KAISA TURUNEN

Long-term Aspects of
Intrahepatic Cholestasis of Pregnancy

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UNIVERSITY OF TAMPERE

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LIST OF ORIGINAL PUBLICATIONS

This thesis is based on the following publications. In the text, these publications are referred to as I-VI. The articles are included with the kind permission of the copyright owners.

I   Turunen K, Sumanen M, Haukilahti R-L, Kirkinen P, Mattila K. Good pregnancy outcome despite intrahepatic cholestasis. Scand J Prim Health Care 2010;28:102-107.

II   Turunen K, Mölsä A, Helander K, Sumanen M, Mattila KJ. Health history after intrahepatic cholestasis of pregnancy. Acta Obstet Gynecol Scand 2012;91:679-685.

III   Turunen K, Helander K, Mattila KJ, Sumanen M. Health behavior after intrahepatic cholestasis of pregnancy. Health 2013;5:96-101.

IV   Turunen K, Helander K, Mattila KJ, Sumanen M. Intrahepatic cholestasis of pregnancy is common among patients' first degree relatives. Acta Obstet Gynecol Scand 2013;92:1108-1110.

V   Mölsä A, Turunen K, Mattila KJ, Sumanen M. Unnecessary confusion about family planning after intrahepatic cholestasis of pregnancy. Contraception 2012;86:639-644.

VI   Turunen K, Helander K, Mattila KJ, Sumanen M. Menopause after a history of intrahepatic cholestasis of pregnancy. Menopause 2013;20:1200-1203.

ABBREVIATIONS

AFOS	alkaline phosphatase
ALAT	alanine aminotransferase
ASAT	aspartate aminotransferase
BMI	body mass index, kg/m^2
GT	glutamyl transferase
HRT	hormone replacement therapy
ICD-8	The International Classification of Diseases, 8th revision
ICD-9	The International Classification of Diseases, 9th revision
ICD-10	The International Classification of Diseases, 10th revision
ICP	intrahepatic cholestasis of pregnancy
LFT	liver function test
UDCA	ursodeoxycholic acid
TUH	Tampere University Hospital
WHI	The Women's Health Initiative
WHO	World Health Organization

SUMMARY

Intrahepatic cholestasis of pregnancy (ICP) is a disorder which is known to have associations with other hepatobiliary diseases. In light of knowledge of the functions of the liver in the human body, and also of the established genetic predisposition to ICP, the disorder may justly be suspected of having further associations with these women's health. A study of the associations of ICP with other health aspects is thus clearly warranted. This study is the first in which the long-term aspects of ICP are widely explored on the basis of information obtained directly from the women themselves.

To gain insight into the long-term aspects of ICP, we chose a population which had experienced ICP during pregnancies in 1969-1988 in Tampere University Hospital, Finland. During those years, altogether 687 cases of ICP were detected, and the number of controls was twice as large.

The research set out with a review of the outcome of ICP pregnancies in 1969-1988. The essential element in this study comprised data from a postal survey made in 2010, where all women for whom postal addresses were available, 544 with a history of ICP and 1235 without, received a questionnaire. The response rate was 66%.

The proportion of ICP pregnancies in 1969-1988 was 0.9%, which is in keeping with the earlier knowledge of the incidence of ICP in Finland. Pregnancy outcome results show that women with ICP were kept in hospital longer, had more often induction of labor and/or cesarean section, and delivered at earlier gestational weeks than the control women. The newborn of ICP mothers were smaller, but their Apgar scores were similar to those of control children. The stillbirth rate in ICP pregnancies is in accord with earlier results.

According to the postal survey, there were only a few differences in the health history between the ICP and the control group. The higher occurrence of hepatobiliary diseases detected in ICP women here confirms the results of earlier studies. New findings were a higher occurrence of breast cancer and hypothyroidism among women with a history of ICP. On the other hand, there was some evidence of a lower prevalence of certain characteristics related to cardiovascular diseases.

In terms of health-connected behavior, the study brought out lower smoking rates among women with a history of ICP. Recent alcohol consumption did not separate the groups.

ICP was more common among close relatives of ICP than of control women, which reinforces the conception of the genetic basis of ICP.

Women with a history of ICP had encountered difficulties in hormonal contraception, and they had also restricted the number of children for health reasons more often than controls. In contrast, when asked of women who had passed menopause, use of hormone replacement treatment had not been restricted in the case of women with a history of ICP. The results imply a need to consider hormone use in these women in view of the higher occurrence of gallstones, which may emerge as complications during hormonal replacement therapy.

If the association between breast cancer and ICP is confirmed in future research, further study is also warranted to establish whether there is a common genetic basis for ICP and breast cancer predisposition. If this is the case, then the use of HRT in women with a history of ICP may also need revision.

Hypothyreosis is probably an underdiagnosed problem, and a history of ICP adds to indications to screen thyroid function in women with symptoms suggestive of hypothyreosis.

As a conclusion, the findings here would imply that ICP has only a few associations with health history, let alone with a number of hepatobiliary diseases. However, there are certain conditions which should prompt a doctor to investigate the patient's ICP history. A higher occurrence of breast cancer was found among

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women with a history of ICP, and further research on registers of cancer and cause of death is warranted.

Tiivistelmä

Raskaudenaikaisen maksansisäisen sapensalpauman eli raskaushepatoosin (intrahepatic cholestasis of pregnancy, ICP) sairastaneilla tiedetään olevan enemmän myös muita maksa- ja sappisairauksia kuin vertailuväestöllä. Maksan toimintojen moninaisuuden ja toisaalta tämän sairauden geneettisen alttiuden vuoksi voidaan ajatella, että sairaudella saattaa olla muitakin kytköksiä. Oli siis tarve tutkia ICP:n yhteyksiä naisen muuhun terveyteen ja elämään. Tämä on ensimmäinen tutkimus, jossa selvitetään laaja-alaisesti raskaushepatoosin pitkän ajan yhteyksiä naisten muuhun terveyteen naisilta itseltään saadun tiedon pohjalta.

Jotta voitiin tarkastella ICP:n pitkän aikavälin näkökohtia, tutkittavaksi väestöksi valittiin ne ICP:n sairastaneet naiset, jotka olivat synnyttäneet Tampereen yliopistollisessa sairaalassa vuosina 1969–1988. ICP-tapauksia löytyi 687. Vertailuryhmäksi otettiin 1374 samassa sairaalassa samaan aikaan synnyttänyttä naista. Aluksi analysoitiin synnytystä koskevat tiedot, jolloin aineisto koostui sairaalan potilasasiakirjoista ja synnytyspäiväkirjasta saaduista tiedoista. Pääosa tästä tutkimuksesta pohjautuu postikyselyaineistoon syksyltä 2010. Kyselylomakkeen sai 544 ICP:n sairastanutta ja 1235 vertailuryhmän naista. Vastausosuus oli 66 %.

ICP:n osuus raskauksista vuosina 1969–1988 oli 0.9 %, joka vastaa aikaisempaa tutkimustietoa sairauden esiintyvyydestä Suomessa. ICP-äidit olivat sairaalassa pidempään ja heidän synnytyksensä käynnistettiin ja/tai he synnyttivät sektiolla, ja synnytys tapahtui varhaisemmilla raskausviikoilla kuin kontrolliryhmän äideillä. Vastasyntyneet olivat pienempiä mutta heidän Apgar-pisteensä eivät eronneet kontrolliryhmän lasten pisteistä. Kuolleena syntyneiden osuus oli aiemman tutkimustiedon mukainen.

Kyselytutkimuksessa selvitettiin laajasti tutkittavien terveyshistoriaa: sairauksia, lääkkeiden käyttöä, koettua terveyttä, oireita ja vaivoja, terveystottumuksia, ICP:n esiintymistä lähisuvussa, perhesuunnittelua ja vaihdevuosien hormonikorvaushoitoa. Maksa- ja sappisairauksien esiintyvyys oli ICP-naisten ryhmässä aiempien tutkimusten tapaan runsaampaa. Uutena tuloksena oli rintasyövän ja kilpirauhasen vajaatoiminnan suurempi esiintyvyys ICP-ryhmässä. Toisaalta joitakin sydän- ja verisuonisairauksiin liittyviä tekijöitä kuten rytmihäiriöitä sekä verenpaine- ja kolesterolilääkityksen käyttöä oli ICP-ryhmässä vähemmän. Sydän- ja verenkiertoelinsairauksien päätetapahtumien suhteen eroja ei ollut. ICP-ryhmän naiset tupakoivat vähemmän mutta käyttivät alkoholia yhtä paljon kuin kontrolliryhmän naiset. ICP-naisilla oli lähisuvussaan enemmän ICP-tapauksia kuin kontrolliryhmän naisilla, mikä vahvistaa tietoa perinnöllisestä alttiudesta tähän sairauteen. ICP-naiset olivat rajoittaneet lapsilukuaan terveyssyistä ja myös kohdanneet ongelmia hormonaalisessa raskaudenehkäisyssä. ICP ei näytä vaikuttaneen vaihdevuosien hormonikorvaushoidon käyttöön.

Varsin hyvien synnytystulosten voidaan ajatella olevan tulosta ICP:n asianmukaisesta havaitsemisesta neuvolassa ja hoidosta obstetrisessa erikoissairaanhoidossa. Sikiön äkkikuoleman riskin vuoksi ICP on kuitenkin edelleen vakavasti otettava äidin raskaudenaikainen sairaus.

ICP:n sairastaneiden naisten yhdistelmäehkäisypillereiden käyttöä on todennäköisesti rajoitettu turhaan. Vaihdevuosien hormonikorvaushoitoa saattaa rajoittaa ICP-naisilla varsin yleinen sappikivisairaus, joka voi komplisoitua hormonien käytön seurauksena. Rintasyöpäriski ICP-naisilla vaatii vielä lisätutkimuksia, eikä ICP-naisille voida tämän tutkimuksen perusteella asettaa hormonihoidon rajoituksia.

Tutkimuksen yhteenvetona voidaan todeta, että raskaushepatoosilla on varsin vähän vaikutusta naisen myöhempään terveyshistoriaan lukuun ottamatta muita maksan ja sapen sairauksia. On kuitenkin joitakin sairauksia, joiden vuoksi hoitavan lääkärin on syytä tietää naisen ICP-historia. Kilpirauhasen vajaatoiminta lienee alidiagnosoitu sairaus, ja sairastettu ICP on lisäindikaatio kilpirauhasen toiminnan

tutkimiselle. Tässä tutkimuksessa todetun ICP-naisten rintasyöpätapausten korkeamman määrän vuoksi syöpärekisteri- ja kuolinsyyrekisteritutkimus on aiheellinen.

1 INTRODUCTION

Intrahepatic cholestasis of pregnancy (ICP) occurs in approximately one per cent of pregnancies in Finland. It is manifested in itching of a healthy skin in late pregnancy, and the diagnosis is verified by abnormal liver function tests (LFTs). Women with ICP need follow-up and care in view of the risks for the fetus. For the mother, ICP is an irritating and tiring disorder which resolves promptly after childbirth. Besides the recurrence risk in subsequent pregnancies, a history of ICP is known to involve an elevated risk of gallstones and several other hepatobiliary diseases.

By reason of the established hormonal, genetic and environmental factors underlying the disorder, and on the other hand, the fundamental role of liver function in the human body, we may justly assume ICP patients also to be susceptible to certain other diseases. As there are only a few scientific studies on diseases or conditions other than hepatobiliary connected with ICP, there was a need to establish whether ICP causes such health-related risks which physicians should be aware of when encountering these women in practice.

This study is a joint project of the Department of General Practice in the School of Medicine at Tampere University, the Department of Obstetrics and Gynaecology in Tampere University Hospital and the Centre for General Practice in the Pirkanmaa Hospital District.

