backache	☐	☐
6	blushing	☐	☐	17	neck and shoulder pain	☐	☐
7	heart palpitations	☐	☐	18	headache	☐	☐
8	foot and/or leg swelling	☐	☐	19	recurring stomach problems	☐	☐
9	urinary problems	☐	☐	20	nausea	☐	☐
(10	gynaecological question – not for men	☐	☐)	21	insomnia	☐	☐
				22	nervousness	☐	☐
11	itching of palms and soles	☐	☐	23	depression	☐	☐

17. In the past 12 months, have you seen a doctor?

Please count all the times you have seen a doctor at health centres, occupational health care centres, private practices and hospital medical services but do not count contacts with doctors as an in-house patient in a hospital ward setting.

1 no

2 yes about _____ times

18. In the past 12 months, have you been hospitalized?

1 no

2 yes about_____ days

19. Has a doctor ever told you that you suffer or have had any of the following diseases or conditions? Please tick the box also when answering no.

Diseases of the digestive system

		no	yes
1	gastric catarrh, gastric or duodenal ulcer	☐	☐
2	helicobacter pylori infection in your stomach	☐	☐
3	gallstones	☐	☐
4	rise in liver function test	☐	☐
5	acute hepatitis	☐	☐
6	chronic hepatitis	☐	☐
7	chronic choledochitis	☐	☐
8	fatty liver	☐	☐
9	liver cirrhosis	☐	☐
10	pancreatitis	☐	☐
11	celiac disease	☐	☐
12	Crohn's disease	☐	☐
13	colitis ulcerosa	☐	☐

Diabetes

		no	yes
14	diabetes managed by diet	☐	☐
15	diabetes requiring tablet or insulin treatment	☐	☐

Diseases of the genitourinary system

		no	yes
16	kidney or urinary tract infection	☐	☐
17	kidney stones	☐	☐
18	renal failure or kidney failure	☐	☐

Diseases of the circulatory system

		no	yes
19	cardiac arrhythmia	☐	☐
20	high cholesterol on medication	☐	☐
21	high blood pressure on medication	☐	☐
22	myocardial infarction	☐	☐
23	chest pain caused by coronary artery disease (angina pectoris)	☐	☐
24	heart failure	☐	☐
25	deep venous thrombosis in lower extremity (treated with blood-thinning injections or pills)	☐	☐
26	blood clot with inflammation in lower extremity (treated with creams such as Trombosol, Hirudoid, Lasonil)	☐	☐
27	blood clot in the lungs	☐	☐
28	cerebral stroke caused by blood clot or thrombosis	☐	☐
29	cerebral stroke caused by cerebral hemorrhage or subarachnoid hemorrhage	☐	☐
30	cerebral stroke by cause unknown to me	☐	☐

Diseases of the musculoskeletal system and connective tissue

31	osteoporosis (porosity of bones)	☐	☐
32	rheumatoid arthritis	☐	☐
33	other chronic inflammatory joint disease	☐	☐
34	osteoarthrosis	☐	☐

Thyroid gland disorders

		no	yes
35	hyperthyroidism	☐	☐
36	hypothyroidism	☐	☐
37	goitre	☐	☐

Lung diseases

		no	yes
38	asthma	☐	☐
39	chronic bronchitis	☐	☐
40	chronic obstructive pulmonary disease (COPD)	☐	☐
41	tuberculosis	☐	☐

Other diseases and conditions

		no	yes
42	cancer, what _____	☐	☐
43	anemia	☐	☐
44	migraine	☐	☐
45	epilepsy	☐	☐
46	hives that lasted at least a month (urticaria)	☐	☐
47	some significant injury, what _____	☐	☐
48	some other significant, longstanding or often recurring disease, what _____	☐	☐

20. Are you allergic to any **medication**(s)?

1 no

2 yes, to which? _____

21. Do you have any **food** allergies?

1 no

2 yes, to which? _____

22. Is there something else that causes you allergic reactions? (such as dog, pollen, nickel)

1 no

2 yes, what? _____

23. Have you had any of the following surgeries?

1 gall bladder surgery
2 gastric or duodenal ulcer surgery
3 other bowel surgery
4 angioplasty
5 coronary artery bypass surgery
6 joint replacement surgery
7 bone fracture surgery
8 benign tumour surgery
9 malignant tumour surgery
10 other, what _____

24. Have you had any of the following bone fractures?

1 hip fracture, _____ times
2 wrist fracture, _____ times
3 spinal or vertebrae fracture, _____ times

MEDICINES

25. **In the past 12 months**, how often have you used the following medicines or products?

	I have not used	I have used occasionally	I have used continuously
painkillers	0	1	2
medicine for high blood pressure	0	1	2
heart medicine	0	1	2
medicine for high cholesterol	0	1	2
gastric acid reducers	0	1	2
dermatologic drugs	0	1	2
eye drops	0	1	2
asthma or allergy medicine	0	1	2
antidepressants	0	1	2
sleeping pills	0	1	2
sedatives	0	1	2
vitamins or trace elements	0	1	2
natural health drugs	0	1	2

MOOD, MENTAL HEALTH

26. Have you ever suffered from a mental disorder?

1 no

2 yes, what? *Circle one or both of the following:*

a depression

b other, what? _____

27. Have you ever been treated for a mental disorder by a doctor or other health care professional?

1 no

2 yes, which problem? *Circle one or both of the following:*

a depression

b other mental health problem, what? _____

28. This section concerns **your mood** during **the past month or 30 days**.

Circle one number on each row. For example, if you have suffered fairly often from insomnia, circle number 2 from the row in question.

	not at all	to some extent	fairly often	extremely often	
I have suffered from insomnia.	0	1	2	3	
I have felt sad, blue and unhappy.	0	1	2	3	
I have felt that everything required a lot of effort.	0	1	2	3	
I have felt fatigue and tired and out of energy.	0	1	2	3	
I have felt lonely.	0	1	2	3	
I have felt hopeless about the future.	0	1	2	3	
I have not enjoyed my life.	0	1	2	3	
I have felt unworthy and useless.	0	1	2	3	
I have felt all pleasure and joy had gone out of my life.		0	1	2	3
I have felt that I could not shake off the blues even with help from family and friends.	0	1	2	3	

SMOKING

29. Have you ever smoked during your life?

1 no *Go to question 34*

2 yes

30. Have you ever smoked regularly (daily or almost daily at least for a year)?

1 no

2 yes, altogether for ____years

31. Do you currently smoke (cigarettes, cigars or pipe tobacco)?

1 I don't smoke

2 I smoke less than once in a week

3 I smoke one day a week

4 I smoke 2–4 days a week

5 I smoke 5–6 days a week

6 I smoke daily

32. How much do you smoke (or smoked before you gave up) **in a day** on average?

a cigarettes _____ pc per day

b cigars _____ pc per day

c pipe tobacco _____ times per day

33. If you don't smoke daily (or did not smoke daily before you gave up smoking), how much do you smoke/ did you smoke **weekly** on average?

a cigarettes _____ pc per week

b cigars _____ pc per week

c pipe tobacco _____ times per week

YOUR ALCOHOL CONSUMPTION IN THE PAST 12 MONTHS

34. How often do you currently drink beer, wine or other alcoholic beverages? *Please count also the times when you drank only small amounts of alcohol such as one bottle of beer or a sip of wine.*

a	never	*Go to question 38*
b	monthly or less	
c	2 to 4 times a month	
d	2 to 3 times a week	
e	4 or more times a week	

35. How many servings of alcohol do you have on a typical day when you are drinking?

a	1 or 2 servings
b	3 to 4 servings
c	5 to 6 servings
d	7 to 9 servings
e	10 servings or more

INSTRUCTIONS FOR ASSESSING SERVING SIZE

1	**serving**	=	a bottle of (0,3 litres) beer (alcohol content 3.7-4.7%)
		or	a glass of (12 cl) table wine
		or	a glass of (8 cl) fortified wine
		or	a glass of (4 cl) spirit or other hard alcohol
1,25	servings	=	a bottle (0,3 litres) of strong beer (alcohol content 4.8-5.8%), Gin Long Drink (factory- produced mixed Finnish drink with grapefruit soda and gin) or strong cider
1,5	servings	=	a half a litre bottle of beer (alcohol content 3.7-4.7%)
2	servings	=	a half a litre bottle of strong beer (alcohol content 4.8-5.8%)
7	servings	=	a bottle (0.75 litres) of wine
10	servings	=	a bottle (0.75 litres) of fortified wine
12	servings	=	a bottle (0.5 litres) of strong spirit (such as Finnish Koskenkorva)

36. How often have you consumed six or more servings of alcohol on one occasion?

a	never
b	less than monthly
c	monthly
d	weekly
e	daily or almost daily

37. In the past 12 months, have you thought you should cut down your alcohol consumption?

a	no
b	yes

DIET

38. Do you have **a special diet** (of your own initiative or by someone else's recommendation)?

1 no

2 yes *Circle one or more of the following.*

- a lactose-free or low-lactose diet
- b gluten-free diet (celiac disease)
- c gallbladder diet
- d low-fat or low-cholesterol diet
- e weight loss diet
- f vegetarian or vegan diet: how old were you when you last ate meat, chicken or fish?

  _____years old
- g other special diet, what _____

  _____

PHYSICAL ACTIVITY

39. How much exercise have you done in the past 12 months? How strenuous would you estimate the exercise/ physical activity you did was? *Circle one alternative on each row.*

	AVERAGE DURATION OF EXERCISE DURING A REGULAR WEEK				
	no exercise at all	less than half an hour weekly	about an hour weekly	2-3 hours weekly	at least 4 hours weekly
INTENSITY OF EXERCISE					
corresponding to walking	0	1	2	3	4
corresponding to brisk walking	0	1	2	3	4
corresponding to light running (jogging)	0	1	2	3	4
corresponding to running	0	1	2	3	4

You can write down any additional comments on this page. If you want to continue your answers to any questions on the previous pages, please include the number of the question at the beginning of your comment.

PUBLICATIONS

PUBLICATION I

Raskaushepatoosi – hankala, mutta ohimenevä vaiva

Hämäläinen ST, Turunen K, Mattila K, Uotila J, Sumanen M.

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SUVI-TUULIA HÄMÄLÄINEN
LL, yleislääketieteeseen erikoistuva lääkäri, tutkija
Tampereen yliopisto, lääketieteen yksikkö, yleislääketieteen oppiala
terveyskeskuslääkäri
Ikaalisten kaupunki
suvi.hamalainen@uta.fi

KAISA TURUNEN
LT, yleislääketieteen erikoislääkäri
vt. osastonlääkäri
Tampereen kaupunki

KARI J. MATTILA
LKT, professori emeritus
Tampereen yliopisto, lääketieteen yksikkö, yleislääketieteen oppiala

JUKKA UOTILA
LT, vt. professori
Tampereen yliopisto, lääketieteen yksikkö, naistentautien ja synnytysten oppiala
osastonylilääkäri
TAYS, naistentautien ja synnytysten vastuualue

MARKKU SUMANEN
LT, apulaisprofessori
Tampereen yliopisto, lääketieteen yksikkö, yleislääketieteen oppiala

Raskaushepatoosi – hankala, mutta ohimenevä vaiva

- Raskaushepatoosiin sairastuu noin 1 % synnyttäjistä.
- Tauti puhkeaa tavallisesti 30. raskausviikon jälkeen.
- Tyypillisenä oireena on ihon kutina. Maksaperäisten transaminaasien ja sappihappojen tai molempien tasot kohoavat.
- Ennenaikaisen synnytyksen, sikiön ahdinkotilan ja kohtukuoleman riskit ovat suurentuneet.
- Äiti lähetetään neuvolasta äitiyspoliklinikalle jatkotutkimuksiin ja seurantaan.
- Synnytyksen jälkeen raskaushepatoosi paranee täysin. Oireet häviävät parissa päivässä ja laboratorioarvot normaalistuvat kahden kuukauden kuluessa.
- Potilaalla on suurentunut maksa-, haima ja sappisairauksien elinikäinen riski.

Äitiysneuvola tavoittaa lähes kaikki raskaana olevat naiset. Neuvolalääkärin ja terveydenhoitajan tehtävänä on seuloa hyvin sujuvista raskauksista ne, joissa tarvitaan lisätutkimuksia ja -hoitoja. Raskaudenaikainen ihon kutina on yleinen ongelma. Kutinasta kärsivien äitien joukosta on tunnistettava raskaushepatoosi, johon sairastuu noin 1–1,5 % synnyttäjistä. Hepatoosin myöhäisvaikutusten vuoksi naisille ja heidän lapsilleen saattaa tulla kysymyksiä useiden erikoisalojen lääkärien vastaanotoilla.

Epidemiologia, etiologia ja patogeneesi

Vuosina 2013–2015 raskaushepatoosin esiintyvyys oli Tampereen yliopistollisessa sairaalassa synnyttäneiden keskuudessa 1,1–1,5 %, kun taas Keski-Euroopassa esiintyvyys on vähäisempää, 0,2–1,0 % (1). Raskaushepatoosin etiologiaa ei ole pystytty osoittamaan aukottomasti. Luultavasti siihen vaikuttavat monet eri tekijät. Sen on ajateltu johtuvan maksan hormonaalisesta ylikuormituksesta geneettisesti alttiilla naisilla. Myös ympäristötekijöitä on ehdotettu taudin syyksi (2,3).

Raskaushepatoosi uusiutuu 50–70 prosentissa seuraavista raskauksista. Riski on suurin (92 %) niillä, joilla esiintyy MDR3-geenissä mutaatio (4). Useat geenit tai geenimutaatiot voivat osallistua taudin monimutkaiseen patogeneesiin (5). Raskaushepatoosiin sairastuneella naisella on useammin lähisuvussa maksan toimintahäiriötä raskauden aikana (6).

Hormonaaliset tekijät ovat olennaisia raskaushepatoosin patogeneesissa. Taudin on ajateltu aiheutuvan riittämättömästä maksan kapasiteetista metaboloida suuria määriä istukan tuottamia steroidihormoneja raskauden aikana (7,8). Maksasoluissa sappihappoja poistavan pumpun toimimattomuus tai hepatosyyttien kyvyttömyys erittää istukan tuottamien steroidien hajoamistuotteita sappeen voivat aiheuttaa turvotusta maksassa ja sapen salpauksen. Monisikiöraskaudessa istukan tuottamien steroidihormonien määrä on suurempi kuin yksisikiöisessä raskaudessa. Raskaushepatoosin riski saattaa tästä syystä olla 2,5–5-kertainen (9,10).

Ympäristötekijät mahdollisesti vaikuttavat raskaushepatoosin ilmaantumiseen. Raskaushepatoosi näyttää olevan talvisin yleisempi ja vaikeampi (3). Lisäksi ravintotekijöillä, esimerkiksi seleenin vähäisyydellä, voi olla merkitystä taudin kehittymisessä (2). Raskaushepatoosia sairastavilla äideillä on keskiraskaudessa tai synnyttäessä matalampi D-vitamiinitaso kuin verrokeilla (11). D-vitamiinitason on todettu olevan käänteisesti verrannollinen lapsiveden lapsenpihkalla värjäämiseen (12). Veren kohonneen glukoositason (13) ja lipidiarvon (14) on havaittu olevan yhteydessä raskaushepatoosiin. Koeputkihedelmöityshoidolla alkaneisiin raskauksiin liittyy lähes nelinkertainen tautiriski (15). Yli 35 vuoden ikä saattaa lisätä raskaushepatoosin riskiä (7).

Raskaushepatoosin pääasiallisen oireen, kutinan, on ajateltu johtuvan seerumin sappihappojen suurentuneesta määrästä ja ihon liiallisesta

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VERTAISARVIOITU

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sappihappopitoisuudesta. Sappihappojen merkitys on kuitenkin kyseenalaistettu, sillä se ei näytä olevan ainoa kutinaa selittävä tekijä (16,17). Kutina voi alkaa jo ennen maksa-arvojen nousua tai vasta sen jälkeen (16). Steroidit ja niiden hajoamistuotteet välittävät sapen salpaukseen liittyvää (kolestaattista) kutinaa (18). Kohonneita histamiinitasoja on havaittu kolestaasipotilailla (19), mutta histamiinilla ei luultavasti ole olennaista merkitystä kutinan välittäjänä. Potilaille, joilla on kolestaattinen kutina, ei kehity samanlaisia ihoreaktioita kuin niille, joilla on kohonnut histamiinitaso. Kaikki hepatoosipotilaat eivät hyödy antihistamiineista kutinan hoidossa (20), mutta voivat hyötyä öisin antihistamiinien väsyttävästä vaikutuksesta (21).

Oireet ja diagnostiikka

Raskaushepatoosi alkaa yleensä 30. raskausviikon jälkeen. Myös varhaisemmin alkavia tautimuotoja, jopa raskausviikolla 8, on kuvattu (3).

Terveen ihon kutina on pääasiallinen oire, joka herättää epäilyn raskaushepatoosista. Pitkään kestävä ja voimakas kutina voi ilmetä raapimisesta aiheutuvina ihorikkoina. Tyypillisesti kutina on voimakkainta kämmenissä, jalkapohjissa ja vatsalla. Se voi olla erityisen häiritsevää öisin ja aiheuttaa unettomuutta ja väsymystä.

Jossakin maissa on todettu keltaisuutta jopa noin 10–15 prosentilla hepatoosia sairastavista äideistä, joskin se on suurimmaksi osaksi lievää (1). Vaihtelevia kliinisiä kuvia on kuvattu: 693 raskaushepatoosipotilaan kohortissa ei yhdelläkään ollut kliinistä keltaisuutta (22). Suomessa hepatoosipotilaiden keltaisuus on hyvin harvinaista.

Jos kliininen epäily hepatoosista herää, varmistetaan asia laboratoriokokeilla. Neuvolassa tarkistetaan P-ALAT ja sappihapot. Jos laboratoriokokeissa (ALAT, ASAT, bilirubiini ja sappihapot) on poikkeavuutta, lähetetään odottaja erikoissairaanhoitoon äitiyspoliklinikalle. Diagnoosiin vaaditaan kutinaoire ja ainakin yhden maksantoimintakokeen suurentunut arvo. Maksabiopsiassa näkyy lievä kolestaasi, jossa on intrasellulaarisia sappipigmenttejä ja kanavissa sapen salpausta, mutta ei nekroosia (23). Mak-

TAULUKKO 1.

Raskaushepatoosin erotusdiagnostiikka.

	Tyypillisin raskauskolmannes	Kutina	Maksa-arvot ↑	Sappihapot ↑	Keltaisuus	Muita oireita tai löydöksiä
Raskaushepatoosi	3.	+	+	+	(+)	
Sappikivitauti	–	(+)	(+)	+	+	
Hepatiitit	–	+	+	+	+	Virusantigeeni löydettävissä
Raskaudenaikainen akuutti rasvamaksa	3.	+	+	(+)	(+)	Pahoinvointi Oksentelu Oikean kylkikaaren kipu Hypoglykemia Vuodot 20 % äidin kuolleisuus
Pre-eklampsia	3.	–	+	–	–	Hypertensio Proteinuria Päänsärky Näköhäiriöt Vatsakipu
Alkuraskauden pahoinvointi	1.	–	(+)	(+)	(+)	
Raskaudenaikainen atooppinen ihottuma	2.	+	–	–	–	Ihottuman tyypillinen ulkonäkö ja tyyppipaikat
Gestationaalinen pemfigoidi	2. tai 3.	+	–	–	–	Rakkulat Sikiön riski pienikokoisuuteen ja ennenaikaisuuteen
Monimuotoinen raskausihottuma	3.	+	–	–	–	Läiskäinen ihottuma Rakkulat mahdollisia

– = ei tyypillistä raskauskolmannesta/ei oiretta tyypillisesti; + = tyypillinen oire; (+) = mahdollinen oire, mutta ei tyypillisin

Terveen ihon kutina on pääasiallinen oire, joka herättää epäilyn raskaushepatoosista.

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sabiopsiaa ei kuitenkaan tarvita tyypillisen raskaushepatoosin diagnostiikassa.

Raskaushepatoosi on yleensä helppo erottaa muista maksan toimintahäiriöistä. Oireiden varhainen alkamisajankohta tai maksa-arvojen pysyminen koholla synnytyksen jälkeen antavat aiheen pohtia muiden maksasairauksien mahdollisuutta (24).

Tärkeimpiä erotusdiagnostisia sairauksia kuvataan taulukossa 1. Niistä tärkeimpiä ovat sappikivitauti ja hepatiitit. Sappikivitaudin vahvistaa kaikututkimuksessa löydetyt sappikivet. Ne oireilevat kuitenkin raskaana olevilla yllättävän harvoin, minkä selittänee raskauden aikainen suuri progestiinipitoisuus (25). Hepatiitit aiheuttavat systeemisiä oireita, ja virusantigeeni on löydettävissä.

Transaminaasiarvot voivat nousta myös vaikeassa pre-eklampsiassa, erityisesti HELLP-oireyhtymässä (hemolysis, elevated liver enzymes, low platelets), mutta siihen ei liity kolestaasia eikä kutinaa. Akuutti raskaudenaikainen rasvamaksa (AFLP) puhkeaa tyypillisesti äkillisesti loppuraskaudessa ja johtaa nopeasti maksan toimintavajaukseen. Se on kuitenkin harvinainen (1/10 000–13 000). Hyperemesis gravidarum eli alkuraskauden pahoinvointi voi myös aiheuttaa lievää hyperbilirubinemiaa ja transaminaasitasojen kohoamista. Alkuraskauden pahoinvointiin ei tyypillisesti liity kutinaa. Raskaushepatoosin varhainen alku ensimmäisellä kolmanneksella on hyvin harvinaista (21).

Raskauden aikana puhkeava atooppinen ihottuma, urtikarinen tai gestationaalinen pemfigoidi ja virusinfektiot, kuten Ebstein-Barrin tai sytomegalovirus, voivat joskus aiheuttaa erotusdiagnostisia haasteita. Näissä esiintyy kuitenkin taudille tyypillisiä ihottumia.

Seuranta ja hoito

Hepatoosiraskaus lisää ennenaikaisen synnytyksen riskiä (12–44 %) (8,22,26), sikiön ahdinkoa (10–44 %) (8,22,27,28) ja kohdunsisäisen kuoleman vaaraa (1–3 %). Näiden sikiöhaittojen aiheuttajana pidetään sappihappoja (22,29). Niiden on osoitettu aiheuttavan istukan laskimoiden vasokonstriktiota ja lisäävän myometriumin herkkyyttä oksitosiinille (30,31). Niiden on myös osoitettu vaikuttavan useilla eri tavoilla istukkaan ja sikiön sydämen sykkeeseen (32,33). Kohdunsisäisen kuoleman riski on yhdistetty sappihappoihin, jotka aiheuttavat sikiölle rytmihäiriöitä (34).

Raskaushepatoosin seuranta ja hoito tapahtuvat äitiyspoliklinikalla. Maksan toimintakokeita, joista ALAT ja sappihapot tärkeimpinä, tarkkaillaan kerran tai kaksi viikossa. Sikiön vointia tarkkaillaan yksilöllisesti kardiotokografian (KTG) ja ultraäänen avulla. Sikiön kuolema on äkillinen tapahtuma, ja käytettävissä olevilla seurantamenetelmillä sitä on vaikea ennustaa (35). Toisinaan päädytään käynnistämään synnytys tai tekemään keisarileikkaus. Kuitenkin tutkimusnäyttö keisarileikkauksen tai varhaisen käynnistämisen eduista puuttuu (36).

Synnytyksen jälkeen maksa-arvot palautuvat normaaleiksi. Niiden seurannan tarpeellisuudesta synnytyksen jälkeen vallitsee erilaisia käsityksiä. Suomessa maksa-arvoja ei yleensä ole seurattu, jos synnyttäjä on parantunut oireettomaksi ja kliininen kuva on ollut tyypillinen. Jos oireet jatkuvat synnytyksen jälkeen, tutkitaan maksakokeet perusterveydenhuollossa (kuvio 1).

Lääkkeettömistä hoidoista vähärasvaista ruokavaliota voidaan suositella vähentämään maksan metabolista taakkaa (37). Oireenmukaisena hoitona voidaan kutinaan käyttää antihistamiineja, vaikkakin niiden tehoa on epäilty kutinan syyteorioiden perusteella (17). Myös viilentävää mentolivoidetta on suositeltu lieventämään ihon kutinaa (24).