2 REVIEW OF THE LITERATURE

ICP was originally presented by F. Ahlfeld in 1883 in *Berichte und Arbeiten aus der Geburtshülflich-Gynaekologischen Klinik zu Giessen*. The condition is described in section IV, *Pathologie der Schwangerschaft*, under the title *Icterus gravidarum*, as recurrent jaundice of pregnancy which resolved following delivery [Ahlfeld, 1883]. As late as 1954 and 1955 benign recurrent cholestatic jaundice of pregnancy was clearly defined [Svanborg, 1954, Thorling, 1955]. Thorling suggested that when pruritus is the only complication of pregnancy it is to be considered an anicteric form of "hepatotoxaemia of pregnancy". In 1964, the first study of Finnish jaundice cases was published, including diagnoses referring to ICP [Ikonen, 1964].

2.1 Terminology of intrahepatic cholestasis of pregnancy

By definition, ICP is a diagnosis of exclusion [Marschall et al, 2013]. It is characterized by otherwise unexplained pruritus combined with elevated bile acids and/or transaminases in the late second and third trimester of pregnancy [Geenes and Williamson, 2009, Lammert et al, 2000]. The pruritus fades within days postpartum, and LFTs usually normalize in four weeks. Particularly an early onset of ICP and failure of liver function to return to normal postpartum must be noted and possible underlying liver diseases identified [McCarthy, 2007].

In the international medical literature intrahepatic cholestasis of pregnancy (ICP) is referred to by a diversity of terms: obstetric cholestasis, cholestatic hepatosis, cholestasis of pregnancy, hepatogestosis, gestational hepatosis, jaundice of pregnancy, recurrent jaundice of pregnancy, icterus gravidarum, prurigo gravidarum, pruritus of pregnancy. Also causal descriptions have been presented, for example "gestational hepatosis derived from intrahepatic cholestasis".

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The current version of the International Classification of Diseases, ICD-10, includes terms under the heading O26.6 Liver disorders in pregnancy, childbirth and the puerperium, as follows: Cholestasis (intrahepatic) in pregnancy, and Obstetric cholestasis. In Latin the respective terms read: O26.6 Morbositates hepatis in graviditate, intra labores et/sive in puerperio: hepatopathia in graviditate, hepatosis gravidarum, cholestasis intrahepatica gravidarum [WHO, 2010].

2.2 Epidemiology

The occurrence of ICP varies from country to country from less than 0.5% to 28% of pregnancies (Table 1). In Finland and Sweden the proportion is 0.5-1.8%, and this pertains to Europe on average. Chile has had the highest rates, the average being 16%, and among some ethnic subgroups, for example women of the Araucanos, up to 28%. However, the reported occurrence of ICP in Chile has more recently decreased to 6.5% or even less. In the United States, figures range from 0.3% to 5.6% according to ethnic origin.

The condition has probably been clinically underdiagnosed in some countries, and might also be regarded as a liver disturbance caused by hepatitis or excess use of alcohol. On the other hand, an underlying liver disease, for example primary biliary cirrhosis (PBC), might have been misdiagnosed as ICP. In some countries the incidence of ICP has increased as physicians have become informed of the disease.

The variation between figures can easily be understood in that different studies have used different diagnostic criteria: the liver function test(s) selected, different limits for LFTs, jaundice and/or pruritus as diagnostic criteria, research concentrating on singleton pregnancies only or including all pregnancies, preeclampsia being included or not, cases with no hepatomegaly, gallstones, absence of parenchymal cell necrosis on liver biopsy, absence of fever or malaise, absence of other liver diseases, case followed by recurrence of ICP or including

recovery postpartum. The reported incidence of ICP in different countries and ethnic groups is presented in Table 1.

Table 1 The reported occurrence of intrahepatic cholestasis of pregnancy (ICP) in different countries and ethnic groups.

Country	ICP proportion of pregnancies (%)	Years of study	References
Australia	0.2	1964-1966	[Reyes et al, 1978]
Australia	1.5	1968-1970	[Steel and Parker, 1973]
Australia	0.1	1965-1974	[Fisk et al, 1988]
Australia	0.2	1975-1984	[Fisk et al, 1988]
Bolivia	9.2	1976	[Reyes et al, 1979]
— **Aimaras**	13.8		
— **Quechas**	4.3		
— **Caucasians**	7.8		
— **Mixed Indian**	7.3		
Canada	0.07	1963-1976	[Johnston and Baskett, 1979]
Chile	24.0	1974-1975	[Reyes et al, 1978]
— **Aimaras**	11.8		
— **Araucanian**	27.6		
— **Caucasian**	15.1		
Chile	4.7	Not available	[Gonzalez et al, 1989]
Chile	6.5	1988-1990	[Rioseco et al, 1994a, Rioseco et al, 1994b]
China (Chongqing)	0.32	1981-1983	[Jiang et al, 1986]
China (Hongkong)	0.05	2003-2005	[Lo et al, 2007]
Finland	1.1	1971-1972	[Laatikainen and Ikonen, 1975]
Finland	0.54	1990-1996	Heinonen and Kirkinen, 1999]
Finland	0.54	1994-1998	[Eloranta et al, 2001]
Finland	1.3	1992-1993	[Savander et al, 2003]
France	0.2	1953-1961	[Perreau and Rouchy, 1961]
France	0.2	Not available	[Gagnaire et al, 1975]
France	0.53	1988-1989	[Roger et al, 1994]
India	0.08	2002-2004	[Rathi et al, 2007]
Italy	0.96	1996-1999	[Paternoster et al, 2002]
Italy	1.0	1989-1997	[Roncaglia et al, 2002]
Poland	1.5	Not available	[Wojcicka-Jagodzinska et al, 1989]
Portugal	1.0	Not available	[Brites et al, 1998]
Sweden	1.5	1971-1974	[Berg et al, 1986]
Sweden	1.0	1980-1982	[Berg et al, 1986]
Sweden	1.5	1999-2002	[Glantz et al, 2004]
Saudi Arabia	0.35	2008-2010	[Al Shobaili et al, 2011]
UK	0.7	1995-1997	[Abedin et al, 1999]
— **Caucasian**	0.62		
— **Indian**	1.24		
— **Pakistani**	1.46		
USA	0.32	1997-1999	[Laifer et al, 2001]
USA (Latina)	5.6	1997-1998	[Lee et al, 2006]
USA (San Francisco)	1.9	2005-2009	[Rook et al, 2012]

Adapted from the Editorial, Table 1 in: Geenes and Williamson. Intrahepatic cholestasis of pregnancy. World J Gastroentelol 2009 7;15(17)2049-2066. Supplemented by the author of this thesis.

2.3   Etiology and pathogenesis

The ultimate reason for ICP is unknown. It is probably of multifactorial origin. The condition is believed to be caused by a hormonal overload on the liver among women with a genetic predisposition. Also environmental reasons have been suggested.

ICP recurs in half of subsequent pregnancies [Heinonen and Kirkinen, 1999, Reyes et al, 2000]. In one out of six cases, ICP is familial, and in such cases recurs in 92% [Hay, 2008]. Diverse genes or gene mutations [de Vree et al, 1998, Dixon et al, 2000, Eloranta et al, 2002, Geenes and Williamson, 2009, Jacquemin et al, 1999, Savander et al, 2003] and different gene expression profiles may contribute to the complex pathogenesis of the disorder [Floreani et al, 2013]. The fact that ICP does not recur in every familial case suggests that there are also other reasons for the condition to emerge.

Hormonal factors are inevitably involved. ICP has been thought to be the result of insufficient liver capacity to metabolize high amounts of placental hormones during pregnancy [Fisk and Storey, 1988, Heinonen and Kirkinen, 1999]. Dysfunction of the bile export pump, or failure to excrete steroid degradation products from hepatocytes to bile might cause edema in the liver, and thus, cholestasis. The risk of ICP is higher in a multiple pregnancy, when the amounts of sex hormones are higher than in a singleton pregnancy [Gonzalez et al, 1989, Rioseco et al, 1994]. The first oral contraceptives were introduced in 1960, and following their widespread use, cases of cholestatic jaundice, similar to the condition seen during pregnancy, were reported [Adlercreutz, 1964], and the effect of steroids on liver function was established. A condition similar to ICP may appear during hormone use, for example when high-level contraceptive pills are involved [Bacq et al, 1997, Kreek et al, 1967, Rannevik et al, 1972].

Environmental reasons for ICP seem probable. There is evidence to indicate that ICP is more common and appears in more severe forms in winter [Berg et al, 1986, Brites et al, 1998, Hay, 2008]. Nutritional factors, for example selenium deficiency, may have a role in the development of ICP [Kauppila et al, 1987, Reyes et al, 2000]. Pregnant women with ICP have a lower vitamin D status at mid-gestation or delivery compared with controls [Dror, 2011], and vitamin D levels are inversely correlated with meconium staining of amniotic fluid [Wikström Shemer and Marschall, 2010]. Dietary factors may contribute to ICP; a low-fat diet may be recommended to reduce the metabolic load on the liver [Leszczynska-Gorzelak et al, 2012, Thomassen, 1979]. Hepatitis C infection has been suggested to be involved in the manifestation of ICP, as affected women develop ICP at earlier weeks [Locatelli et al, 1999], but it has also been established that women with a predisposition to ICP are also susceptible to hepatitis C [Marschall et al, 2013, Ropponen et al, 2006]. Also drug-induced cholestasis has been described [Lang et al, 2007] with references to genetic predisposition.

Besides the liver and its functions, other functions of the human body, including food and other intake digestion, absorption and metabolism are probably involved in the pathogenesis of ICP. At least ICP is associated with blood glucose [Wojcicka-Jagodzinska et al, 1989] and lipid [Dann et al, 2006] profiles. Also the concept of "leaky gut" has been suggested to explain a part of the pathogenesis of ICP, namely enhancement of the absorption of bacterial endotoxins [Reyes et al, 2006]. Cytokines might favor this absorption to initiate a hepatic inflammatory cascade.

Aging [Heinonen and Kirkinen, 1999] and multiparity have been proposed to increase the occurrence of ICP.

Itching, the principal symptom of ICP, has been thought to be caused by bile acids which present in excess amounts in the skin after high levels of serum bile acids caused by cholestasis. The role of bile acids has been challenged; at least they might not be the only possible reason for itching. Pruritus may emerge either prior to or after abnormal liver function is detected [Kenyon et al, 2001]. It has been suggested that in ICP, the expression of autotaxin, the enzyme which converts

lysophosphatidylcholine into lysophosphatidic acid (LPA), is induced and this increases the amount of LPA, a potent neuronal activator, near unmyelinated nerve endings of itch fibres [Oude Elferink et al, 2011]. Steroids and their degradation products, of which steroid sulfates and disulfates prominently of progesterone origin, are held to play an unquestionable role in mediating cholestatic pruritus [Glantz et al, 2008]. Elevated levels of histamine have been detected in cholestatic patients [Gittlen et al, 1990], but histamine probably has no central role as a mediator of pruritus: patients with cholestatic pruritus do not exhibit the dermatologic reactions seen in patients with elevated histamine levels. The view has been presented that patients with cholestatic pruritus do not benefit from antihistamines [Jones and Bergasa, 2000].

2.4   Symptoms and signs

ICP usually manifests in the third trimester of pregnancy, mostly after gestational week 30, but earlier onsets, even as early as the 8th week, have been reported [Berg et al, 1986] .

Itching (pruritus) is the principal symptom arousing the suspicion of ICP. In medical textbooks, the pruritus linked to ICP is defined as itching of otherwise healthy skin. With long duration or intensity, the itching might lead to skin eruptions caused by scratching. It typically emerges and is most intense on the palms, soles and abdomen, and may be extremely disturbing at night and thus cause insomnia and fatigue.

Approximately 10-15% of pregnant women with ICP are affected by clinical jaundice, for the most part mild [Geenes and Williamson, 2009]. Varying figures have been presented: in a cohort of 693 patients with the diagnosis ICP, no patient presented with clinical jaundice [Glantz et al, 2004].

Laboratory tests are indicated when a clinical suspicion of ICP arises. Any or all of the following serum readings are elevated: ALAT, ASAT, AFOS, bilirubin and bile acids. Of these, bile acid level has been presented as the most important

predictor of pregnancy outcome [Chen et al, 2013a, Glantz et al, 2004]. The lowest abnormal limit value for bile acids varies from 6 to 10 µmol/l [Joutsiniemi et al, 2014, Leszczynska-Gorzelak et al, 2012]. Glutamyl transferase (GT), on the other hand, though commonly used as an indicator of hepatic function, is not used in the diagnostics of ICP.

2.5   Diagnosis and differential diagnostics

ICP is usually easy to differentiate from other liver disorders. Itching of an otherwise healthy skin with onset in the late second or during the last third of pregnancy and abnormal liver test values verify the diagnosis. Icterus is uncommon, and, if any, emerges for a couple weeks after the onset of pruritus. In a normal pregnancy, LFT levels do not change except for a slight rise in alkaline phosphatase (AFOS) [Joshi et al, 2010]. In ICP the levels of serum transaminases (ALAT) and/or other LFTs and/or bile acids are elevated. ALAT may rise before or after bile acids [Heikkinen, 1983, Shaw et al, 1982]. Itching usually fades a few days postpartum, and laboratory test values return to normal in two to eight weeks at the latest. Other liver diseases must be excluded. Particularly an early onset of ICP and failure of liver function to return to normal postpartum must be noted and the underlying liver diseases identified [McCarthy, 2007].

The most relevant differential diagnoses, or co-existing diagnoses, are usually established by ultrasound (cholelithiasis) and markers of hepatitis. Atopic eczema, urticarial or gestational pemphigoid and infections by viruses such as Epstein-Barr or cytomegalo may sometimes cause differential diagnostic problems. During pregnancy, transaminase levels may also be elevated in severe preeclampsia, especially in the HELLP syndrome (hemolysis, elevated liver enzymes, low platelets), but in such cases, unlike ICP, the condition is not cholestatic, and itching does not occur. Acute steatohepatitis (acute fatty liver of pregnancy, AFLP) has an abrupt breakout typically in late pregnancy, and is uncommon (1/10 000 – 13 000 pregnancies) [Cunningham et al, 2001, Krakow, 2008]. Hyperemesis gravidarum may cause mild hyperbilirubinemia and elevation of transaminase levels

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[Cunningham et al, 2001], but its early onset in the first trimester is too uncommon to suggest ICP and does not typically provoke pruritus.

Liver biopsy shows mild cholestasis with intracellular bile pigments and canalicular bile plugging without necrosis [Cunningham et al, 2001], but liver biopsy is not needed for the diagnosis in a typical case of ICP.

2.6   Risks of ICP for mother and fetus

The prognosis for an ICP mother is excellent, although itching may cause fatigue during pregnancy. Pruritus fades out in a couple of days [Geenes and Williamson, 2009], and icterus, if there is any, within two weeks. Laboratory test values normalize within two to eight weeks. The ICP definition entails that the woman recover completely postpartum and thus ICP is an exclusion diagnosis. In cases where the condition persists after an ICP pregnancy, an underlying liver disease has to be considered [Ropponen et al, 2006].

A pregnancy with ICP needs follow-up and management by reason of the risks involved for the fetus. ICP increases the risk of preterm birth (12-44%) [Fisk and Storey, 1988, Glantz et al, 2004, Rioseco et al, 1994], fetal distress during labor (10-44) [Alsulyman et al, 1996, Fisk and Storey, 1988, Glantz et al, 2004, Laatikainen and Tulenheimo, 1984] and intrauterine fetal death (1-3%) [Alsulyman et al, 1996, Fisk and Storey, 1988, Laatikainen and Tulenheimo, 1984]. In the UK, severe ICP affects 0.1% of pregnancies and is associated with an increased risk of preterm delivery, neonatal unit admission and stillbirth [Geenes et al, 2014]. Bile acids have been considered to be responsible for the adverse effects for the fetus [Chen et al, 2013a, Glantz et al, 2004]. They have been shown to induce vasoconstriction of the human placental chorionic veins, and myometrial sensitivity to oxytocin [Germain et al, 2003, Sepulveda et al, 1991]. They have also been shown to signal via several pathways in the placenta and the fetal heart [Serrano et al, 1998, Williamson et al, 2011]. The risk of intrauterine death in ICP has been attributed to bile acids, which induce arrhythmia in the fetal heart [Rainer et al, 2013].

2.7 Management and treatment of ICP

2.7.1 Management and care of pregnancy

After detection of ICP, the pregnant woman should be referred to an obstetric clinic. The follow-up is individual. Liver function figures, of which ALAT and bile acid concentrations are the most indicative, are checked once or twice a week. Cardiotocography and ultrasound are monitored individually.

There is evidence that the risk of adverse fetal and perinatal outcome increases significantly when the total bile acid value exceeds 40 µmol/l [Chen et al, 2013a, Geenes et al, 2014]. Grading of the bile acid subgroup profile has been suggested for clinical assessment of the severity of each ICP case [Chen et al, 2013b] .

A low-fat diet may be recommended to reduce the metabolic load on the liver [Leszczynska-Gorzelak et al, 2012, Thomassen, 1979].

2.7.2 Medication

As a symptomatic medication, antihistamines may be used for itching, although there have been doubts as to their effectiveness in light of some theories of the mechanism of pruritus [Imam et al, 2012]. Also cool aqueous menthol cream has been recommended topically to relieve pruritus [McCarthy, 2007], but does not improve biochemical abnormalities [Geenes and Williamson, 2009].

Ursodeoxycholic acid (UDCA) is considered the most effective treatment for the symptoms and abnormal biomarkers of ICP. Based on one meta-analysis, UDCA is effective in reducing pruritus and improving liver test results in patients with ICP and might also benefit fetal outcome [Bacq et al, 2012]. UDCA reduces and replaces endogenic bile acids in the bile, normalizes liver enzyme levels in all intrahepatic cholestatic conditions, and has positive effects on bilirubin concentrations. UDCA improves placental bile acid export and thus reduces the risk of fetal arrhythmia [Rainer et al, 2013, Serrano et al, 1998, Williamson et al, 2011]. In a recent

randomized, double-blind, placebo-controlled study, UDCA improved maternal itching scores and LFTs without interfering with feto-placental estrogen production in patients with ICP, and was well tolerated, and no fetal or neonatal adverse effects could be detected [Joutsiniemi et al, 2014].

S-adenosyl-L-methionine (SAMe), which has an important role in the synthesis of phosphatidylcholine, has been shown to prevent ethinylestradiol-induced elevations in AST/ALT, bile acids and bilirubin in women with a history of ICP [Frezza et al, 1988]. In a placebo controlled study, SAMe and UDCA, separately and in combination were compared [Nicastri et al, 1998]. The combination of UDCA and SAMe was more effective than placebo or either drug alone.

There have been successful trials in which rifampicin has been used together with UDCA in severe cases where UDCA alone has proved insufficient [Geenes and Williamson, 2009, Geenes et al, 2014].

Dexamethasone has been used for its decelerating effects on estrogen production in the feto-placental unit [Kauppila et al, 1976, Kauppila et al, 1979]. Dexamethasone reduces bile acid levels and relieves pruritus [Hirvioja et al, 1992].

Barbiturates have been used for their enzyme-inducing effects on the liver, this enhancing the liver's ability to metabolize steroids. Barbiturates do not reduce bile acid levels in ICP, but transaminases have a slight tendency to decrease [Heikkinen et al, 1982a]. Barbiturates deepen sleep and might thus relieve pruritus.

Cholestyramine medication aims at reducing intestinal absorption of bile acids into the liver circulation. However, the benefits are minor. Cholestyramine may also reduce the intestinal absorption of fat-soluble vitamin K, increasing the risk of hemorrhage for the mother and fetus [Sadler et al, 1995] and is thus no longer a first-line therapy for ICP. Neither has guar gum, although relieving pruritus [Gylling et al, 1998, Riikonen et al, 2000], nor activated charcoal, despite its minor benefits [Kaaja et al, 1994], been proved effective for ICP.

Vitamin K has been administered in view of the risk of fat-soluble vitamin malabsorption in ICP, to guard against the theoretical risk of fetal antepartum and

maternal intra- or postpartum hemorrhage [McCarthy, 2007]. This practice has not been consolidated by research so far [Geenes and Williamson, 2009].

In conclusion regarding medication for ICP, UDCA is at present the drug of choice, and antihistamines may give some relief from itching.

2.7.3   Timing and management of delivery

Up to recent years, the common guidelines have recommended delivery of an ICP patient at 37-38 gestational weeks [Geenes and Williamson, 2009]. There have been suggestions for continuing clinical follow-up right up to full-time gestation. Some studies have shown that the risks for the fetus increase significantly when the level of bile acids exceeds 40 µmol/l [Chen et al, 2013a, Glantz et al, 2004]. The delivery-postponing policy lowers frequencies of inductions and cesarean sections among ICP patients without significantly increasing the risk of adverse fetal outcome. However, there are authoritative views that the risk of stillbirth cannot be excluded even at bile acid levels only slightly elevated [Stefanovic and Ylikorkala, 2011].

2.7.4   Postpartum follow-up

The diagnostic criteria for ICP presume that the symptoms and signs disappear completely postpartum, this is including laboratory abnormalities in two to eight weeks at latest. Persisting clinical or biomedical abnormalities adumbrate some other underlying disease, and further investigations are indicated [McCarthy, 2007, Ropponen et al, 2006].

ICP does not cause any permanent damage to the liver, but it recurs in half of subsequent pregnancies [Germain et al, 2002, Reyes, 1997], in familial cases more or less invariably [Savander et al, 2003].

At present, the briefs or recommendations for ICP patients' future healthcare, pregnancies, contraception and menopausal hormone treatment are individual and probably sporadic.

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2.7.5 A woman with ICP in the Finnish maternity health care system

In the Nordic countries, maternity care is arranged almost exclusively within a primary healthcare setting [Sigurdsson, 2003]. In Finland, health centres maintain maternity health clinics [Laes and Gissler, 2006], where a nurse or midwife and a general practitioner are responsible for care. During pregnancy and postpartum, a woman makes regularly altogether 10-15 visits to the nurse or midwife and four visits to the doctor. Practically all pregnant women use these free facilities [Viisainen, 1998]. In Finland, women deliver almost exclusively in hospitals; elective home deliveries are rare.

ICP is usually detected in the maternity health clinics in primary health care. If an expectant mother complains of pruritus, a blood test is made for ALAT and bile acids. If one of these values is elevated the mother is referred to an obstetrician [Duodecim, 2012]. The obstetric clinic is usually situated in the same hospital where delivery is to be carried out. If the pruritus is severe and intolerable the patient is sent directly to hospital without waiting for laboratory results. Likewise, if a patient with ICP complains of acutely worsening pruritus she is sent to hospital as an urgent case.

When a woman has been registered in an obstetric clinic, she may still continue regular visits to the primary health care maternity clinic if adequate.