Ursodeoksikoolihappoa (UDCA) pidetään raskaushepatoosin tehokkaimpana hoitona. Se vaikuttaa tehokkaalta vähentämään kutinaa ja parantamaan maksa-arvoja, ja se voi myös ehkäistä sikiön ahdinkoa (38). Ursodeoksikoolihappo vähentää ja korvaa sapen endogeenisiä sappihappoja, normalisoi maksaentsyymien tasoja kaikissa intrahepaattisissa kolestaattisissa tiloissa ja pienentää bilirubiinipitoisuuksia. Se myös parantaa sappihappojen kuljetusta pois istukasta ja siten voisi vähentää tautiin liittyviä sikiön riskejä (38,39). Tuoreessa kotimaisessa tutkimuksessa ursodeoksikoolihappo helpotti äidin kokemaa kutinaa ja paransi maksan toimintakokeita vaikuttamatta kuitenkaan sikiöön ja istukan estrogeenituotantoon (40). Tarvitaan kuitenkin lisää tutkimusta sen vaikutuksista sikiöön (21).

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Myös muita valmisteita on käytetty raskaushepatoosin hoidossa, joskaan yhtä tehokasta ja turvallista kuin ursodeoksikoolihappo ei ole toistaiseksi löytynyt. Aiemmin on käytetty muun muassa barbituraatteja, rifampisiinia, kolestyramiinia ja deksametasonia (41). Rifampisiini on antibiootti, jolla on vaikutuksia sapen erittymiseen. Sitä käytetään primaarisen biliaarisen kirroosin hoidossa. On esitetty, että ursodeoksikoolihappo yhdistettynä rifampisiiniin olisi tehokkaampi kuin kumpikaan monoterapiana, mutta satunnaistettuja tutkimuksia ei tästä ole. Kolestyramiini voi heikentää ursodeoksikoolihapon ja rasvaliukoisten vitamiinien imeytymistä suolistosta ja lisätä verenvuodon riskiä synnytyksen aikana tai sen jälkeen. Siksi sitä ei suositella ensilinjan hoidoksi (21). Joissakin tapauksissa deksametasoni lievittää tehokkaasti hepatoosin oireita ja alentaa seerumin sappihappotasoja (42,43,44). Deksametasonin toistuvat suuret annokset on kuitenkin yhdistetty pieneen syntymäpainoon (45) ja poikkeavaan hermoston kehitykseen (46), minkä vuoksi sitä ei suositella raskaushepatoosin ensilinjan hoidoksi.

Ennuste

Raskaushepatoosi lisää ennenaikaisen synnytyksen ja vastasyntyneen erityishoidon tarvetta (7). Havaintoja syntyneiden lasten matalammista Apgar-pisteistä on julkaistu (7), mutta kaikki tutkimukset eivät ole vahvistaneet tällaista havaintoa (47).

Raskaushepatoosilla on hyvä ennuste. Synnytyksen jälkeen kutina häviää parissa päivässä (1). Jos keltaisuutta on ollut, se häviää puolestaan parissa viikossa. Laboratoriokokeet normalisoituvat 2–8 viikon aikana. Jos oireet jatkuvat synnytyksen jälkeen, on etsittävä taustalta piilevää maksasairautta (48). Seuraavassa raskaudessa hepatoosi on yleinen (4), mutta raskauden seuranta voi tapahtua normaalisti neuvolassa. Kutinan ilmaantuessa ohjelmoidaan maksa-arvojen tutkimukset.

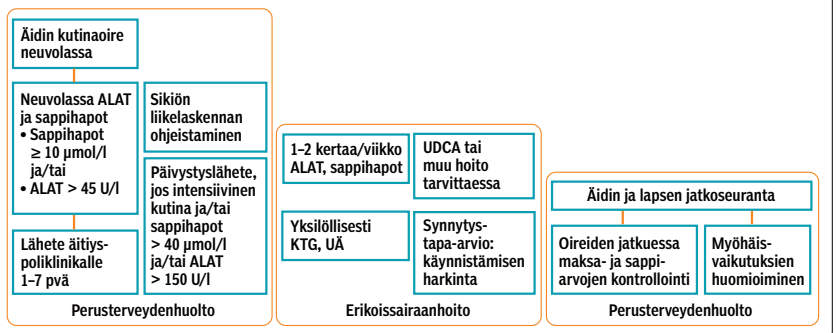
Pitkäaikaisvaikutukset

Raskaushepatoosiin liittyy useiden maksa-, sappi- ja haimasairauksien lisääntynyt riski. Kotimaisessa suuressa tutkimuksessa todettiin kolminkertainen hepatiitti C:n riski ja kahdeksankertainen alkoholiin liittymättömän maksakirroosin riski. Sappikivien ja sappirakon tulehduksen riski oli lähes nelinkertainen. Alkoholiin liittymättömän haimatulehduksen riski oli puolestaan kolminkertainen, mutta riskin kasvua voi selittää myös sappikivien suurempi esiintyvyys (48). Toisessa kotimaisessa tutkimuksessa on lisäksi hypotyreoosin ja rintasyövän havaittu olevan yleisempiä hepatoosiin sairastuneilla naisilla (49).

Suomalaisessa potilasryhmässä taudin ei ole todettu vaikuttavan juurikaan naisten terveystottumuksiin pidemmällä aikavälillä (50). Raskaushepatoosin sairastaneet naiset ovat harvemmin käyttäneet yhdistelmäehkäisypillereitä,

KUVIO 1.

Raskaushepatoosin hoito, seuranta ja lähettämisindikaatiot.



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ja heidän on havaittu rajoittaneen lapsilukuaan terveyssyistä useammin kuin verrokkien (51). Hormonikorvaushoitojen määrään ei taudin ole todettu kotimaisessa väestöryhmässä vaikuttavan, mutta naiset ovat muita useammin kohdanneet kieltoja niiden käyttämisestä (52).

Nykyisten matalahormonisten yhdistelmäehkäisypillerien käyttö näyttää turvalliselta raskaushepatoosin jälkeen. On kuitenkin ehdotettu, että potilaalle kerrotaan kutinan mahdollisuudesta ja testattaisiin rutiinimaisesti maksakokeet kolmen ja kuuden kuukauden jälkeen yhdistelmäehkäisypillerien aloituksesta (53). Progestiinia sisältävien minipillerien käyttö on turvallista eikä laboratoriokontrolleja tarvita (54).

Raskaushepatoosiin liittyy geneettinen tekijä, mutta tietoa lasten myöhemmästä terveydestä on vähän. Kahdessa suomalaistutkimuksessa päätulos oli, ettei hepatoosin sairastaneiden äitien tyttärien tai poikien terveys eronnut verrokeista (55,56). Tyttärien riski sairastua raskaushepatoosiin omassa raskaudessaan on suurentunut (6).

Oraalisen tai transdermaalisen hormonikorvaushoidon ei ole havaittu haittaavan maksan toimintaa hepatoosin sairastaneilla naisilla (57), joten nykytiedon valossa se näyttää olevan turvallista.

Raskaushepatoosin sairastaminen lisää jonkin verran joidenkin sairauksien riskiä (58), mutta hepatoosi on kuitenkin äidille varsin harmiton. Naisia tulee rohkaista elämään normaalia elämää raskaushepatoosin sairastamisen jälkeen.

Lopuksi

Raskaushepatoosi on äidille varsin vaaraton tauti, mutta sikiön riskien vuoksi tila vaatii seurantaa erikoissairaanhoidossa. Ursodeoksikoolihappo on tällä hetkellä suositelluin lääkehoito. Tietoa tautiin mahdollisesti liittyvistä pitkäaikaisseurauksista on kertymässä. ●

SIDONNAISUUDET
Suvi-Tuulia Hämäläinen, Kaisa Turunen, Kari J. Mattila, Jukka Uotila, Markku Sumanen: ei sidonnaisuuksia.

English summary | www.laakarilehti.fi | in english
Intrahepatic cholestasis of pregnancy

English summary

SUVI HÄMÄLÄINEN
M.D., Researcher, University of Tampere
General Practioner, Ikaalinen Health Center
suvi.hamalainen@uta.fi

KAISA TURUNEN
KARI J. MATTILA
JUKKA UOTILA
MARKKU SUMANEN

Intrahepatic cholestasis of pregnancy

Intrahepatic cholestasis of pregnancy (ICP) is a liver disorder where bile flow is impaired. The prevalence of ICP is approximately 1% in Finland. ICP usually manifests after 30 gestational weeks, and the main symptom is itching especially on the palms, soles and abdomen. For the diagnosis of ICP also a rise in liver function parameters, typically ALAT and/or bile acids, is also required.

The etiology and pathogenesis of ICP is complex. In addition to the genetic susceptibility and the hormonal component during pregnancy, environmental factors have also been suggested. The disease is quite non-harmful to the mother, although itching can be irritating and disturb her sleep. From primary health care, the pregnant woman with ICP should be referred to an obstetric clinic, where she will be carefully monitored by laboratory tests, CTG (cardiotocography) and ultrasound because of the fetal risks. ICP increases the risk of premature delivery, and fetal distress during labour and stillbirth. The recommended treatment is ursodeoxycholic acid, which may improve liver function tests and reduce fetal risks. In certain cases induction of labour or caesarean section is indicated.

Itching subsides within a couple of days after labour and laboratory tests normalize within eight weeks. Women with a history of ICP have an increased risk of liver, pancreatic and biliary disorders. Likewise, higher frequencies of hypothyroidism and breast cancer have been reported.

PUBLICATION II

Intrahepatic cholestasis of pregnancy and co-morbidity: A 44-year follow-up study.

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PUBLICATION III

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Research Article Open Access

Intrahepatic Cholestasis of Pregnancy and Cancer: A Cohort Study

Suvi-Tuulia Hämäläinen[1,2*], **Kaisa Turunen**[1], **Kari J Mattila**[1], **Elise Kosunen**[1,3] and **Markku Sumanen**[1]

[1]*Department of General Practice, Faculty of Medicine and Life Sciences, University of Tampere, Tampere, Finland*

[2]*Janakkala Health Centre, Turenki, Finland*

[3]*Centre for General Practice, Pirkanmaa Hospital District, Tampere, Finland*

[*]**Corresponding author:** Suvi-Tuulia Hämäläinen, Department of General Practice, Faculty of Medicine and Life Sciences, University of Tampere, Tampere, Finland, Tel: +358368011; E-mail: hamalainen.suvi.t@student.uta.fi

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Abstract

Objective: In a previous questionnaire study, more breast cancers were reported by women with intrahepatic cholestasis of pregnancy (ICP) than by the controls. The aim of this study was to establish whether ICP is associated with cancer in the Finnish Cancer Registry data, the study population being the same cohort as in the questionnaire study.

Methods: The study population comprised 571 women with ICP in at least one pregnancy and 1,333 controls from Tampere University Hospital in Finland during 1969–1988. The cancer data were obtained from the Finnish Cancer Registry. The cancers were classified by ICD-O-3 and diagnosed during the period 1953−2013.

Results: In the ICP group, the odds ratio of cancers (OR 1.26, 95% CI 0.96–1.64), and breast cancer in particular (OR 1.36, 95% CI 0.91–2.03), was slightly higher than in the control group. Seven percent of the ICP group and 5.3% of the control group had breast cancer.

Conclusion: Based on this study there is not a significant association between ICP and cancer. Earlier observation in the questionnaire study regarding association between ICP and breast cancer cannot be confirmed by this registry based study.

Keywords Intrahepatic cholestasis of pregnancy; ICP; Cancer

Introduction

Intrahepatic cholestasis of pregnancy (ICP) is a reversible liver disorder with pruritus as the main symptom, especially on the palms and soles. An elevated serum bile acid and transaminase concentration is also required for diagnosis [1]. In Europe, the incidence of ICP is approximately 1%, but rates vary geographically [2]. In Finland, the incidence is approximately 1.0−1.5% [3] and in Sweden the incidence is 0.5−0.75% [4]. Hormonal factors seem to contribute to the pathogenesis of ICP [5,6]. Estrogen may participate in the development of cholestasis [7] and progesterone may impair hepatic bile homeostasis [8]. Genetic factors are known to be involved in the pathogenesis; ICP is inherited as a sex-limited dominant phenotype and multiple genes are influential [9]. Multidrugresistant protein 3 (MDR3) is associated with up to 15% of ICP cases [10,11]. Environmental factors may also have a role in the pathogenesis of the disorder [12]. In addition, a positive family history [13] and twin pregnancies raise the risk of ICP [14].

Excessive exposure of endogenous estrogen over the lifetime may be a causative factor of breast cancer [15]. Hormonal, genetic, and environmental factors are known to have an impact on the aetiology and pathogenesis of cancers and ICP. Cancer antigen 15-3 (CA15-3) is a glycoprotein commonly found in breast cancer cells, and its levels in serum reflect the amount of breast cancer cells in the body. CA15-3 levels are raised during pregnancy in general, but they are higher in ICP pregnancies than in controls [16]. In an extensive registry-based study, ICP was associated with an increased risk for later hepatobiliary cancer. Hepatitis C infection was strongly associated with liver cancer, but after adjusting for this diagnosis, women with ICP were still at increased risk for liver malignancy. In addition, in a separate analysis excluding all women with gallstone disease or cholangitis, women with ICP had an increased risk for biliary tree malignancies [17].