In the obstetric clinic, an ICP woman usually attends as an outpatient until continuous care and monitoring, complete bed rest or urgent management is needed. The follow-up is individual. Liver functions, of which ALAT and bile acid concentrations are the most indicative, are checked once or twice a week, and cardiotocography and ultrasound are monitored individually [Stefanovic and Ylikorkala, 2011]. Timing and mode of delivery are managed according to the clinical situation.

2.8 Long-term aspects of intrahepatic cholestasis of pregnancy

The central role of the liver in metabolism derives from its diverse functions and broad metabolic capacity and its location between the gastrointestinal canal and the other organs. Its functions include processing absorbed nutrients and vitamins, and eliminating products harmful for the organism from the circulation. In addition, the liver also functions as a fagocyting, immunogenetic and exocrine organ [Jokelainen, 2013]. It is crucial in the metabolism of glucose, fat and protein, enzyme and vitamin production, various steps in the blood clotting cascade as well as in inflammation and infection, and as a reservoir of blood. The liver produces bile, and bile acids are needed in the intestine for converting fat and cholesterol into absorbable forms.

We might thus hypothesize that intrahepatic cholestasis during pregnancy is associated with a number of other disorders during lifetime, for example via the genetic constitution which leads to diverse metabolic pathways. In addition, a serious disease during pregnancy, for example ICP, might lead to conscious or unconscious changes in lifestyle or health habits possibly reflected in health history.

2.8.1 Pregnancy outcome

A pregnancy with ICP calls for follow-up and measures in view of the risks for the fetus. ICP increases the risk of preterm birth (12-44%) [Fisk and Storey, 1988, Glantz et al, 2004, Rioseco et al, 1994], fetal distress during labor (10-44) [Alsulyman et al, 1996, Fisk and Storey, 1988, Glantz et al, 2004, Laatikainen and Tulenheimo, 1984] and intrauterine fetal death (1-3%) [Alsulyman et al, 1996, Fisk and Storey, 1988, Laatikainen and Tulenheimo, 1984]. One Finnish study has shown an increased risk of preterm delivery and the need for neonatal care [Heinonen and Kirkinen, 1999], and affected women were delivered by cesarean significantly more often than the general obstetric population. In the UK, severe ICP affects 0.1% of pregnancies and is associated with an increased risk of preterm delivery, neonatal unit admission and stillbirth [Geenes et al, 2014].

2.8.2 Health history

It has been established that women with a history of ICP are more prone to a number of liver and biliary disorders including non-alcoholic cirrhosis, non-specific hepatitis, hepatitis C, cholelithiasis and pancreatitis, even before the first episode of ICP [Marschall et al, 2013, Ropponen et al, 2006].

ICP is associated with metabolic adversities such as dyslipidemia [Dann et al, 2006], higher serum glucose concentrations [Martineau et al, 2014, Wojcicka-Jagodzinska et al, 1989] and an increased risk of gestational diabetes [Martineau et al, 2014] when compared with healthy control subjects. In addition, ICP women are reported to have lower vitamin D concentrations, these also being inversely correlated by meconium staining [Wikström Shemer and Marschall, 2010].

The so-called "leaky gut" has been suggested to play a role in the pathogenesis of ICP, namely enhancement of the absorption of bacterial endotoxins, where cytokines might favor this absorption to initiate a hepatic inflammatory cascade [Reyes et al, 2006].

2.8.3 Health behavior

Pregnancy is an important episode in a woman's and a family's life and opens up an opportunity to revise health behavior in short and long view.

To the author's knowledge, the association between ICP and subsequent health behavior has not been studied. On the other hand, we do not know whether women with a history of ICP would need or benefit from health-promoting guidance different from that for women without the history.

2.8.4 Heredity

The genetic predisposition to ICP is a subject of increasingly intense research, and has proved to be complex. In 16% of pregnancies ICP is familial, and the pedigree

structures show dominant inheritance [Savander et al, 2003]. In such cases the condition recurs in 92% of pregnancies and laboratory test levels are higher than in non-familial cases. The occurrence of ICP in first-degree relatives of ICP patients has been reported to be 6% in singleton pregnancies [Eloranta et al, 2001]. Either gender has been proposed to transmit the ICP-predisposing trait [Reyes et al, 1976]. A dominant mode for ICP inheritance has been presumed, either autosomally or X-chromosome-linked [Hirvioja and Kivinen, 1993, Holzbach et al, 1983]. Several different cholestatic genes have been proposed to transmit the metabolic disorder in ICP [Eloranta et al, 2003, Mullenbach et al, 2005, Pauli-Magnus et al, 2004]. Moreover, differences in gene expression may contribute to the complex pathogenesis of ICP [Floreani et al, 2013]. In a previous Finnish study, ICP patients appeared to be aware of the ICP history of their relatives [Eloranta et al, 2001].

2.8.5   Family planning

Cholestatic conditions have been provoked by hormonal contraceptives in women with a history of ICP [Drill, 1974]. In one case report, a woman with ICP in all her pregnancies developed an identical clinical picture with jaundice and abnormal LFTs when exposed to ethinyl estradiol (1mg daily) [Kreek et al, 1967]. Consequently ICP was considered a contraindication to the use of oral contraceptives [Gagnaire et al, 1975]. The doses of hormones were higher in the early hormonal contraceptives than in modern preparations. In 1982, twenty women were treated with biphasic combined oral contraceptive pills (containing ethinyl estradiol 0.05 mg and levonorgestrel 0.050-0.125 mg), and no significant changes were found in bile acid level or profile, although ALAT activity was significantly increased after twelve months' treatment [Heikkinen et al, 1982b]. In medical textbooks and studies, there is some divergence in comments on the use of combined hormonal contraception. The conception that cholestasis often recurs concomitant with estrogen-containing contraceptive use in women with a history of ICP has been presented [Cunningham et al, 2001]. A French study in 1997 claimed that low-dose oral contraceptives can be prescribed to ICP women since they did not

cause pruritus or any major rise in liver function readings for most ICP women [Bacq et al, 1997].

The Reproductive Health and Research unit of the World Health Organization (WHO) updated the recommendations for contraception in 2009 [WHO, 2010]. Combined hormonal contraception for women with a history of ICP was moved from the 2004 category 3 to category 2, which signifies that the method can generally be used. The category scale is from 1 to 4, where category 1 is defined as a condition for which there is no restriction on use of the method, and category 4 as a condition which entails an unacceptable health risk if the method is used. The progestin-only method for women with a history of ICP is situated in category 1.

2.8.6   Menopause

Since ICP is a hormone-induced condition, it is fully understandable that it has constituted at least a relative contraindication for hormone replacement therapy (HRT). Experience from the early hormonal contraceptives as provoking cholestatic conditions in susceptible women augmented such a conception. Modern guidelines do not contraindicate HRT for a woman with a history of ICP. Neither oral nor transdermal HRT has proved to have adverse effects on liver function in women with a history of ICP [Tuomikoski et al, 2008].

It has been reported that estrogen increases the occurrence of symptomatic gallstones and their complications when used by women with asymptomatic gallstones [Dhiman and Chawla, 2006, Hart et al, 2008], and this might be relevant to women with a history of ICP, among whom cholelithiasis is more common than among controls [Ropponen et al, 2006].

Research and discussion regarding the risks and benefits of HRT is active. Considering the indications, timing and duration of HRT, its benefits are held to exceed the risks. HRT is considered the most effective treatment for menopausal symptoms. Estrogen increases bone mineral density even at very low doses, especially in older women [Prestwood et al, 2003], and the Women's Health

Initiative (WHI) reported a decreased risk of bone fractures with estrogen-progestin treatment [Cauley et al, 2003]. There is some early evidence that HRT reduces the risk of coronary heart disease events when started on healthy women within a few years of menopause [Harman et al, 2011], but more research on the subject is warranted. HRT has been associated with an increased risk of breast cancer. Estrogen use for less than five years is associated with a reduced risk of breast cancer, whereas estrogen use for five years or more leads to four to six extra breast cancers for every 10 000 woman-years [Lyytinen et al, 2006]. Estrogen combined with progestin increases the risk of breast cancer even when used for less than five years [Lyytinen et al, 2009].

2.9   Summary of the literature

Globally, the occurrence of ICP varies from less than 0.5% up to 28% of pregnancies, and in Finland it has been approximately 1%. The risks for the fetus are the reason why ICP needs to be detected: preterm birth, intrauterine fetal death, stillbirth, fetal distress during labor and need for neonatal care. The risks cause changes in pregnancy follow-up and management.

Women with a history of ICP are more prone to a number of liver and biliary disorders, for example non-alcoholic cirrhosis, non-specific hepatitis, hepatitis C, cholelithiasis and pancreatitis.

The association between ICP and later health behavior has not been studied.

The disease has been considered to be hereditary in 16%, and in such cases it recurs in practically every subsequent pregnancy. ICP patients have appeared to be aware of the ICP history of their relatives.

Combined oral hormonal contraception has been reported to cause cholestasis similar to ICP in susceptible women when using the early "high-dose" pills. Cholestasis from "low-dose" pills is uncommon.

It has been proved that neither oral nor transdermal HRT has adverse effects on liver function in women with a history of ICP. Cholelithiasis is common in women with a history of ICP. Women with cholelithiasis should not have HRT on account of the risk of complications.

3 AIMS OF THE STUDY

The aims of this study were:

1. to explore the occurrence of ICP and the success of the outcome in ICP pregnancies in Finland.
2. to obtain information as to whether a history of ICP is associated with other diseases.
3. to study whether ICP affects sufferers' health behavior.
4. to establish how common ICP is among sufferers' close relatives.
5. to study whether ICP has an effect on the sufferers' sexual health and family planning.
6. to establish whether ICP has an effect on the sufferers' hormone replacement therapy or postmenopausal health.

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4   MATERIAL AND METHODS

4.1   Study design

To explore the long-term aspects of ICP, it was necessary to have a lengthy time period between the episode of ICP and the survey moment. It was decided to collect all ICP patients available during 20 years in Tampere University Hospital in order to establish a broad study population. The years were appropriate for the study design in that with the implementation of ICD-8 (in 1969) and ICD-9 (in 1987), diagnostic codes were applied in the hospital discharge registers. A postal questionnaire survey was chosen as data collecting method to obtain subjective answers regarding diverse aspects of health from the study population. The option of register-based research was also retained.

Research approval was obtained from the Ethics Committee of the Pirkanmaa Hospital District (R02149).

Access to the maternity ward diary and the patient registry with researcher's limited rights was allowed by the Director of Division, Chief Physician of the obstetric clinic in Tampere University Hospital and the Medical Director of the Pirkanmaa Hospital District, respectively.

4.2   Study population

The study population was selected from the Tampere University Hospital patient discharge register according to diagnosis codes. During 1969-1986 ICD-8 was used, and in 1987-1988 ICD-9. The version ICD-8 did not include a precise code for ICP, and we noted all obstetric code numbers entailing a possibility of ICP: 637.99 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 contained more precise codes 6467A Hepatosis gravidarum and 6467X Hepatopathia alia.
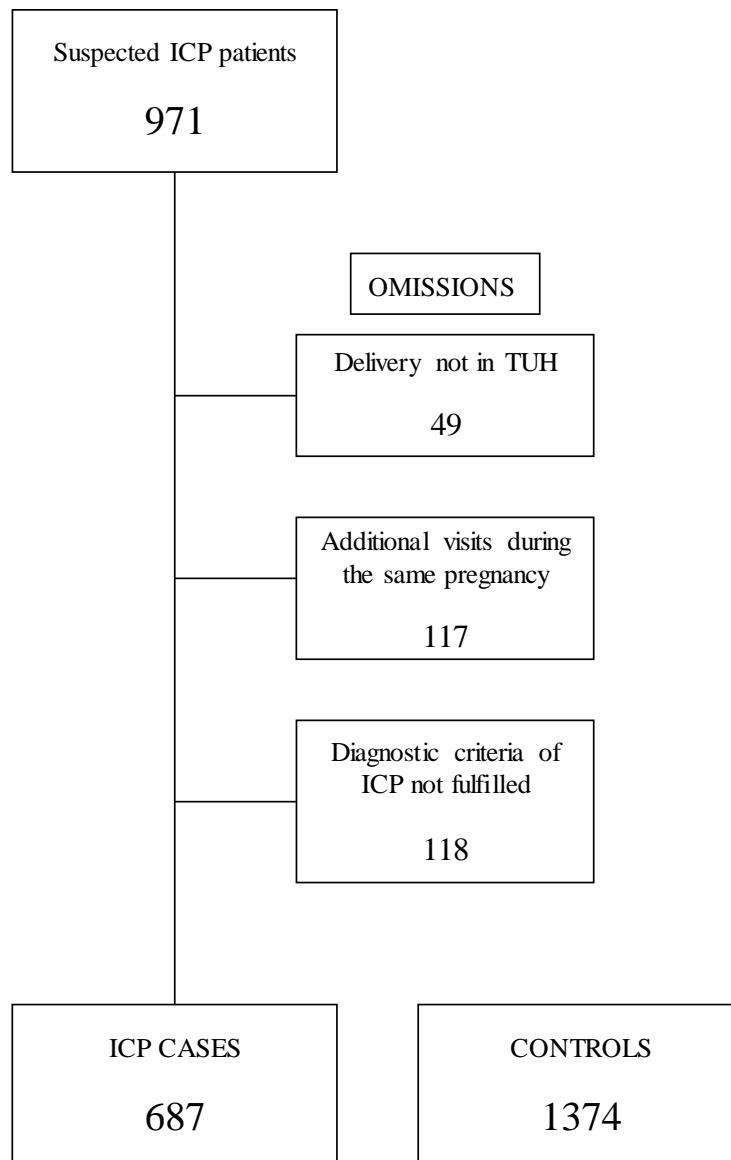

Figure 1. Flow chart of ICP patients and controls in Tampere University Hospital (TUH) during1969–1988. [Turunen et al, 2010]

Finally, the diagnosis was verified from each patient record by the presence of the main symptom of itching, and abnormal laboratory findings. At least one of the following was required: ASAT >35 U/l, ALAT >40 U/l, or bile acids 6 µmol/l or more. Of the total of 79 508 deliveries in Tampere University Hospital during the twenty years' period, we found 687 ICP cases. Both singleton and twin pregnancies were included. The proportion of twin pregnancies was 5.1% in the ICP group and 2.1% in the control group. For each ICP case, two controls were taken, namely the previous and the next subject in the maternity ward diary, altogether 1374 controls. If a control proved to be an ICP patient in our whole data, she was replaced with the next suitable woman. The flow chart (Figure 1) illustrates study population collection

In 2010, postal addresses were obtained from the Finnish Population Register Centre. In September 2010, a postal questionnaire (Appendix 2), an explanatory letter (Appendix 1) and a reply-paid envelope were sent to all women who had postal addresses in Finland. By August 2010, altogether 22 women (3.8%) out of those with a history of ICP, and 71 women (5.2%) without the history, had died. However, the difference was not statistically significant. Questionnaires were sent to 544 ICP women and 1235 controls. With one reminder, 66.2% of the envisaged study population responded. The following flow chart (Figure 2) shows the population of the mail survey. Altogether 371 (68.2%) of the ICP mothers and 807 (65.3%) of controls responded.