A low number of child births has been associated with an increased risk for breast cancer. Since mothers with ICP have been found to limit their child number more often than controls [18], it may be speculated whether this has increased the incidence of breast cancers. Primary healthcare arranges almost exclusively maternity care in the Nordic countries [19]. In Finland health centres maintain maternity health clinics where a nurse or a midwife and a Family Doctor are responsible for care [20]. The maternity health clinics in primary health care usually detect ICP. If a pregnant woman complains of pruritus her ALAT and bile acids values are screened. Either of these values being elevated the mother is referred to an obstetrician [21]. If pruritus is intolerable the mother is referred to the obstetric clinic without waiting the results of the blood test.

A questionnaire study observed that ICP may be associated with an elevated risk for breast cancer [22]. However, the study was based on subjective information obtained from self-reports. The aim of the present study was to investigate, using objective registry data, whether ICP has an association with breast cancer or other cancers when using the same cohort as the questionnaire study.

Material and Methods

All ICP pregnancies at Tampere University Hospital (TUH) during 1969–1988 were collected from the patient records. From 1969 to 1986, ICD-8 was used at TUH. Because ICD-8 did not include a precise code for ICP, we checked all the obstetric codes that might contain ICP: 637.9 Toxicosis NUD, 639.00 Pruritus, 639.01 Icterus gravis, 639.09 Necrosis acuta et subacuta hepatis, and 639.98 Aliae definitae. Thereafter, we checked the written diagnosis behind the code, and if it referred to ICP, we included the case for further selection. ICD-9 was used between 1987 and 1988, and it contained the appropriate codes 6467A Hepatosis gravidarum and 6467X Hepatopathia alia. The diagnosis was verified from each patient record with the presence of the main symptom of itching and abnormal laboratory test results. At least one of the following was required: ASAT >35 U/l, ALAT >40 U/l, or bile acids 6 µmol/l or more.

The study population comprised 687 ICP deliveries. The data included some women with repeated ICP deliveries and each of these women was studied as an individual case. The ICP group thus contained 575 women. The proceeding and following subjects in the maternity ward diary were taken as controls for each ICP case. There were 1,374 controls in total. The groups were comparable regarding age, educational level, and body mass index. The deliveries of mothers with ICP took place at earlier gestational weeks than those of the controls. Four women were ruled out from the ICP cases and 41 from the controls because of a missing personal identity code. The final data comprised 571 women with ICP and 1,333 controls.

The cancer data were obtained from the Finnish Cancer Registry in January 2014 based on personal identity codes. All physicians, hospitals, and other relevant institutions have had an obligation to report every cancer to the Finnish Cancer Registry since 1961. The database contains all the diagnosed cancers and cancer deaths in Finland since 1961 and the most of cancers since 1953, when systematic cancer registration was started [23]. The Finnish Cancer Registry also contains information on all death certificates that mention cancer. The Registry takes notice of the completeness and accuracy of its data, and its completeness has been shown to be over 99% [24]. The Registry is upheld by the National Institute for Health and Welfare of Finland. The study data included all reported cancers of the cohort during 1953–1960, all registered cancers during 1961–2013, and the location and behaviour of the cancer. The cancers were reported by ICD-O-3 topographical codes [25]. Women who had had more than one cancer were also included in the study. The cancers were classified by ICD-O-3 codes into larger subgroups. Cancer behaviour was classified as benign, unclear behaviour, carcinoma in situ, or malignant.

The data were analysed using the SPSS System for Windows, Version 22.0. The results are presented as frequencies and percentages. Statistical significance was tested with a chi-squared test. Binary logistic regression analysis was performed to obtain odds ratios (OR) and 95% confidence intervals (CI). The dependent variable was "ICP or not". T-test was performed to explore difference regarding age at the diagnose moment of cancer. The cohort did not obtain informed consent because the study is retrospective and does not have an effect on treatment. The study has the approval of the Regional Ethics Committee of Tampere University Hospital (R02149) and the National Institute for Health and Welfare in Finland (THL/1051/5.05.00/2014).

Results

In the ICP group, 96 women (16.8%) had been diagnosed with at least one cancer, compared to 185 women (13.9%) in the control group. The difference was not statistically significant (p=0.098). Mothers with ICP had a slightly higher risk for cancer (OR 1.26, 95% CI 0.96–1.64) than the control mothers. None of the mothers with ICP and fifteen (1.1%) of the controls had been diagnosed with two or more separate cancers (p=0.011). One of the controls had had three separate cancers. Three women had been diagnosed with a cancer before labour and all of them were controls.

The occurrence of cancers is presented in Table 1. Breast cancer was the most common cancer in both groups. The mothers with ICP had a slightly higher risk for breast cancer (OR 1.36, 95% CI 0.91–2.03) than the control mothers. Breast cancer was diagnosed at a slightly older age in the ICP group than in the control group but the difference was not statistically significant.

ICD-10 code	Cancer	Mothers with ICP n=571		Control mothers n=1,333		Difference	
		n	%	n	%	% units	p-value
C50	Breast	40	7.0	70	5.3	1.7	0.133
C73-C75	Thyroid and other endocrine glands	6	1.1	5	0.4	0.7	0.075
C64-C68	Urinary tract	4	0.7	3	0.2	0.5	0.116
C42	Haematopoietic and reticuloendothelial systems	2	0.4	2	0.2	0.2	0.382
C30-C39	Respiratory and intrathoracic organs	1	0.2	3	0.2	0.0	0.827
C40-C41	Bone and articular cartilage	1	0.2	3	0.2	0.0	0.827
C80	Unknown primary site	1	0.1	1	0.1	0.0	–
C00-C14	Lip, oral cavity, and pharynx	0	0.0	1	0.1	-0.1	0.513
C15-C26	Digestive organs	7	1.2	19	1.4	-0.1	0.731
C45-C49	Mesothelial and soft tissue	0	0.0	1	0.1	-0.1	0.513
C43-C44	Melanoma and other malignant neoplasms of skin	18	3.2	38	2.9	-0.1	0.721
C51-C58	Female genital organs	14	2.5	35	2.6	-0.1	0.826
C69-C72	Eye, brain, and other parts of central nervous system	3	0.5	8	0.6	-0.1	0.844
C77	Lymph nodes	2	0.4	7	0.5	-0.1	0.610

Table 1: The occurrence of cancers in mothers with ICP and the controls.

Melanoma and other malignant neoplasms of the skin as well as cancers of the female genital organs were among the most common cancers in both groups. Cancers of the thyroid and other endocrine glands and urinary tract cancer were more common in the mothers with ICP than in the controls, but the differences were not statistically significant. Of the digestive organ cancers, hepatobiliary cancer was also examined separately. Hepatobiliary cancer was found in one mother with ICP and among none of controls. Most of the cancers (nearly 90%) were malignant in both groups (Table 2). The difference between the groups was not statistically significant (p=0.758).

Cancer behaviour	Mothers with ICP (n=96) (%)	Control mothers (n=185) (%)
Malignant	87.5	86.5
Carcinoma in situ	6.3	5.4
Unclear behaviour	0.0	1.1
Benign	6.3	7.0

Table 2: Cancer behaviour according to ICD-O-3 among mothers with ICP and the controls.

The mothers with ICP had been diagnosed with cancer at a slightly older age, the mean age being 53.0 years in the ICP group and 51.8 years in the control group. The difference was 1.2 years (p=0.315). The mean age of mothers who had not been diagnosed with cancer was 61.5 years among ICP mothers and 61.3 years among controls in 31/12/2013.

Discussion

The ICP group and the control group evinced minor differences in most of the study outcome measures. The findings are in agreement with former observations on the association of cancer and ICP. In the control group, there were women who had been diagnosed with two or more separate cancers, but in the ICP group each woman with cancer had been diagnosed with only one cancer. ICP was associated with a slightly higher risk for cancer, especially breast cancer.

The aim of the present study was to establish whether ICP is associated with an increased risk for cancers, and especially for breast cancer, which was the result found from the earlier study based on self-reports. Despite the small loss of cases, the data were adequate. The data obtained from the Finnish Cancer Registry can be considered reliable.

Medications may have an impact on the risk for cancer. Over the past decades, various treatments have been used for ICP. We have not collected information about the medication for ICP among our study population, and consequently the role of medication regarding the risk for cancer cannot be evaluated.

A recent Swedish study did not find any clear association between overall cancer and ICP [17], which is in agreement with our findings. In the same study, an increased risk for later hepatobiliary cancer in women with ICP was found (liver cancer: HR 3.61; and biliary tree cancer: HR 2.62). In the aforementioned study, the occurrence of hepatobiliary cancers was small in the ICP group (0.1–0.2%). Based on the above study, the expectation value to find any hepatobiliary cancers in our study was very small. However, one hepatobiliary cancer was found in our ICP group, which exceeds the expectation value.

There is higher risk of hepatobiliary disease and particularly chronic hepatitis among women with a history of ICP [26,27]. The latter disease causes liver cirrhosis and is often complicated by hepatocellular cancer[17]. Also cholelithiasis and chronic cholangitis are associated with ICP [26,27] and are associated with gallbladder and cholangiocellular cancer[17].

The Swedish registry study did not find any association between breast cancer and ICP (HR 1.03). In our study, mothers with ICP had a slightly higher risk for breast cancer than the control mothers (OR 1.36), although the difference was not statistically significant. The occurrence of breast cancer was lower in the Swedish population (1.6%) than in our Finnish population. Women's risk for having breast cancer before the age of 75 is 9.9% in Finland and 9.6% in Sweden [28]. Our longer follow-up time and the younger age of mothers in the Swedish study might explain the difference. Nevertheless, the cohort should be followed even longer because now the cohort represents those who had been diagnosed with cancer at a fairly young age.

Premature delivery (gestation weeks <37) seems to increase the mother's risk for breast cancer later in life [29]. Formerly, it has been found that ICP is associated with an elevated risk for delivery in gestation weeks under 37 [14]. It can be considered that premature delivery may increase the number of breast cancer cases among ICP women.

A questionnaire study observed that the women with ICP reported more breast cancer (6.3% vs. 3.7%, p=0.047) [22]. In our study, breast cancer was found among 7.0% in the ICP group and among 5.3% in the control group, the cohort being the same as in the questionnaire study. In this registry study, however, the difference between the groups is not statistically significant.

ICP has found to have a multifactorial genetic base. It may be speculated that ICP is one expression of a larger group of genetic diseases. Hormonal factors may be relevant in the pathogenesis of ICP and breast cancer [5,6,15]. It may be speculated whether the same hormonal factors have an effect on both diseases.

This is the first Finnish registry study on the potential association between ICP and cancer. According to the writers' knowledge there is only one registry based study investigating the association between ICP and cancer [17], and therefore the findings in this study may be considered unique. However, former observations regarding the association between ICP and breast cancer in the questionnaire study could not be confirmed by this registry based study. A larger number of ICP women and a longer follow-up time of the cohort might be needed to confirm the results. Based on this study doctors do not have to change their treating strategies and screen cancers because a woman has a history of ICP.

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Conflict of Interest

The authors have no conflicts of interest.

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PUBLICATION IV

Long-term survival after intrahepatic cholestasis of pregnancy: A follow-up of 571 mothers.