For study I, where the occurrence of ICP and the pregnancy outcome was investigated, all verified ICP cases and controls were included. For studies II-V, where the postal survey data were investigated, all those who responded, were included. In study VI those respondents who had passed menopause were included, altogether 189 women with and 416 women without a history of ICP.
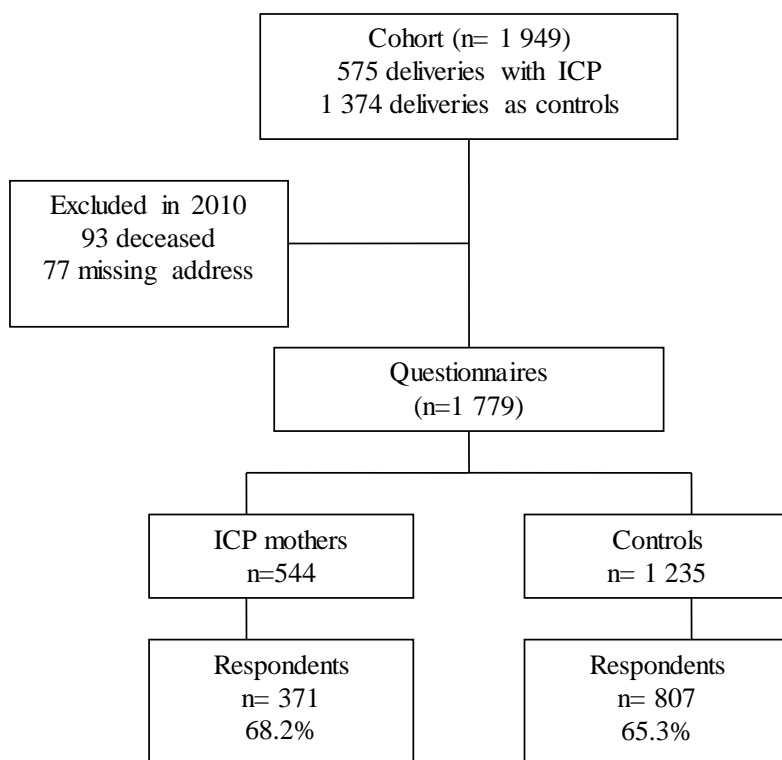
```
                    ┌─────────────────────────────┐
                    │      Cohort (n= 1 949)      │
                    │  575 deliveries with ICP    │
                    │  1 374 deliveries as controls│
                    └─────────────────────────────┘

┌─────────────────────┐
│  Excluded in 2010   │
│    93 deceased      │
│  77 missing address │
└─────────────────────┘

                    ┌─────────────────────────────┐
                    │       Questionnaires        │
                    │         (n=1 779)           │
                    └─────────────────────────────┘

        ┌─────────────────┐          ┌─────────────────┐
        │   ICP mothers   │          │    Controls     │
        │     n=544       │          │    n= 1 235     │
        └─────────────────┘          └─────────────────┘

        ┌─────────────────┐          ┌─────────────────┐
        │   Respondents   │          │   Respondents   │
        │     n= 371      │          │     n= 807      │
        │     68.2%       │          │     65.3%       │
        └─────────────────┘          └─────────────────┘
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Figure 2. Flow chart of the survey population. ICP, intrahepatic cholestasis of pregnancy. [Turunen et al, 2012]

4.3   Questionnaire and measurements

For study I, the ages of the respondents were coded as full years on the last day of the delivery year, the mean age of ICP patients being 27.5 years, and controls 27.2 years. The difference between the groups was not statistically significant. In the case of the postal survey for studies II-VI, the ages of the respondents were coded as full years on the last day of the year 2010, the mean being 58 years in both groups.

Education was estimated as "high" for those who had taken the matriculation examination (gymnasium/grammar school), and "low" for those who had not [Korkeila et al, 2004]. The proportion of women with a high education level was 33% in both groups, and the groups were thus comparable. Education was registered

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according to the postal survey responses in 2010, and is thus concerned in studies II-VI.

In the questionnaire, the respondents were asked their present height and weight, and their weights at different points in time: weight at birth, weight at 20 years, highest weight during pregnancy or breast-feeding periods and highest weight at any other point in time. Body mass indices (BMIs) were calculated from the reported weights and heights, expressed in kg/m^2, and then divided into two (≤ 29.9 and ≥ 30.0) or three (≤ 25, 25.0-29.9 and ≥ 30.0) categories. In the analysis, the only statistically significant difference between the groups was found in the highest BMIs during pregnancy, ICP mothers having the lower figures.

For study I, information on all ICP and control parturients during 1969-88 was extracted from the maternity ward diary. The data consisted of the following: date of admission to the hospital ward, discharge date, week of pregnancy at entry, date of the delivery, notes of the mode of delivery as follows: induction, vacuum extraction, forceps, manual procedures made by a doctor, cesarean section, manual extraction of placenta, inspection/exploration of uterus, abrasion of uterus, excision of membranes, episiotomy, rupture of perineum, bloodshed, blood transfusion and afterbirths. From the dates given, pregnancy weeks at delivery, as well as the length of the period in the hospital ward, were counted. Regarding the fetus/child, the following aspects were registered: presentation, gender, live/dead, weight (g) and Apgar score.

The data for studies II-VI were collected by postal survey. The questionnaire (Appendix 2) was accompanied by an explanatory letter (Appendix 1), identical for both groups.

The design of the questionnaire (Appendix 2) aimed to ensure a broad collection of information on ICP and control women's lives from diverse perspectives of health or details which might be connected with health. Some questions had already been validated in medical research and practice, as AUDIT (Alcohol Use Disorders Identification test), some were obtained from the Finnish HESSUP (Health and Social Support) survey [Korkeila, 2005, Korkeila et al, 2004], and some were

modified from general/public health screening survey questionnaires such as the health inquiries for women at certain stages of life, and FINRISKI [THL 2013], a national health survey. A major part of the questions were planned for this survey only.

To assess and improve the questionnaire, a piloting run was performed. We asked the pilot respondents to fill in the questionnaire, to report on assets, disadvantages, errors and points of possible misunderstanding in the questionnaire, as well as the time used to fill in the questionnaire. On the basis of the responses, the questionnaire was revised.

In study II, a broad range of health history was charted. The main focus was on diseases the respondents reported. The heading read: "Has a doctor ever told you that you suffer or have suffered from the following diseases or conditions?" Below there were tick boxes for various diseases, among them gastroenterological, hepatobiliary, endocrinological, urological, gynecological, oncological, bone- and articulation-related, respiratory and cardiovascular diseases. A few separate disorders such as migraine, epilepsy and anemia were included. There were also queries on bone fractures in wrist, hip and vertebral column. Major surgery was also asked after. Separate questions were included for mental disorder history, and a screening panel (DEPS) for present depression.

Regular or occasional use of 13 different medicines or natural health drugs was also charted.

We also inquired into the respondents' perceived health, irrespective of any diseases, and gave five alternatives: good, fairly good, moderate, fairly poor and poor. In the analysis, we combined the first two alternatives into "good" and the rest into "poor".

To assess the number of minor negative or inconvenient health experiences among study subjects, we offered a panel of 24 common symptoms and complaints which might have been bothering them during the past year.

As aspects of healthy behavior in study III we inquired into the following among the study population: smoking history, alcohol consumption (AUDIT-C), physical activity and body mass index (BMI), the last being at least partly a result of overall health behavior. We also charted the dietary choices the respondents reported. Seven major diets are discussed here.

Study IV sought to reveal how common ICP is in close female relatives. We thought that a postal survey would be an appropriate means of obtaining data on heredity, since in an earlier study ICP patients appeared to be aware of the ICP history of their relatives [Eloranta et al, 2001]. The respondents were asked whether their mothers, sisters or daughters had ever suffered from liver dysfunction during their pregnancies. Here we interpreted "liver dysfunction during pregnancy" as ICP because ICP is the most common pregnancy-induced liver dysfunction. Of sisters and daughters, only those who had delivered were included in the analysis.

For study V, a detailed gynaecological anamnesis was taken via the questionnaire: age at menarche, number of pregnancies, abortions, miscarriages, ectopic pregnancies and deliveries, as well as operations such as cesarean, hysterectomy and sterilization. Contraception was an essential item in the questionnaire. Questions on the importance of sexuality and satisfaction with sex life and relationship were also included, the scale being a Likert 7-type scale.

The population in study VI comprised women who had answered that their menstruation had ceased naturally due to menopause. We aimed to ascertain the possible difference in HRT use between the two groups. We also asked what other kind of medications or treatments respondents had used to alleviate menopausal symptoms. We explored the occurrence of the diseases the respondents reported. Of the 24 common symptoms and complaints during the past 12 months, we included in the menopause study (VI) the following: vaginal and vulvar dryness, chest pain, blushing, headache, insomnia, heart palpitations, nervousness, sweating, urinary problems and depression.

4.4   Statistical analysis

Analyses were undertaken using the SPSS System for Windows (SPSS Inc., Chicago, IL, USA), release 16.0 in articles I, II and V, and release 20.0 in articles III, IV and VI. The results were presented as frequencies and/or percentages, and mean and/or median values. Statistical significance was tested by t-test and chi-squared test. Logistic regression analysis (OR with 95% CI) was also used.

5 RESULTS

5.1 Occurrence of ICP and pregnancy outcome in ICP pregnancies (Study I)

The proportion of ICP in 1969-88 was 0.9% of pregnancies. If we omit the three first years as years of rehearsal for ICD-8 implementation, we get an ICP occurrence of 1%. During the years 1972-88 the occurrence of ICP varied from 0.6% to 1.5%.

ICP mothers were kept in hospital significantly longer than control mothers. ICP mothers' labors were more often induced and/or carried out by cesarean, and delivery took place at earlier gestational weeks more often than control labors, the differences being statistically significant. The birth weights of ICP mothers' children were statistically significantly lower than those of control children. However, the Apgar scores at 1 minute and 5 minutes of age presented no statistically significant differences. The stillbirth rate among ICP children was 1.2% and among controls 0.7%, the difference being not statistically significant. Multiple pregnancies were significantly more common in ICP than in control pregnancies.

5.2 Health history (Study II)

Of the reported diseases, the following hepatobiliary disorders were statistically significantly more frequent in the ICP than the control group: cholelithiasis, elevation in LFTs (except during pregnancy) and chronic choledochitis (Table 2). Of other reported diseases, hypothyreosis and breast cancer were significantly more common in the ICP group, whereas high cholesterol on medication, high blood pressure on medication, as well as cardiac arrhythmia were significantly more common in the control group (Table 2).

Table 2. Diseases diagnosed by a doctor in the ICP and control groups.

	ICP group (n=353-370)	Controls (n=741-796)	Difference	
	%	%	% units	Significance p
Diseases of the digestive system				
Cholelithiasis	37.2	12.1	25.1	< 0.001
Rise in liver function test results (except during pregnancy)	16.8	9.2	7.6	< 0.001
Gastric catarrh, gastric or duodenal ulcer	17.3	13.6	3.7	0.099
Chronic choledochitis	5.0	1.5	3.5	0.001
Helicobacter pylori infection	8.3	7.5	0.8	0.633
Pancreatitis	1.9	1.1	0.8	0.294
Fatty liver	4.9	4.2	0.7	0.555
Acute hepatitis	1.9	1.3	0.6	0.389
Crohn's disease	0.8	0.3	0.5	0.174
Celiac disease	2.2	2.0	0.2	0.861
Chronic hepatitis	0.5	0.4	0.1	0.686
Liver cirrhosis	0.0	0.1	-0.1	0.497
Colitis ulcerosa	1.4	2.2	-0.8	0.361
Endocrine, nutritional and metabolic diseases				
Hypothyreosis	17.2	11.6	5.6	0.011
High cholesterol on medication	21.1	26.6	-5.5	0.041
Diabetes on medication	7.4	8.9	-1.5	0.390
Diseases of the genitourinary system				
Endometriosis	12.1	8.9	3.2	0.091
Malignant neoplasms				
Breast cancer	6.3	3.7	2.6	0.047
Any other than breast or gynegologic cancer	4.2	3.1	1.1	0.354
Gynecologic cancers	1.9	1.4	0.5	0.512
Diseases of the respiratory system				
COPD	1.7	0.8	0.9	0.171
Asthma	9.1	10.3	-1.2	0.558
Diseases of the circulatory system				
Thrombophlebitis in lower extremity	8.5	8.0	0.5	0.778
Deep venous thrombosis in lower extremity	2.2	3.3	-1.1	0.292
Myocardial infarction	0.5	1.7	-1.2	0.124
Cardiac arrhythmia	15.2	21.8	-6.6	0.008
High blood pressure on medication	31.6	38.3	-6.7	0.027

[Turunen et al, 2012]

Reports of surgery involving a cholecystectomy (38.2% vs. 9.8%, p <0.001) or a malignant tumour (8.9% vs. 5.1%, p = 0.012) were significantly more common among women with a history of ICP. The incidence of bone fractures in the wrist,

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hip or vertebral column did not significantly separate the groups. There were no significant differences between the groups in terms of mental health history and the risk for present depression. As a whole, regarding most of the diseases reported, there were no significant differences between the two groups.

Of medicines and health products, use of gastric acid reducers was statistically significantly more common among women with an ICP history (40.4% vs. 32.5%). There was a trend for women with a history of ICP to use more pain killers and fewer antidepressants, medicines for high cholesterol and for high blood pressure than the control women, the differences being not significant. Natural health drugs were used by 51.9% of women with an ICP history, and by 45.9% of controls, the trend again being not statistically significant.

Good health was reported by 70.7% of the respondents in the ICP group and 72.2% in the control group, the difference being not significant.

Of the 24 common symptoms and complaints during the past 12 months, cough and itching of palms and soles were significantly more frequently reported among women in the control group. The women with an ICP history more often reported chest pain (13.7% vs. 9.8%), the difference approaching significance, p=0.054.

5.3   Health behavior (Study III)

Among women with an ICP history, current smoking was not as common as among controls, and the overall smoking history expressed in smoking pack years was lighter than that of controls, the difference being statistically significant. Alcohol use did not separate the groups. Alcohol abstinence during the past 12 months was more common among ICP women (18.3% vs. 14.9%), but the difference was not statistically significant. In respect of physical activity, no significant differences appeared between the groups when examined by the score of metabolic units (MET)/day. BMI scores, when divided into two categories ($\leq$29.9 and $\geq$30.0), showed no statistically significant differences between the groups as to BMI at 20 years or currently. With regard to the highest BMIs during pregnancy, there were

significantly more women with BMI>30 among the control women than among those with a history of ICP.

Gallbladder diet and weight loss dieting were more common in the ICP group, the difference being statistically significant. A vegetarian diet was uncommon in both groups, however, more common in the control group. In dietary choices such as lactose-free/low-lactose, gluten-free, low-fat/low-cholesterol or others, no statistically significant differences were found.