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Full length article

Long-term survival after intrahepatic cholestasis of pregnancy: A follow-up of 571 mothers

Suvi-Tuulia Hämäläinen[a,b,c,d,*], Kaisa Turunen[a], Kari J. Mattila[a], Elise Kosunen[a,c,d], Markku Sumanen[a]

[a] Department of General Practice, Faculty of Medicine and Health Technology, Tampere University, Arvo Ylpön katu 34, 33520 Tampere, Finland
[b] Janakkala Health Centre, Tapailanpiha 13 B, 14200 Turenki, Finland
[c] Science Center, Tampere University Hospital, 33521 Tampere, Finland
[d] Centre for General Practice, Pirkanmaa Hospital District, 33521 Tampere, Finland

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ABSTRACT

Objective: Intrahepatic cholestasis of pregnancy (ICP) is the most common liver disorder during pregnancy. ICP has been associated with morbidity but little is known about women's long-term survival. Our aim was to determine whether ICP is associated with mothers' long-term survival.
Study design: The study population comprised 571 women with ICP in at least one pregnancy seen at Tampere University Hospital in Finland between 1969–1988. The reference group comprised 1333 women: the previous and the following participant in the maternity ward diary. The data were obtained from Statistics Finland in March 2017 containing deaths among the study participants between 1971–2015. The follow-up time of the cohort was 27–46 years. The Kaplan-Meier method was used.
Results: Totally, 39 of the mothers with ICP (6.8%) and 111 of the reference group (8.3%) had died by the end of 2015 ($p = 0.267$). The mean survival time of ICP women was 77.4 years and of the reference group 79.2 years ($p = 0.288$). The mean survival time from labour in the ICP group was 45.0 years and in the reference group 44.8 years ($p = 0.259$).
Conclusions: Based on this study ICP does not seem to be associated with women's survival. There is no need to follow-up ICP mothers' health because of the nonexistent risk of premature death.
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Introduction

Intrahepatic cholestasis of pregnancy (ICP) is a pregnancy-specific liver condition which occurs most often in the late second or third trimester. The incidence is estimated to be between 0.2% and 2% and it varies geographically [1,2]. The disease is more common in South Asia, South America and Scandinavia. The diagnosis requires the key symptom pruritus and a rise in serum bile acids and transaminases [1]. During pregnancy the importance of ICP is related to its effects on the fetus [3]. Fetal complications such as prematurity, fetal distress and stillbirth are associated with ICP [4,5]. Within 48 h of delivery the mother's ICP symptoms usually resolve, and biochemical abnormalities resolve within 2–8 weeks [6].

Genes, hormonal and environmental factors have an effect on the pathogenesis of intrahepatic cholestasis of pregnancy. Several gene mutations have an impact on its pathogenesis [7–14]. Family clustering, the presence of ethnic and geographic variations, and mutations in gene coding for hepatobiliary transport proteins refer to genetic predisposition of ICP [1,2]. Progesterone and estrogen seem to have an effect on the disease, and ICP patients have an altered steroidogenesis [15]. Selenium deficiency and time of year may be involved in ICP's pathogenesis [16–18].

Recently, there has been growing interest in comorbidity associated with intrahepatic cholestasis of pregnancy. Increased risk for hepatobiliary diseases and cancers, some autoimmune diseases, and cardiovascular diseases have been found [19–21]. Women who have experienced ICP seem to have more gestational diabetes and pre-eclampsia than controls [22,23]. The disease seems to be linked to hepatitis C infection [20,24–26]. ICP women was found to have a higher HCV viral load [26].

Little attention has been paid to ICP women's survival. The condition being the most common pregnancy related liver disease, it is important to know about ICP's association regarding survival and public health. According to the writers' knowledge, ICP mothers' survival over such a long follow-up time has not been studied prior to this study. As ICP is associated with specific genetic

* Corresponding author at: Janakkala Health Centre, Tapailanpiha 13 B, 14200 Turenki, Finland.
E-mail address: suvi.hamalainen@tuni.fi (S.-T. Hämäläinen).

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profile and morbidity, the aim of this study was to determine whether there is an association between ICP and survival.

Material and methods

The study population comprised all ICP pregnancies at Tampere University Hospital, Finland, between 1969 and 1988. Patients with ICP were identified in the hospital discharge register using diagnosis codes. From 1969 to 1986, ICD-8 was used at Tampere University Hospital. Because ICD-8 did not include a precise code for ICP, we checked all the obstetric codes that might contain ICP: 637.9 Toxicosis NUD, 639.00 Pruritus, 639.01 Icterus gravis, 639.09 Necrosis acuta et subacuta hepatis, and 639.98 Aliae definitae. Thereafter, we checked the written diagnosis behind the code, and if it referred to ICP, we included the case for further selection. ICD-9 was used between 1987 and 1988, and it contained the appropriate codes 6467A Hepatosis gravidarum and 6467X Hepatopathia alia. The diagnosis was verified from each patient record with the presence of the main symptom of itching and abnormal laboratory test results. At least one of the following was required: ASAT > 35 U/l, ALAT > 40 U/l, or bile acids 6 μmol/l or more. The study population comprised 687 ICP deliveries [27]. The diagnosis of ICP was made in the special health care of University Hospital.

The study population included some women with repeated ICP deliveries, and each of these women was studied as an individual case. The ICP group thus contained 575 women. The reference group consisted of two women for each ICP delivery; the previous and the next women in the maternity ward diary. It was verified from the patient records that the women in the reference group were not diagnosed with ICP. Altogether, the reference group consisted of 1374 women. Four women were ruled out from the ICP cases because of a missing personal identity code, as were 41 women from the reference group. The final cohort comprised 571 women with ICP and 1333 women as a reference. Totally five hepatitis cases were diagnosed among the cohort until 2013, and two of them were hepatitis-C.

We collected the cohort's dates of death from Statistics Finland. The data contain all deaths to 2015. The follow-up time of the cohort was 27–46 years. The data were analysed using SPSS for Windows, version 22.0. The results were analysed with the Kaplan-Meier method.

The patients' consent was not required for this registry study. The study was approved by the Regional Ethics Committee of Tampere University Hospital (R02149) and the National Institute for Health and Welfare in Finland (THL/1051/5.05.00/2014).

Results

Totally, 39 of the mothers with ICP (6.8%) and 111 of the reference group (8.3%) had died by the end of 2015 ($p = 0.267$). There were no differences between the groups regarding age at labour, at death and age of those who were living at the end of 2015 (Table 1).

The mean survival time from birth among ICP women was 77.4 years and among reference group 79.2 years, p-value being 0.288 (Fig. 1). The mean survival time after labour in the ICP group was 45.0 years and in the reference group 44.8 years, p-value being 0.259 (Fig. 2).

Discussion

Statistically significant differences were not found in the survival between the ICP and the reference groups.

The cohort includes all ICP cases detected in Tampere University Hospital during 1969–1988. Practically 100 percent of the deaths can be found in the data of Statistics Finland [28]. The strength of our study is the long follow-up time, 27–46 years after delivery.

A weakness of the study is that it presents deaths at relatively early ages. Even a longer follow-up time is needed to examine whether ICP is associated with differences in survival among those who die older. The levels of bile acids and/or transaminases used for diagnosis of ICP were somewhat lower than more recent criteria and this can be regarded as a weakness of the study. The lack of knowledge of potential confounding factors such as body mass index can be considered weakness of the study.

Previously ICP has been associated with age over 35 years [29]. However, such an association was not found among this cohort. Thus, the cohort can be considered comparable with reference group regarding age. According to a questionnaire study with an excellent response rate, the groups were comparable regarding body mass index and education level [30]. In the cohort, ICP women seem to have had fewer deliveries compared to the reference group [31].

Within the same cohort, a questionnaire study showed that smoking was less common among the ICP patients than in the reference group [32]. No differences regarding recent alcohol consumption or physical activity were found. Within the same cohort, the women with a history of ICP reported less high cholesterol and high blood pressure requiring medication [30]. However, aforementioned diseases and health behaviour had no effect on survival.

Comorbidity has been recognized to be associated with ICP. In the questionnaire study made within the same cohort, ICP women reported more hypothyroidism and hepatobiliary diseases [30]. Hepatobiliary diseases have shown to be associated with ICP in registry-based studies [19,20]. Additionally, a registry-based study linked hypothyroidism and some other autoimmune diseases to ICP and found also an increased risk for cardiovascular diseases among ICP women [21]. Moreover, gestational diabetes and pre-eclampsia have been associated with ICP [22,23].

The association between intrahepatic cholestasis of pregnancy and cancers has been studied. The questionnaire study suggested an association between ICP and breast cancer [30]. In later registry-based studies, the linkage was not found [21,33]. Instead, a connection between ICP and hepatobiliary cancer has been found [21]. As a summary, ICP increases the woman's risk for certain diseases. Although ICP is associated with certain comorbidity, the survival seems to be similar compared to controls.

Table 1
Median ages and age ranges of the cohort at labour, at death, and those still living at the end of 2015.

	Mothers with ICP			Reference group		
	n	median age	age range	n	median age	age range
At labour	571	27.6	16.9 – 41.1	1333	27.1	15.0 – 46.4
At death	39	56.7	34.1 – 78.5	111	55.9	28.1 – 83.8
Living at the end of 2015	532	63.7	48.0 – 80.8	1222	63.3	46.3 – 85.0

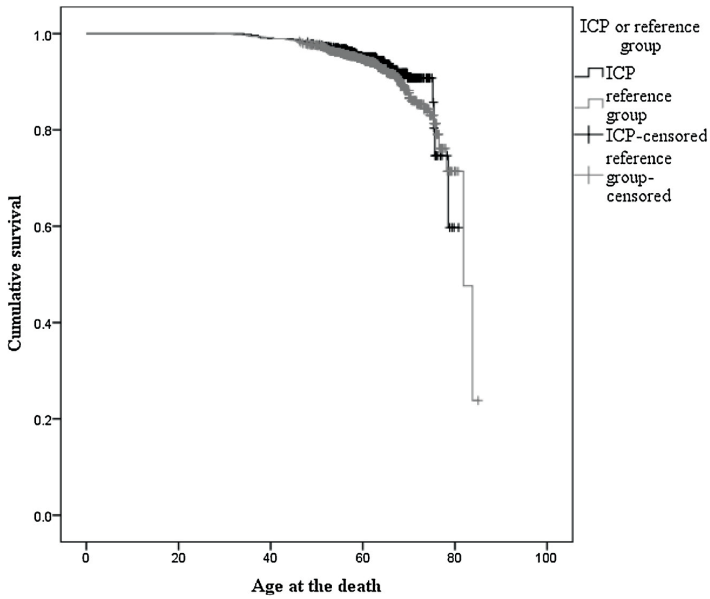

Fig. 1. Survival in the ICP and the control groups regarding age. The censored line indicates the subjects who are alive at the end of the follow-up time.

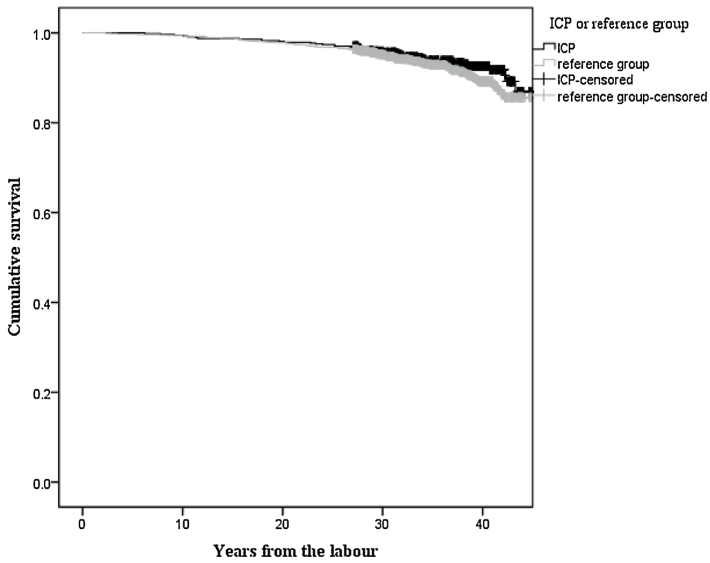

Fig. 2. Survival in the ICP and the control groups regarding years after labour. The censored line indicates the subjects who are alive at the end of the follow-up time.

Hepatitis C has been associated with increased risk of occurrence of coronary atherosclerosis [34]. Although hepatitis C has been associated with ICP [20,24,25], in our cohort there were no differences in the hepatitis C incidence between ICP women and the reference group. Thus, in our cohort hepatitis C comorbidity does not have an effect on survival.

ICP is associated with a certain genetic profile [1,2]. The same profile may have an influence on the survival among ICP patients. Indeed, ICP itself might not have an effect on the survival but this specific genetic profile might have. This research brings a new insight for long-term aspects of ICP as studying survival over such a long follow-up time.

During the follow-up time no statistically significant differences in the survival between the ICP and the reference group were found. Based on this study ICP does not seem to be associated with women's survival in middle or younger age. This finding is relieving for women with a history of ICP as it is not associated with their life expectation. In addition, there is no need for the health care system to follow-up ICP mothers' health because of the nonexistent risk of premature death.

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PUBLICATION V

Intrahepatic cholestasis of pregnancy and associated causes of death: A cohort study with follow-up of 27-46 years.