5.4   Occurrence of ICP among close relatives (Study IV)

Of the respondents classified as ICP women, 12% reported of their mother, 15.9% of their sister, and 10.3% of their daughter, having suffered liver dysfunction during their pregnancies. Of the control women, the respective figures were 1.6%, 3.1% and 2.3%. The differences between the figures reported by ICP and control women were statistically significant.

5.5   Family planning (Study V)

Ages at menarche did not separate the two study groups. An ICP history had some statistically significant associations with sexual health and family planning. The use of combined oral contraceptives was less common among women with a history of ICP than among controls. The ICP women reported having limited their number of children for health reasons and had more often a single child than the control women. Cesarean sections were more frequent in the ICP group, but there were no statistically significant differences between the groups in terms of abortions, miscarriages or ectopic pregnancies. In the ICP group, multiple pregnancies were statistically significantly more common than in the control group. Sterilizations were equally common in both groups.

There were no statistically significant differences in ratings of satisfaction with sex life and current relationship. However, women with a history of ICP considered sex significantly less important than the control women.

5.6   Menopause (Study VI)

There were no statistically significant differences between the ICP and control groups as regards age at menarche or at the last period indicating menopause.

The ICP women reported more obstacles to or prohibitions for HRT use, but 46.6% of them had nevertheless used HRT at some time, as against 43.3% of control women. However, the difference was not statistically significant. Current HRT use was reported by 30.7% and 34.4%, the difference again being not significant. HRT was the most common means to alleviate menopausal symptoms in both groups. In the case of other means of alleviation, no significant differences between the groups could be seen, although medicines for heart arrhythmia and palpitations, as well as antidepressants, were slightly more commonly used in the control group.

Of the diseases or conditions reported, the occurrence of gallstones, chronic choledochitis and rise in liver function readings (except during pregnancy) were significantly more common among women with a history of ICP than among controls. Also breast cancer, hypothyroidism and goiter were significantly more common in the ICP group. Cardiac arrhythmia was more common among the control women than among ICP women. A similar trend, though not statistically significant, could be seen in figures for myocardial infarction, in favor of the ICP group. No statistically significant differences emerged in osteoporosis and bone fractures.

6   DISCUSSION

6.1   Main results of the study

The proportion of ICP pregnancies among women who delivered in Tampere University Hospital during the years 1969-88 was 0.9%. Women with ICP stayed in the hospital ward longer, experienced labor induction or/and cesarean section more often and delivered at earlier weeks of gestation than women in the control group. ICP mothers' children were smaller at birth. All these differences between the ICP and control groups were statistically significant. However, the Apgar scores of the newborns were similar in both groups. The stillbirth rate was small but slightly higher in the ICP than the control group, albeit not statistically significantly.

According to the questionnaire survey in 2010, women with a history of ICP had statistically significantly higher incidences of breast cancer, hypothyroidism and hepatobiliary diseases, but lower incidences of cardiac arrhythmia and lesser use of medication for hypercholesterolemia and high blood pressure, when compared with women without a history of ICP.

ICP was associated with a lower frequency of smoking, while no statistically significant difference was detected in recent use of alcohol. Women with a history of ICP reported more cases of ICP among their close relatives than women without the history, the difference being statistically significant.

The ever-use of combined oral contraceptives was significantly less common among women with the ICP history than among those without. One-child families were significantly more common among ICP women than among controls. In contrast to the use of combined oral contraceptive pills, the use of HRT was as common among the women with a history of ICP as among the control women.

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6.2　Reflections on the study setting, material and methods

The study population was extensive, including all verified ICP cases during twenty years (1969-88) in Tampere University Hospital (TUH). Our starting-point here was that the symptoms, signs and diagnoses had been documented appropriately in the hospital registers. Diagnostic criteria were the symptom pruritus and at least one abnormal liver function result. The quality of patient records has proved to involve certain weaknesses [Vainiomäki et al, 2008]. It is probable that the years 1969-1971 were rehearsal years in the recording of codes of diagnoses in the case records and discharge registers. It is possible that some cases have been misdiagnosed as ICP, because itching is not uncommon during pregnancy, and slightly elevated liver function readings might have occurred without relevance to ICP. Although TUH is practically the only option for most women in the district, deliveries were also carried out in district hospitals and central hospitals in the TUH "million range". From these hospitals, women with the most complicated pregnancies were referred to TUH. Thus, women delivered in TUH do not represent precisely the average parturient population in Finland. This selection can be seen for example in the 2.1% occurrence of multiple pregnancies in the control group while the average twin pregnancy proportion at the time was 1.1%.

Power calculations were not carried out prior to the study. We simply included all verified ICP cases. To add weight to the study, two controls for each ICP case were fixed. Some ICP patients may have been falsely chosen as controls if they had had an ICP pregnancy and delivery in some other hospital than TUH.

In this setting, some results might not be statistically significant when ascertained by power calculations. One example of this is the difference in stillbirths (1.2% among children born to ICP mothers and 0.7% among children born to control mothers), where we estimated that 6000 ICP cases should have been the size of the population where the power of the study would be statistically weighty. In this study, we chose to analyse a large population from a local, well-documented source, and we also sought subjective answers from living women.

Altogether postal addresses were available for more than 90% of the original study population in August 2010. No payment or other recompense was granted for responding to the 22-page questionnaire, only the reply envelope was ready-paid. With one reminder, the total response rate was 66%, which can be regarded as good [Asch et al, 1997]. Reasons for the good response rate can be taken to depend on the season of the year, the target population, the questionnaire and the explanatory letter. The postal survey was carried out in September and October 2010, clearly after summer holidays and before the Christmas season. The target population was limited, and the subjects presumably found answering interesting and important. The questionnaire and the explanatory letter can be considered successful also in that the response rates were good in both groups. We did not seek to hide nor to highlight the fact that the important issue here was ICP. We wished to maintain the option of researching the diagnoses of the study population from national registers, and consent for that was requested. Most gave their consent. Hitherto the registers have not been accessed. The causes of death or the diseases of the women who did not respond have not been investigated.

Data from questionnaires may involve errors. The respondents might not have remembered details of their health history, might have originally misunderstood matters and misinterpreted their symptoms, or the questions were difficult or misleading. In a large Finnish study Health and Social Support, some respondents reported having cancer with no confirmation in the Finnish Cancer Registry [Korpimäki et al, 2012]. However, we consider these matters to pertain to both groups in our study. By questionnaire we received abundant information directly from the women themselves. For example the question concerning perceived health has proved statistically significantly predictive of patients' future health and risk of death, even more so than objective measures or risk assessments [Mossey and Shapiro, 1982]. Judging from our results we could say that self-rated health is associated with the perceived previous history and present situation.

6.3   Discussion of the results

Occurrence of ICP and pregnancy outcome

The 0.9-1.0% occurrence of ICP found in our study is in keeping with earlier findings in Finland and Scandinavia [Berg et al, 1986, Heinonen and Kirkinen, 1999, Laatikainen and Tulenheimo, 1984]. Also the stillbirth proportion fits in with previous results [Alsulyman et al, 1996, Fisk and Storey, 1988, Laatikainen and Tulenheimo, 1984]. We suggest that the good pregnancy outcome derives from timely detection of the disorder and appropriate follow-up, management and care of these women's pregnancies and delivery. The stillbirth rate, though low, would indicate that ICP is a serious gestational condition calling for early detection in primary health care, and appropriate management and care of the mother in the obstetric clinic.

Health history after ICP

The crucial importance of liver functions in the human body, and ICP, being at least in one in six cases hereditary, led us to consider whether ICP has associations with other diseases or health problems in life. The occurrence of gallstones and other hepatobiliary diseases was higher among women with a history of ICP, which reinforces findings in earlier studies.

Previous studies of ICP pregnancies have suggested a higher risk of metabolic syndrome [Dann et al, 2006, Wojcicka-Jagodzinska et al, 1989] and correspondingly cardiovascular diseases and osteoporosis [Wikström Shemer and Marschall, 2010] in these women, but this was not the case. We may speculate that metabolic disorders prevail in pregnancy only, and the duration is too short for major negative effects. An explanation may also be found in health-connected behavior. The crucial role of the liver in the blood clotting cascade led us to consider the occurrence of thromboembolic or hemorrhagic conditions, but no excess of these diseases could be seen.

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In studies II and VI, the fact that the occurrence of breast cancer was statistically significantly higher (p = 0.047 and p = 0.001, respectively) among ICP women as against controls, is a new finding. One explanation might be sought in the lower number of pregnancies [DiSaia and Creasman, 2002]. Further, we may suggest genetic differences in estrogen and progesterone metabolism.

The statistically significantly higher occurrence of hypothyroidism (p = 0.011) in women with a history of ICP than in controls, is another new finding. In association with ICP, a genetic, viral or autoimmune origin of hypothyroidism can be suggested.

The lower occurrence of cardiac arrhythmia, and the lesser use of medication for high blood pressure or cholesterol among ICP women may again be of genetic origin, but differences in health-connected behavior must also be considered. We may also speculate whether ICP had primed these women to be better aware of their health status and different symptoms, and made them more ready to consult a doctor and also participate in screening tests. If so, for example hypothyroidism and breast cancer will have been diagnosed earlier.

Health behavior after ICP

Pregnancy has been thought to be a favorable period in motivating a woman and her family to revise their health habits for the pregnancy and even for the rest of their lives. Prenatal care has been proved to reduce the proportion of low-birth- weight infants, improve perinatal survival and reduce the occurrence of respiratory distress and intraventricular hemorrhage [Leveno et al, 1985]. By lifestyle changes people can lower their morbidity for typical national diseases such as diabetes mellitus type 2 [Tuomilehto et al, 2001].

By charting health behavior among the study population we sought to establish whether ICP, a serious disease during pregnancy, has an association with the sufferers' health habits. We also aimed to detect clues or explanations for certain particularities in these women's health history (Study II). Here, ICP was associated with a significantly lower smoking rate. The result is interesting when we compare

it with the equal rates of alcohol use in the groups. A history of ICP and non-smoking cannot directly be considered a causal relationship.

ICP sufferers most certainly become aware of the hepatic origin of the disorder during pregnancy. People also generally know well that the liver is crucial in alcohol turnover. It might thus be possible that consciously or unconsciously, a woman after an episode of ICP might seek to protect her liver – or her health overall - in different ways, for example by limiting her alcohol consumption.

Heredity of ICP

The complexity of the genetics and expression of ICP raises the question, how the hereditary nature of the disease shows in our study population. It has previously been reported that ICP women are aware of a positive ICP history in their families [Eloranta et al, 2001]. Our study underlines the hereditary component of ICP occurrence. Thus, the anamnestic question of close relatives' gestational disorders, including hepatic conditions, is appropriate in maternity care. If the answer is positive, the pregnant woman will be provided with updated information, and will be ready to react if similar symptoms arise.

Family planning

Contraception brought ICP women the problems we anticipated: limited use of combined oral contraceptives. The shift from pills containing 150 µg estrogen to 50 µg was carried out by 1970, and even to 20-35 µg in 1974, when high-dose pills were withdrawn from the market [Hirvonen and Idänpään-Heikkilä, 1990, Mishell, 1991]. The change was made on account of reports of thromboembolic cases [Mishell, 1991]. Probably the restrictions in the use of combined oral contraceptives for women with a history of ICP in our study were mostly unnecessary [Bacq et al, 1997]. Medical textbooks and even commercial pharmaceutical information may be outdated. Women with a history of ICP can use modern combined oral contraceptives provided their LFT values and symptoms are followed. Physicians