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BMC Women's Health

RESEARCH ARTICLE Open Access

Intrahepatic cholestasis of pregnancy and associated causes of death: a cohort study with follow-up of 27–46 years

Suvi-Tuulia Hämäläinen[1,2,3*], Kaisa Turunen[1], Kari J. Mattila[1] and Markku Sumanen[1]

Abstract

Background: The aim of this study was to determine whether intrahepatic cholestasis of pregnancy (ICP) is associated with causes of death during on average 35 years follow-up after the delivery.

Methods: The study population comprised 571 women with ICP in at least one pregnancy seen at Tampere University Hospital, Finland, between 1969 and 1988. ICP was verified from patient records. The previous and following subjects in the maternity ward diary were taken as controls for each ICP case. In total, there were 1333 controls. All underlying causes of death were obtained from Statistics Finland in March 2017. The deaths occurred during 1971–2015 and the causes of death were classified according to ICD-10.

Results: Altogether, 39 of the mothers with ICP (6.8%) and 111 of the controls (8.3%) had died by the end of 2015 ($p = 0.267$). There were more underlying causes of death from gastrointestinal diseases (15%) in the ICP group than in the control group (4%) ($p = 0.011$). The number of underlying causes of death due to diseases of the circulatory system were lower in the ICP group (13%) than in the control group (26%), although the finding was not statistically significant ($p = 0.088$). Moreover, neoplasms were the underlying cause of death in 46% of cases among mothers with ICP and in 41% of cases among the controls ($p = 0.609$). Diseases of the other organ systems were rare in both groups.

Conclusion: Women with a history of ICP do not have an increased overall mortality. However, deaths from gastrointestinal diseases are overrepresented among women with a history of ICP.

Keywords: Intrahepatic cholestasis of pregnancy, Causes of death, Mortality

Background

Intrahepatic cholestasis of pregnancy (ICP) is a reversible liver dysfunction during pregnancy. It is characterized by otherwise unexplained pruritus, especially on the palms of the hands, soles of the feet, and the abdomen. The diagnosis also requires a rise in serum bile acids and transaminases [1]. ICP is associated with perinatal complications, for example meconium staining of the amniotic fluid, stillbirth and preterm delivery [2, 3]. Ursodeoxycholic acid is the primary treatment used for ICP [4]. The mother's ICP symptoms usually resolve within 48 h of delivery and biochemical abnormalities resolve within 2–8 weeks [5].

Mutations of several genes may influence the pathogenesis of ICP [6–13]. In addition, hormonal factors, especially estrogen and progesterone, may be involved in the pathogenesis of ICP [14]. Genetic predisposition to ICP is revealed by family clustering, the presence of ethnic and geographic variations, and mutations in gene coding for hepatobiliary transport proteins [1, 14]. Intrahepatic cholestasis has been associated with hepatobiliary cancers, some autoimmune diseases, and cardiovascular diseases [15]. Also increased risk for gestational diabetes and pre-eclampsia has been reported among women with a history of ICP [16, 17].

To examine factors influencing causes of death, a long follow-up is required. Due to the genetic background and higher occurrence of some diseases, the objective was to determine whether ICP is associated with causes of death during on average 35 years follow-up after the

* Correspondence: hamalainen.suvi.t@student.uta.fi
[1]Department of General Practice, Faculty of Medicine and Life Sciences, University of Tampere, 33100 Tampere, Finland
[2]Janakkala Health Centre, Tapailanpiha 13 B, 14200 Turenki, Finland
Full list of author information is available at the end of the article

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delivery. To the authors' knowledge, this is the first study to investigate this association over such a long follow-up time.

Methods

Data source and study population

The study population comprised all ICP pregnancies at Tampere University Hospital (TUH) between 1969 and 1988. Patients with ICP were identified in the hospital discharge register using diagnosis codes. From 1969 to 1986, ICD-8 was used at TUH. Because ICD-8 did not include a precise code for ICP, we checked all the obstetric codes that might contain ICP: 637.9 Toxicosis NUD, 639.00 Pruritus, 639.01 Icterus gravis, 639.09 Necrosis acuta et subacuta hepatis, and 639.98 Aliae definitae. Thereafter, we checked the written diagnosis behind the code, and if it referred to ICP, we included the case for further selection. ICD-9 was used between 1987 and 1988, and it contained the appropriate codes 6467A Hepatosis gravidarum and 6467X Hepatopathia alia. The diagnosis was verified from each patient record with the presence of the main symptom of itching and abnormal laboratory test results. At least one of the following was required at that time at Tampere University Hospital: ASAT > 35 U/l, ALAT > 40 U/l, or bile acids 6 μmol/l or more. The study population comprised 687 ICP deliveries.

The study population included some women with repeated ICP deliveries, and each of these women were studied as an individual case. The ICP group thus contained 575 women. Two controls for each ICP delivery were taken; these controls were the previous and the next subjects in the maternity ward diary. Altogether, there were 1374 controls. The groups were comparable regarding age, educational level, and body mass index [18]. Four women were ruled out from the ICP cases because of a missing personal identity code, as were 41 women from the controls. The final cohort comprised 571 women with ICP and 1333 controls. The groups were comparable regarding the participants' age at labour, age at death, and age of those living at the end of 2015 (Table 1).

For the deceased in the cohort, we obtained the underlying causes of their death from 1971 to 2015 from Statistics Finland. The coverage of the underlying cause of death statistics is practically 100% [19]. The follow-up time of the cohort's mothers was 27–46 years. The causes of death were classified using ICD-10 [20], and the older ICD-8 and ICD-9 codes were changed to the corresponding ICD-10 codes.

Statistical analysis

The data were analysed using SPSS for Windows, version 22.0. The results are presented as frequencies and percentages. From cross tabulation, *p*-values were calculated using the Chi-squared test, and values of 0.05 or lower were considered statistically significant. Binary logistic regression analysis was performed to obtain odds ratio (OR) and 95% confidence intervals (CI). The dependent variable was "ICP or not".

Results

Altogether, 39 of the mothers with ICP (6.8%) and 111 of the controls (8.3%) had died by the end of 2015 ($p = 0.267$). The underlying causes of death are presented in Table 2. Each deceased has one underlying cause of death.

The most common underlying causes of death were neoplasms, 46% of cases among mothers with ICP and in 41% of cases among the controls ($p = 0.609$). There were no hepatobiliary neoplasms in the ICP group and only one in the control group. Malignant neoplasms of digestive system were the underlying causes of death in 28% ($n = 5$) of ICP women and in 26% ($n = 12$) of controls ($p = 0.890$). In the ICP group the malignant neoplasms were colon ($n = 2$), small intestine (n = 1) and stomach (n = 2) cancers. Respectively, malignant neoplasms in the control group were pancreas ($n = 3$), ampulla of Vater (n = 1), colon ($n = 6$) and stomach (n = 2) cancers.

Diseases of the circulatory system were the underlying cause of death in 13% of cases among mothers with ICP and in 26% of cases among the controls ($p = 0.088$). Diseases of the circulatory system were the second common underlying cause of death among the controls.

Diseases of the digestive system were more often the underlying cause of death in the ICP group than in the control group (15% vs. 4%, $p = 0.011$). The risk to have a gastrointestinal cause of death was nearly 5-fold in ICP group compared to controls (OR = 4.85, 95% CI 1.29–18.18). Diseases of the digestive system were the second common underlying cause of death among mothers with

Table 1 Median ages of patients at labour, at death, and those still living at the end of 2015

	Mothers with ICP			Controls		
	n	age	age range	n	age	age range
At labour	571	27.6	16.9–41.1	1333	27.1	15.0–46.4
At death	39	56.7	34.1–78.5	111	55.9	28.1–83.8
Living at the end of 2015	532	63.7	48.0–80.8	1222	63.3	46.3–85.0

Table 2 Underlying causes of death among women with and without a history of ICP

Underlying cause of death (ICD-10)	Mothers with ICP $n = 39$		Controls $n = 111$		Difference	
	n	%	n	%	% units	*p*-value
Neoplasms (C00–D48)	18	46	46	41	5	0.609
Diseases of the digestive system (K00–K93)	6	15	4	4	11	0.011
External causes of morbidity and mortality, injury, poisoning and certain consequences of external causes (V01–Y98, S00–T98)	5	13	17	15	-2	0.705
Diseases of the circulatory system (I00–I99)	5	13	29	26	−13	0.088
Endocrine, nutritional and metabolic diseases (E00–E90)	2	5	5	5	0	0.874
Diseases of the nervous system (G00–G99)	2	5	5	5	0	0.874
Diseases of the musculoskeletal system and connective tissue (M00–M99)	1	3	1	1	2	0.420
Diseases of the respiratory system (J00–J99)	0	0	4	4	−4	0.230

ICP. Within gastrointestinal diseases, hepatobiliary diseases were the underlying cause of death among 67% ($n = 4$) of ICP mothers and 75% ($n = 3$) of controls ($p = 0.778$). Alcoholic liver diseases were found in four ICP mothers and in two controls and cirrhosis of liver in one control. Diseases of pancreas and alcohol-induced chronic pancreatitis were the underlying causes of death among two women with ICP. Gastro-oesophageal laceration-haemorrhage syndrome was the underlying cause of death in one control. In total, diseases of the digestive system and malignant neoplasms of the digestive system were the underlying causes of death in 28% ($n = 11$) of ICP women and 14% ($n = 16$) of controls ($p = 0.054$).

Diseases of the other organ systems were rare in both groups.

Discussion

The main finding was that women with a history of ICP do not have an increased overall mortality. There were more deaths from gastrointestinal diseases in the ICP group than in the control group. Diseases of the circulatory system were twice as frequently the underlying cause of death in the control group than in the ICP group.

Strengths and limitations

The data in our study were relevant and the methods were valid and reliable. One limitation of the study was the small number of death cases. Nevertheless, the follow-up time of this study was long, 27–46 years, comprising all ICP cases at TUH during the 1969–1988 period. A long follow-up time is required when investigating the causes of death of mothers. Although the follow-up time was long, the deaths represent those who died relatively young. Life expectancy of Finnish women at the age of 65 years was 21 years in 2014 [21]. The life expectancy of ICP mothers ($n = 532$) living at the end of the follow-up in 2015 is over 20 years. An extended follow-up time would show whether causes of death are the same for the mothers who die older.

A weakness of the study is that the levels of bile acids and/or transaminases used for diagnosis of ICP were somewhat lower than more recent criteria. There is a possibility of existing liver disease at the time of ICP diagnosis. However, the diagnosis of ICP requires exclusion of other reasons and the diagnosis was made by an obstetrician.

Comparison with existing literature

It seems that the mothers with ICP die of cardiovascular diseases less frequently than expected and the controls more frequently than expected. The number of deaths from circulatory diseases seems to be lower in the ICP group, even though ICP has been associated with circulatory diseases [15]. On the other hand, women with ICP have reported less cardiac arrhythmia, high cholesterol, and high blood pressure requiring medication [22]. In 2015, diseases of the circulatory system were the underlying cause of nearly 38% of deaths among Finnish women over 15 years old [23]. In our study, diseases of the circulatory system were the underlying cause of death among 26% of the controls. Our cohort represents those who died younger, and the proportions of the causes of death might change if the cohort would be followed even longer. Although there were fewer deaths due to diseases of the circulatory system in the ICP group, it cannot be concluded that ICP protects from diseases of the circulatory system. ICP has been associated with gestational diabetes and pre-eclampsia [16, 17]. Gestational diabetes increases risk of type 2 diabetes, hypertension and ischemic heart disease [24]. An increased risk in cardiovascular diseases have been associated with pre-eclampsia [25]. Nevertheless, the mortality to circulatory system diseases was not higher in our study.

Despite the rather small number of deaths, statistically significant differences were found. The findings may be

considered clinically relevant. Increased risk of hepatobiliary diseases has been reported among women who experience ICP [15, 22, 26, 27]. The increased occurrence of hepatobiliary diseases may be reflected in the increase of deaths from gastrointestinal diseases among the ICP group.

Hepatobiliary neoplasms as underlying causes of death were not detected in this study among ICP mothers. Previously an association between ICP and liver cancer and biliary tree cancer has been reported [15]. Nevertheless, the incidence of these cancers has been found to be 0.1% so that the expected number of these rare cancers in our cohort is rather low. In this study, we did not investigate the incidence of different cancers but the underlying causes of death in the cohort.

Risk consumption of alcohol was not remarkably different among ICP mothers compared to controls in a questionnaire study of the same cohort [28]. According to a large Swedish study alcoholic cirrhosis was less likely to be diagnosed with women with ICP compared to controls [27]. Alcohol consumption might have an effect on the underlying causes of death, particularly on hepatobiliary diseases. Women with a history of ICP have an increased risk of liver fibrosis and cirrhosis which might be caused by hepatitis C infection [24]. This finding may reflect on the increased risk of deaths from gastrointestinal diseases in ICP women.

Many genetic mutations have been found to be associated with ICP [6–13]. Our hypothesis is that ICP is a manifestation of a genetic background that exposes the individual to certain diseases and causes of death.

Conclusion

Women with a history of ICP do not have an increased overall mortality. However, gastrointestinal diseases are overrepresented in the underlying causes of death among women with a history of ICP. This is the first study to examine the association between ICP and underlying causes of death over such a long follow-up time. An even longer follow-up time is required to investigate further the association between ICP and gastrointestinal causes of death. This would confirm whether the phenomenon found in our study continues among those who die older.

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Availability of data and materials

This study includes the subjects' personal information which are given to authors with a permission of the National Institute for Health and Welfare in Finland. The authors are not permitted to share the data.

Authors' contributions

STH, KT, KJM and MS have participated in the design of the study, interpretation of data and drafting of the manuscript. STH and KT have additionally participated in data collection. All authors have read and approved the manuscript to be published.

Ethics approval and consent to participate

The study has approvals from the Regional Ethics Committee of Tampere University Hospital (R02149) and from the National Institute for Health and Welfare in Finland (THL/1051/5.05.00/2014). The patients' consent was not required for this registry study.

Competing interests

The authors declare that they have no competing interests.

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Author details

[1]Department of General Practice, Faculty of Medicine and Life Sciences, University of Tampere, 33100 Tampere, Finland. [2]Janakkala Health Centre, Tapailanpiha 13 B, 14200 Turenki, Finland. [3]Science Center, Tampere University Hospital, 33521 Tampere, Finland.

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Men's Health Is Not Affected by Their Mothers' Intrahepatic Cholestasis of Pregnancy

Suvi-Tuulia Hämäläinen, MD[1,2], Kaisa Turunen, MD, PhD[1], Elise Kosunen, MD, PhD[1,3], Kari J. Mattila, MD, PhD[1], and Markku Sumanen, MD, PhD[1]

Abstract

Little is known about the effects of mother's intrahepatic cholestasis of pregnancy (ICP) on the health of sons born to these mothers. The purpose of the present study was to explore the health of sons born to mothers with ICP. The study design was a retrospective study of ICP mothers' sons. In the region of Tampere University Hospital in Finland, 365 sons of mothers with ICP during 1969 to 1988 and 617 sons of mothers without ICP were sent a questionnaire in 2010. The response rates were 37.8% (n = 138) and 36.6% (n = 226), respectively. Only minor differences were reported between the two groups. Self-evaluated health was similar. There were no significant differences between the groups regarding symptoms and complaints, diagnosed diseases, mental health, and use of medicines. Cough was 10.8 percentage points less common among ICP mothers' sons than among controls (p = .034). Urticaria was more common among ICP mothers' sons, the difference in percentage points being 2.2 (p = .026). In general, a mother's ICP does not affect her son's health.

Keywords

intrahepatic cholestasis of pregnancy, men's health, urticaria, cough, smoking

Introduction

Men's health is affected by genetic, environmental and exposure agents, and their health behavior. Factors during pregnancy and labor are associated with men's health in adulthood (Curhan et al., 1996). Intrahepatic cholestasis of pregnancy (ICP) is a reversible liver disorder during pregnancy, where the bile flow is impaired (Lammert, Marschall, Glantz, & Matern, 2000). ICP usually manifests in the third trimester of pregnancy and is characterized by mother's pruritus, especially on the palms and soles and an increase in serum bile acid and transaminases (Reyes, 1997). The incidence of ICP varies geographically and is 0.1% to 1.5% in Europe, United States, Canada, and Australia (Geenes & Williamson, 2009). In Finland, the incidence is approximately 1.0% to 1.5% (Laatikainen & Tulenheimo, 1984).

The etiology of ICP remains unknown, but the disorder seems to be related to hormonal factors (Reyes, 1997, 2008). It has been proposed that ICP may be inherited by the X-chromosome or is autosomal-linked, and a variety of genes influence its pathogenesis (Eloranta et al., 2003; Karlsen & Hov, 2010; Mullenbach et al., 2005; Noe et al., 2005; Pauli-Magnus et al., 2004; Reyes, Ribalta, & Gonzalez-Ceron, 1976). Adenosine triphosphate binding cassette, subfamily B, member 4 (ABCB4/abcb4) gene is associated in up to 15% of the ICP cases. This gene, also known as multidrug resistant protein 3 (MDR3), encodes a transporter for phospholipids across the canalicular membrane of liver hepatocytes (Pan & Perumalswami, 2011; Poupon, 2005). Environmental factors may also be involved (Lammert et al., 2000; Reyes, 2008).

ICP does not cause severe problems for a mother during pregnancy, although itching can cause insomnia and use of medications (Geenes & Williamson, 2009). ICP increases the risk of stillbirth, fetal distress, and preterm delivery (Alsulyman, Ouzounian, Ames-Castro, & Goodwin, 1996; Glantz, Marschall, & Mattsson, 2004), although Apgar scores have been only slightly lower for

[1]University of Tampere, Tampere, Finland
[2]Ikaalinen Health Center, Ikaalinen, Finland
[3]Pirkanmaa Hospital District, Tampere, Finland

Corresponding Author:
Suvi-Tuulia Hämäläinen, University of Tampere, Lääkärinkatu 1, 33014 Tampereen yliopisto, Tampere, Finland.
Email: suvi.hamalainen@uta.fi

ICP mothers' newborns (Turunen, Sumanen, Haukilahti, Kirkinen, & Mattila, 2010).

ICP appears to have some effects on the mothers' long-term health. Women with ICP have been observed to more often have hypothyroidism and liver, biliary, and pancreatic diseases (Ropponen, Sund, Riikonen, Ylikorkala, & Aittomäki, 2006; Turunen, Mölsä, Helander, Sumanen, & Mattila, 2012). Likewise, more breast cancer is reported (Turunen et al., 2012). Epilepsy has been more frequent among the daughters of ICP mothers than among controls (Vimpeli, Turunen, Helander, Mattila, & Sumanen, 2013). The health of ICP mothers' sons has not been studied previously.

In terms of clinical presentation, from the maternal viewpoint, the main consideration is intense pruritus, which may become so intolerable that delivery is considered as early as 35 to 37 weeks (Pathak, Sheibani, & Lee, 2010). For the fetus, there is concern for meconium staining of the amniotic fluid, fetal respiratory distress, intrauterine fetal demise, and sudden death postnatally. Due to increased incidence of cardiac, adrenal, and neurologic disorders perinatally, one might expect an increased incidence of diseases for men. In view of the genetic background and the fetal and obstetric risks associated with ICP, the present study sought to establish whether there is a connection between a mother's ICP and her son's health.

Material and Method

In autumn 2010, a postal survey was conducted among sons of women who had suffered from ICP. The cohort comprised 982 men, 365 of whom were sons of ICP mothers and 617 sons of control mothers. The diagnoses in the hospital discharge register that referred to ICP were verified. Criteria for ICP diagnosis were the main symptoms, itching and abnormal laboratory tests, and at least one of the following: aspartate aminotransferase >35 U/L, alanine aminotransferase >40 U/L, or bile acids ≥6 µmol/L. The mothers had been diagnosed with ICP during pregnancy in the obstetric department of Tampere University Hospital during the period 1969 to 1988, and two control women were chosen for each, namely, the previous and following parturient in the maternity ward diary (Turunen et al., 2012). Once these criteria were fulfilled, there were no more inclusion or exclusion criteria. Because this study only deals with men's (not women's) questionnaires, the cohort size is not fully 2:1.

Postal addresses were obtained from the Population Register Centre in Finland. Eight stillborns and 27 deceased sons were excluded together with 82 whose addresses were not found. Of ICP mothers' sons 138 (37.8%) and of controls' 226 (36.6%) responded (Figure 1).

Men's mean age was 30 years, the minimum being 21 years and maximum 40 years. In categorizing the respondents' age, 30 years was set as a cutoff point. Education was classified as "high" for those who had completed high school and "low" for those who had not. The respondents' body mass index (BMI) was categorized and 25 kg/m² was set as a cutoff point. With respect to age and BMI, the two groups were comparable. The groups were not comparable as to education. There were more in the higher education group among sons of ICP mothers (63.0%) than of controls (46.2%; $p = .002$; see Table 1).

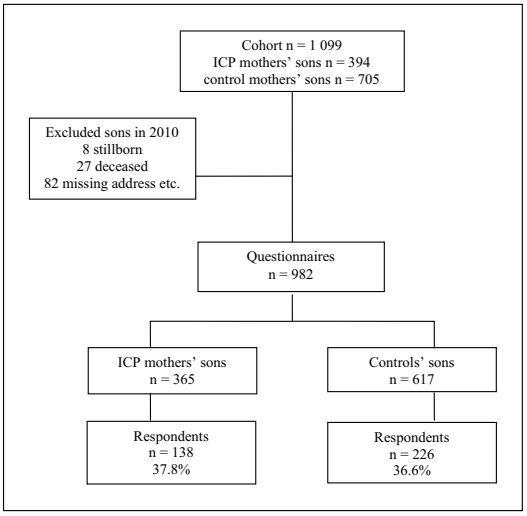

Figure 1. Flow chart of the survey population.
Note. ICP = intrahepatic cholestasis of pregnancy.

The two groups received identical questionnaires. The questionnaire was composed of 39 items; the main aspects relevant to this study being present health, symptoms and complaints, diseases diagnosed by a doctor, use of medicines, and mental health. Smoking and alcohol usage were assessed.

The respondents were asked to evaluate their present health by choosing one of the following alternatives: good, fairly good, moderate, rather poor, and poor. There were questions concerning symptoms and complaints during the past 12 months. Questions regarding diseases diagnosed by a doctor were asked, which focused on gastrointestinal, endocrine and metabolic, urinary tract, heart and circulatory system, respiratory diseases, musculoskeletal system, and connective tissue disorders. It was further asked if the respondent had been diagnosed with cancer, migraine, urticaria, epilepsy, or some significant injury or disease. Respondents were also asked whether they had undergone any major surgery or had ever suffered hip, wrist, or vertebral fractures.

Table 1. Characteristics of Sons of ICP Mothers and Controls.

	ICP group, *n* = 134-138 (%)	Controls, *n* = 218-226 (%)	Difference in percentage points	Difference (*p* value)
Age (years)				.933
<30	42.0	42.5	−0.5	
≥30	58.0	57.5	0.5	
Education				.002
Low	37.0	53.8	−17.0	
High	63.0	46.2	17.0	
Body mass index				.181
BMI < 25.0	44.0	51.4	−7.4	
BMI ≥ 25.0	56.0	48.6	7.4	

Note. ICP = intrahepatic cholestasis of pregnancy; BMI = body mass index.

Use of medicines, natural health drugs, and vitamins during the past year was assessed. Mental health was evaluated by two mental health-related questions and the Depression Scale. The questions concerned whether the respondent had suffered from a mental health disorder or had undergone treatment for a mental health disorder. The Depression Scale is a validated Finnish test screening for the risk of present clinical depression (Salokangas, Poutanen, & Stengård, 1995). Points in the Depression Scale differ from 0 to 30. If the result is 9 or more points, the probability of depression is clinically relevant and 12 or more points refers to quite probably a depression diagnosis.

This study had the consent of the Ethics Committee of Pirkanmaa Hospital District (R02149). Responding to the questionnaire was regarded as consent to the survey and the subjects were not compensated for responding. Statistical analyses were made using the SPSS System for Windows, release 22.0. Results are presented as frequencies and percentages. Statistical significance was tested by the chi-square test.

Results

The number of respondents was 365 in the group of ICP mothers' sons and 617 in the group of controls' sons. These were the base figures in percentage calculation. Table 2 presents symptoms and complaints during the past 12 months, Table 3 presents diagnosed diseases, and Table 4 presents medications used.

In general, there were only minor differences between the two groups. The two groups did not differ in respect to self-evaluated current health status. Of ICP mothers' sons, 89.1% and of controls' sons, 87.6% rated their health as good or fairly good.

The most common symptoms in both groups were backache, neck and shoulder pain, headache, and coughing. Of ICP mothers' sons, 26.8% and of controls' sons, 37.6% reported coughing during the past 12 months, the difference being 10.8 percentage points (p = .034). Otherwise, there were no significant differences between the groups with respect to other symptoms. Blushing, palpitation, and neck and shoulder pain were more common among ICP mothers' sons in percentage points. In turn, nervousness, recurring stomach problems, sweating, and cough were more common among controls' sons. Only concerning coughing was there a statistically significant difference, although the difference concerning blushing was close to significant (p = .053; see Table 2).

Among sons of ICP mothers, 52.2% and 65.9% of controls had smoked at least once in their life-time (p = .021). Currently, 29.7% of the ICP mothers' sons smoked and 41.6% of controls' sons, the difference being statistically significant (p = .023). There were no significant differences between the groups concerning smoking calculated in pack years. Of the ICP mother's sons, 39.1% and 46.9% of controls' sons smoked or had smoked regularly (p = .147). There was no difference between the groups regarding use of alcohol, number of used alcohol doses, or whether the respondent had ever considered reducing alcohol consumption.

There were only minor differences between the groups in respect to diagnosed diseases (see Table 3). Acute hepatitis and cholelithiasis were 1.4 percentage points more common among ICP mothers' sons (p = .07). Migraine was the most common disease among ICP mothers' sons with a prevalence of 8.7%. Some significant injury (6.5%), rise in liver function test results (6.5%), asthma (5.1%), kidney or urinary tract infection (5.1%), and cardiac arrhythmia (4.3%) were fairly common among ICP mothers' sons. However, there were no significant differences between the groups.

Urticaria was the only disorder which was more common among ICP mothers' sons. Altogether, 2.2% (n = 3) of ICP mothers' sons and 0.0% (n = 0) of controls reported urticaria. The difference was statistically significant (p =

Table 2. Symptoms and Complaints During the Past 12 Months Among Sons of ICP Mothers and Controls.

Symptoms and complaints	ICP mothers' sons, *n* = 138 (%)	Controls' sons, *n* = 226 (%)	Difference in percentage points	Difference (*p* value)
Heart palpitation	14.5	8.4	6.1	.069
Blushing	10.1	4.9	5.2	.053
Neck and shoulder pain	37.7	33.6	4.1	.432
Dryness of eyes and mouth	13.0	10.2	2.8	.401
Insomnia	21.7	19.0	2.7	.531
Rheumatic pains	5.1	2.7	2.4	.228
Headache	31.9	29.6	2.3	.653
Urinary problems	5.8	3.5	2.3	.308
Nausea	7.2	6.2	1.0	.695
Foot and/or leg swelling	3.6	3.1	0.5	.785
Dyspnea	8.7	8.4	0.3	.924
Depression	13.0	12.8	0.2	.953
Dizziness	10.1	10.2	−0.1	.992
Chest pain	8.7	8.8	−0.1	.960
Itching of palms and soles	3.6	4.0	−0.4	.863
General itching of skin	14.5	17.3	−2.8	.488
Backache	38.4	42.0	−3.6	.494
Arthralgia, joint pain	14.5	19.0	−4.5	.267
Nervousness	15.2	20.8	−5.6	.185
Recurring stomach problems	9.4	15.0	−5.6	.121
Sweating	14.5	20.4	−5.9	.159
Coughing	26.8	37.6	−10.8	.034

Note. ICP = intrahepatic cholestasis of pregnancy.

.026). Diseases of the circulatory system were less common among ICP mothers' sons, the findings not being statistically significant.

Of sons of ICP mothers, 12.3% and of controls, 12.4% had 9 or more points in the Depression Scale. ICP mothers' sons, 5.1% and controls', 6.2% had more than 12 points in the Depression Scale. Of the ICP mothers' sons, 17.4% and 18.1% of controls had suffered from some mental health disorder or had have treatment for it, the difference being not statistically significant. Wrist, back, or hip fractures were reported by 10.1% of sons of ICP mothers and 9.3% of controls, the difference not being statistically significant.

The most used medicines among sons of ICP mothers were painkillers (89.1%), vitamins or trace elements (62.3%), asthma and antiallergic medication (23.9%), as well as gastric acid inhibitors (23.2%; see Table 4). Slightly more commonly, sons of ICP mothers had used painkillers (2.4 percentage points) and sleeping pills (2.3 percentage points) compared with sons of controls. A few more sons of controls had used dermatologic drugs (5.9 percentage points) and natural health drugs (4.7 percentage points). However, the differences were not statistically significant.

Discussion

The two groups evinced only minor differences in most of the survey questions. The main findings were a lower frequency of cough during the past 12 months and ever-smoking among ICP mothers' sons and a higher incidence of urticaria among ICP mothers' sons. A trend for increased blushing and heart palpitation complaints during the prior 12 months was reported. Moreover, there was a trend for increased incidence of physician-diagnosed acute hepatitis or cholelithiasis, although this cannot be regarded as clinically relevant.

The material received was relevant and sufficient for this kind of analysis. Postal addresses were found for most sons and response activity was fairly good; 37.8% of ICP mothers' sons and 36.6% of controls' sons responded. The response rates did not differ markedly between the groups. Data were collected by a questionnaire filled in at home. The respondents were fairly young and the response rate might have been higher if the questionnaire had also been available on the Internet.

The two groups were not comparable in respect of education levels. This may be linked to the observation that ICP mothers' more often have only one child in their families (Mölsä, Turunen, Mattila, & Sumanen, 2012). It

Table 3. Diseases Diagnosed by a Doctor Among Sons of ICP Mothers and Controls.

	ICP mothers' sons, *n* = 138 (%)	Controls' sons, *n* = 226 (%)	Difference in percentage points	Difference (*p* value)
Diseases of the digestive system				
Acute hepatitis	1.4	0.0	1.4	.070
Cholelithiasis	1.4	0.0	1.4	.070
Colitis ulcerosa	1.4	0.4	1.0	.303
Crohns' disease	0.7	0.0	0.7	.200
Chronic choledochitis	0.0	0.0	0.0	—
Liver cirrhosis	0.0	0.0	0.0	—
Chronic hepatitis	0.0	0.4	−0.4	.434
Pancreatitis	0.0	0.4	−0.4	.434
Rise in liver function test results	6.5	7.1	−0.6	.838
Helicobacter pylori infection	0.0	0.9	−0.9	.268
Fatty liver	0.7	1.8	−1.1	.406
Gastric catarrh, gastric or duodenal ulcer	2.2	4.0	−1.8	.348
Celiac disease	0.0	2.2	−2.2	.079
Endocrine and metabolic diseases				
Goiter	0.7	0.0	0.7	.200
Hyperthyroidism	0.0	0.0	0.0	—
Diabetes on medication	0.0	0.9	−0.9	.268
Diabetes on diet therapy	0.0	0.9	−0.9	.268
Hypothyroidism	0.0	1.3	−1.3	.174
Diseases of the respiratory system				
Bronchitis	2.2	0.4	1.8	.124
Pulmonary tuberculosis	0.0	0.0	0.0	—
Chronic obstructive pulmonary disease (COPD)	0.0	0.4	−0.4	.434
Asthma	5.1	8.0	−2.9	.290
Diseases of the circulatory system				
High blood pressure on medication	2.2	5.3	−3.1	.144
High cholesterol on medication	1.4	1.8	−0.4	.816
Pulmonary embolus	0.0	0.4	−0.4	.434
Cardiac failure	0.0	0.4	−0.4	.434
Cardiac arrhythmia	4.3	5.3	−1.0	.681
Myocardial infarction	0.0	0.0	0.0	—
Angina pectoris	0.0	0.0	0.0	—
Deep venous thrombosis	0.0	1.3	−1.3	.174
Blood clot with inflammation in lower extremity	0.0	0.4	−0.4	.434
Urinary tract diseases				
Kidney or urinary tract infection	5.1	3.1	2.0	.342
Kidney stones	0.0	0.0	0.0	—
Renal failure or kidney failure	0.7	0.4	0.3	.724
Diseases of the musculoskeletal system and connective tissue				
Other chronic inflammatory joint disease than rheumatoid arthritis	2.9	2.2	0.7	.683
Osteoporosis	0.0	0.0	0.0	—
Osteoarthrosis	2.2	4.0	−1.8	.348
Rheumatoid arthritis	0.0	0.4	−0.4	.434
Other diseases				
Some significant injury	6.5	10.6	−4.1	.186
Urticaria	2.2	0.0	2.2	.026
Anemia	2.9	1.8	1.1	.476
Epilepsy	2.2	1.8	0.4	.785
Cancer	0.0	1.3	−1.3	.174
Migraine	8.7	10.6	−1.9	.551

Note. ICP = intrahepatic cholestasis of pregnancy.

Table 4. Used Medications During the Past 12 Months Among Sons of ICP Mothers and Controls.

Medication	ICP mothers' sons, n = 138 (%)	Controls' sons, n = 226 (%)	Difference in percentage points	Difference (p value)
Painkillers	89.1	86.7	2.4	.499
Sleeping pills	9.4	7.1	2.3	.424
Heart medication	1.4	0.4	1.0	.303
Vitamins or trace elements	62.3	61.5	0.8	.877
Sedatives	5.1	4.9	0.2	.930
Lipid lowering drugs	1.4	1.8	−0.4	.816
Gastric acid inhibitors	23.2	23.9	−0.7	.878
Asthma or antiallergic medication	23.9	25.7	−1.8	.708
Antidepressants	4.3	7.1	−2.8	.289
Antihypertensive medication	2.9	6.2	−3.3	.159
Eye drops	15.9	19.5	−3.6	.397
Natural health drugs	13.0	17.7	−4.7	.239
Dermatologic drugs	10.9	16.8	−5.9	.119

Note. ICP = intrahepatic cholestasis of pregnancy.

may be speculated that in families with one child parents encourage the child to aspire to a higher education. As the groups differed in education level, it may be concluded that the two might evince differences in lifestyle diseases, which might explain the difference in smoking and cough.

Although it has been presented that daughters of ICP mothers have a higher frequency of epilepsy (Vimpeli et al., 2013), this was not reported among the sons. The methodologies in the studies of the daughters and the sons were basically the same, and consequently the two studies and their results are comparable. Women with a history of ICP show higher frequencies of several liver, biliary and pancreatic diseases, breast cancer, and hypothyroidism, but this was not the case among the sons. The sons being relatively young, not all diseases may have been detected. Nevertheless, hypothyroidism often emerges at a relatively young age, albeit more rarely among men than women.

The frequencies of the diseases noted in our cohort are quite similar to those in the average population in Finland. The prevalence of migraine among working-age men in Finland is 11% (Rantala, Sumanen, & Mattila, 2007). Previously, the cough symptom of chronic bronchitis has been reported by 12% (Aromaa & Koskinen, 2004) and asthma was reported in 8% of men in the Health 2011 survey (Koskinen, Lundqvist, & Ristiluoma, 2012). In our study, the frequency of cough symptoms may have been higher due to respiratory diseases. Infectious respiratory disease were reported by 22% of 30- to 44-year-old men in the Health 2000 survey (Aromaa & Koskinen, 2004). In the Health 2000 survey, backache was reported during the previous month by an average of 30% of men of the same age as in this study. On average, 80% of men had had back pain at some time. In our study, back pain during the past year was assessed and the results can thus be considered congruent. A permanent injury or disability caused by an accident was reported by 13% to 18% of men under 55 years old (Aromaa & Koskinen, 2004). This rate was lower in our cohort. The rise in liver function tests may be caused by obesity, medication, and alcohol consumption. There was no significant difference between the groups in this context, although ICP manifests as a rise in liver function tests.

Urticaria was more common among ICP mothers' sons than controls. This finding can be considered clinically irrelevant as the frequencies were low. It may be speculated that ICP mothers' sons are conscious of their health and make appointments with a doctor more often as they have a higher education level.

ICP has a genetic background, and consequently it may be speculated whether the genome of the sons of ICP mothers is different from that of control mothers' sons. The treatment of ICP mothers and the fetal outcome did not appear to be associated with sons' health in the long term. The current study limitations were the young age of the men limiting detection of diseases that would occur with aging, small sample size, likelihood of recall bias, unclear on severity of ICP which likely affects the chances of long-term sequela, the trimester of clinical presentation, peak bile acid levels (percentage of mothers with levels greater than 40), presence of jaundice, average gestation at delivery, percentage of men delivered before 37 weeks, and presence of other perinatal complications since those are likely to affect long-term health.

To our knowledge, this is the first survey to explore whether a mother's ICP has effects on her son's health in the long term. The health of women with a history of ICP and their daughters' health has previously been studied

(Turunen et al., 2012; Vimpeli et al., 2013). Based on our findings, a mother's ICP does not affect her son's health later in life, and mothers' concerns may be relieved with this information.

Declaration of Conflicting Interests

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