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encountering women in family planning clinics should be provided with and follow modern guidelines.

Menopause and HRT

Besides hormonal contraception, ICP might well have meant restrictions in HRT for menopausal symptoms. Thereby after decades, ICP might have affected women's quality of life, and also the emergence of diseases which might be avoided or postponed by HRT. Restrictions would have been unnecessary, because neither oral nor transdermal HRT has proved to have adverse effects on liver function in women with a history of ICP [Tuomikoski et al, 2008].

The result is encouraging: a history of ICP does not limit the use of HRT. Breast cancer was more common among ICP women, but solely on the basis of our study restrictions on HRT use for ICP women cannot be imposed.

The previous knowledge that gallstones are common in women with ICP was strengthened in this study. The guideline on caution in prescribing HRT for a woman with gallstones is still current and especially so in women with a history of ICP.

7   CONCLUSIONS AND FUTURE IMPLICATIONS

In this study of long-term aspects of intrahepatic cholestasis of pregnancy, we sought information as to whether a history of ICP is associated with other diseases. We wished to establish whether there are any clinical implications which physicians would need to consider when consulting these women.

Our results on the outcome of ICP pregnancies in 1969-1988 indicate that with appropriate screening, management and care, also taking account of the elevated risks of surgery, the outcome of ICP pregnancies is good. In view of the risks for the fetus, ICP is still a severe gestational disorder which requires attention in health care. In Finland, maternity health clinics in primary health care are conventionally in key position in the early detection of the disorder and referral to obstetric clinics. Future research will probably reveal the basic etiology and mechanism of ICP. Consequently, its precise diagnostics, individual follow-up and target medication and care for at-risk cases would reduce the need for induction of labor and cesarean section. The conception of ICP heredity was confirmed in this study. We suggest that all pregnant women in primary health care be asked whether their close relatives have suffered from liver disorders during their pregnancies, to prepare those in question to react in case of a potential disorder.

We conclude that ICP is followed by a health history not dramatically different from that of controls. Our study strengthens the conception of an elevated risk of hepatobiliary diseases in women with a history of ICP. However, a few new associations were also found: a higher occurrence of breast cancer and of hypothyroidism. On the other hand, ICP women seemed in some respects to be at an advantage, that is, concerning a few aspects related to cardiovascular diseases: a

decreased occurrence of arrhythmia, and fewer women using medication for high blood pressure or cholesterol.

ICP had associations with problems in obtaining hormonal contraception but not HRT. Use of hormones is not contraindicated for women with a history of ICP. It is important that physicians update their knowledge in order to be able to provide their patients with the best possible medication, considering the risks and benefits but avoiding unnecessary limitations.

Further research on the association between ICP and the elevated occurrence of breast cancer is warranted. The next step is investigation of the occurrence of breast cancer in ICP women, using the Finnish Cancer Register. Subsequently, the register of causes of death might reveal whether breast cancer in these women is life-shortening or not, likewise possibly other connected diseases.

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REFERENCES

Abedin P, Weaver JB, Egginton E (1999): Intrahepatic cholestasis of pregnancy: prevalence and ethnic distribution. Ethn Health 4: 35-37

Adlercreutz H (1964): Steroid-Induced Jaundice. Nord Med 72: 1004-1005

Ahlfeld F (1883): Icterus gravidarum. In Berichte und Arbeiten aus der Geburtshülflich-Gynaekologischen Klinik zu Giessen, Ahlfeld F (ed) pp 148-153. Verlag von Fr. Wilh. Grunow: Leipzig

Al Shobaili HA, Hamed HO, Al Robaee A, Alzolibani AA, Amin AF, Ahmad SR (2011): Obstetrical and fetal outcomes of a new management strategy in patients with intra-hepatic cholestasis of pregnancy. Arch Gynecol Obstet 283: 1219-1225

Alsulyman OM, Ouzounian JG, Ames-Castro M, Goodwin TM (1996): Intrahepatic cholestasis of pregnancy: perinatal outcome associated with expectant management. Am J Obstet Gynecol 175: 957-960

Asch DA, Jedrziewski MK, Christakis NA (1997): Response rates to mail surveys published in medical journals. J Clin Epidemiol 50: 1129-1136

Bacq Y, Sapey T, Brechot MC, Pierre F, Fignon A, Dubois F (1997): Intrahepatic cholestasis of pregnancy: a French prospective study. Hepatology 26: 358-364

Bacq Y, Sentilhes L, Reyes HB, Glantz A, Kondrackiene J, Binder T, Nicastri PL, Locatelli A, Floreani A, Hernandez I, Di Martino V (2012): Efficacy of ursodeoxycholic acid in treating intrahepatic cholestasis of pregnancy: a meta-analysis. Gastroenterology 143: 1492-1501

Berg B, Helm G, Petersohn L, Tryding N (1986): Cholestasis of pregnancy. Clinical and laboratory studies. Acta Obstet Gynecol Scand 65: 107-113

Brites D, Rodrigues CM, van-Zeller H, Brito A, Silva R (1998): Relevance of serum bile acid profile in the diagnosis of intrahepatic cholestasis of pregnancy in an high incidence area: Portugal. Eur J Obstet Gynecol Reprod Biol 80: 31-38

Cauley JA, Robbins J, Chen Z, Cummings SR, Jackson RD, LaCroix AZ, LeBoff M, Lewis CE, McGowan J, Neuner J, Pettinger M, Stefanick ML, Wactawski-Wende J, Watts NB, Women's Health Initiative Investigators (2003): Effects of estrogen plus progestin on risk of fracture and bone mineral density: the Women's Health Initiative randomized trial. JAMA 290: 1729-1738

Chen H, Zhou Y, Deng DR, Hao HY, Dang J, Li J (2013a): Intrahepatic cholestasis of pregnancy: Biochemical predictors of adverse perinatal outcomes. J Huazhong Univ Sci Technolog Med Sci 33: 412-417

Chen J, Deng W, Wang J, Shao Y, Ou M, Ding M (2013b): Primary bile acids as potential biomarkers for the clinical grading of intrahepatic cholestasis of pregnancy. Int J Gynaecol Obstet 122: 5-8

Cunningham F, Gant N, Leveno K, Gilstrap L, Hauth J, Wenstrom K (2001): Gastrointestinal Disorders: Diseases of the Liver. In Williams Obstetrics, Cunningham F, Gant N, Leveno K, Gilstrap L, Hauth J and Wenstrom K (eds) pp 1283-1293. McGraw-Hill, Medical Publishing Division: USA

Dann AT, Kenyon AP, Wierzbicki AS, Seed PT, Shennan AH, Tribe RM (2006): Plasma lipid profiles of women with intrahepatic cholestasis of pregnancy. Obstet Gynecol 107: 106-114

de Vree JM, Jacquemin E, Sturm E, Cresteil D, Bosma PJ, Aten J, Deleuze JF, Desrochers M, Burdelski M, Bernard O, Oude Elferink RP, Hadchouel M (1998): Mutations in the MDR3 gene cause progressive familial intrahepatic cholestasis. Proc Natl Acad Sci U S A 95: 282-287

Dhiman RK and Chawla YK (2006): Is there a link between oestrogen therapy and gallbladder disease? Expert Opin Drug Saf 5: 117-129

DiSaia P and Creasman W (2002): Breast diseases. In Clinical gynecologic oncology, DiSaia PJ and Creasman WT (eds) pp 399-402. Mosby: St. Louis (Mo)

Dixon PH, Weerasekera N, Linton KJ, Donaldson O, Chambers J, Egginton E, Weaver J, Nelson-Piercy C, de Swiet M, Warnes G, Elias E, Higgins CF, Johnston DG, McCarthy MI, Williamson C (2000): Heterozygous MDR3 missense mutation associated with intrahepatic cholestasis of pregnancy: evidence for a defect in protein trafficking. Hum Mol Genet 9: 1209-1217

Drill VA (1974): Benign cholestatic jaundice of pregnancy and benign cholestatic jaundice from oral contraceptives. Am J Obstet Gynecol 119: 165-174

Dror DK (2011): Vitamin D status during pregnancy: maternal, fetal, and postnatal outcomes. Curr Opin Obstet Gynecol 23: 422-426

Duodecim (2012): Evidence-based medicine guidelines, Cholestasis of pregnancy (hepatosis), www.terveysportti.fi/ebmg/. Accessed Nov 19th 2013

Eloranta ML, Heinonen S, Mononen T, Saarikoski S (2001): Risk of obstetric cholestasis in sisters of index patients. Clin Genet 60: 42-45

Eloranta ML, Heiskanen JT, Hiltunen MJ, Mannermaa AJ, Punnonen KR, Heinonen ST (2002): Multidrug resistance 3 gene mutation 1712delT and estrogen receptor alpha gene polymorphisms in Finnish women with obstetric cholestasis. Eur J Obstet Gynecol Reprod Biol 104: 109-112

Eloranta ML, Häkli T, Hiltunen M, Helisalmi S, Punnonen K, Heinonen S (2003). Association of single nucleotide polymorphisms of the bile salt export pump gene with intrahepatic cholestasis of pregnancy. Scand J Gastroenterol 38: 648-652

Fisk NM, Bye WB, Storey GN (1988): Maternal features of obstetric cholestasis: 20 years experience at King George V Hospital. Aust N Z J Obstet Gynaecol 28: 172-176

Fisk NM and Storey GN (1988): Fetal outcome in obstetric cholestasis. Br J Obstet Gynaecol 95: 1137-1143

Floreani A, Caroli D, Lazzari R, Memmo A, Vidali E, Colavito D, D'Arrigo A, Leon A, Romero R, Gervasi MT (2013): Intrahepatic cholestasis of pregnancy: new insights into its pathogenesis. J Matern Fetal Neonatal Med 26: 1410-1415

Frezza M, Tritapepe R, Pozzato G, Di Padova C (1988): Prevention of S-adenosylmethionine of estrogen-induced hepatobiliary toxicity in susceptible women. Am J Gastroenterol 83: 1098-1102

Gagnaire JC, Descos L, Magnin P (1975): Significance of pruritus during pregnancy. Relations with the hepatic disorders of gestation. Nouv Presse Med 4: 1105-1108

Geenes V, Chappell LC, Seed PT, Steer PJ, Knight M, Williamson C (2014): Association of severe intrahepatic cholestasis of pregnancy with adverse pregnancy outcomes: A prospective population-based case-control study. Hepatology 59: 1482–1491

Geenes V and Williamson C (2009): Intrahepatic cholestasis of pregnancy. World J Gastroenterol 15: 2049-2066

Germain AM, Carvajal JA, Glasinovic JC, Kato CS, Williamson C (2002): Intrahepatic cholestasis of pregnancy: an intriguing pregnancy-specific disorder. J Soc Gynecol Investig 9: 10-14

Germain AM, Kato S, Carvajal JA, Valenzuela GJ, Valdes GL, Glasinovic JC (2003): Bile acids increase response and expression of human myometrial oxytocin receptor. Am J Obstet Gynecol 189: 577-582

Gittlen SD, Schulman ES, Maddrey WC (1990): Raised histamine concentrations in chronic cholestatic liver disease. Gut 31: 96-99

Glantz A, Marschall HU, Mattsson LA (2004): Intrahepatic cholestasis of pregnancy: Relationships between bile acid levels and fetal complication rates. Hepatology 40: 467-474

Glantz A, Reilly SJ, Benthin L, Lammert F, Mattsson LA, Marschall HU (2008): Intrahepatic cholestasis of pregnancy: Amelioration of pruritus by UDCA is associated with decreased progesterone disulphates in urine. Hepatology 47: 544-551

Gonzalez MC, Reyes H, Arrese M, Figueroa D, Lorca B, Andresen M, Segovia N, Molina C, Arce S (1989): Intrahepatic cholestasis of pregnancy in twin pregnancies. J Hepatol 9: 84-90

Gylling H, Riikonen S, Nikkilä K, Savonius H, Miettinen TA (1998): Oral guar gum treatment of intrahepatic cholestasis and pruritus in pregnant women: effects on serum cholestanol and other non-cholesterol sterols. Eur J Clin Invest 28: 359-363

Harman SM, Vittinghoff E, Brinton EA, Budoff MJ, Cedars MI, Lobo RA, Merriam GR, Miller VM, Naftolin F, Pal L, Santoro N, Taylor HS, Black DM (2011): Timing and duration of menopausal hormone treatment may affect cardiovascular outcomes. Am J Med 124: 199-205

Hart AR, Luben R, Welch A, Bingham S, Khaw KT (2008): Hormone replacement therapy and symptomatic gallstones - a prospective population study in the EPIC-Norfolk cohort. Digestion 77: 4-9

Hay JE (2008): Liver disease in pregnancy. Hepatology 47: 1067-1076

Heikkinen J (1983): Serum bile acids in the early diagnosis of intrahepatic cholestasis of pregnancy. Obstet Gynecol 61: 581-587

Heikkinen J, Mäentausta O, Ylöstalo P, Jänne O (1982a): Serum bile acid levels in intrahepatic cholestasis of pregnancy during treatment with phenobarbital or cholestyramine. Eur J Obstet Gynecol Reprod Biol 14: 153-162

Heikkinen J, Ylöstalo P, Mäentausta O, Jänne O (1982b): Serum bile acids during biphasic contraceptive treatment with ethinyl estradiol and norgestrel. Contraception 25: 89-95

Heinonen S and Kirkinen P (1999): Pregnancy outcome with intrahepatic cholestasis. Obstet Gynecol 94: 189-193

Hirvioja ML, Kivinen S (1993). Inheritance of intrahepatic cholestasis of pregnancy in one kindred. Clin Genet 43: 315-317

Hirvioja ML, Tuimala R, Vuori J (1992): The treatment of intrahepatic cholestasis of pregnancy by dexamethasone. Br J Obstet Gynaecol 99: 109-111

Hirvonen E and Idänpään-Heikkilä J (1990): Cardiovascular death among women under 40 years of age using low-estrogen oral contraceptives and intrauterine devices in Finland from 1975 to 1984. Am J Obstet Gynecol 163: 281-284

Holzbach RT, Sivak DA, Braun WE (1983). Familial recurrent intrahepatic cholestasis of pregnancy: a genetic study providing evidence for transmission of a sex-limited, dominant trait. Gastroenterology 85: 175-179

Ikonen E (1964): Jaundice in Late Pregnancy. Acta Obstet Gynecol Scand 43: Suppl 5:1-130

Imam MH, Gossard AA, Sinakos E, Lindor KD (2012): Pathogenesis and management of pruritus in cholestatic liver disease. J Gastroenterol Hepatol 27: 1150-1158

Jacquemin E, Cresteil D, Manouvrier S, Boute O, Hadchouel M (1999): Heterozygous non-sense mutation of the MDR3 gene in familial intrahepatic cholestasis of pregnancy. Lancet 353: 210-211

Jiang ZH, Qiu ZD, Liu WW, Liu YH, Wang QN, Miao HZ, Zhou ZC, Wu XL, Xu BY, Gu CH (1986): Intrahepatic cholestasis of pregnancy and its complications. Analysis of 100 cases in Chongqing area. Chin Med J (Engl) 99: 957-960

Johnston WG and Baskett TF (1979): Obstetric cholestasis. A 14 year review. Am J Obstet Gynecol 133: 299-301

Jokelainen K (2013): Maksan toiminta. In Gastroenterologia ja hepatologia, Färkkilä M, Isoniemi H, Kaukinen K and Puolakkainen P (eds) pp 687-695. Kustannus Oy Duodecim: Keuruu

Jones EA and Bergasa NV (2000): Evolving concepts of the pathogenesis and treatment of the pruritus of cholestasis. Can J Gastroenterol 14: 33-40

Joshi D, James A, Quaglia A, Westbrook RH, Heneghan MA (2010): Liver disease in pregnancy. Lancet 375: 594-605

Joutsiniemi T, Timonen S, Leino R, Palo P, Ekblad U (2014): Ursodeoxycholic acid in the treatment of intrahepatic cholestasis of pregnancy: a randomized controlled trial. Arch Gynecol Obstet 289:541-547

Kaaja RJ, Kontula KK, Räihä A, Laatikainen T (1994): Treatment of cholestasis of pregnancy with peroral activated charcoal. A preliminary study. Scand J Gastroenterol 29: 178-181

Kauppila A, Jouppila P, Karvonen P, Tuimala R, Ylikorkala O (1976): Effect of dexamethasone on blood levels of ACTH, cortisol, progesterone, estradiol and estriol during late pregnancy. Int J Gynaecol Obstet 14: 177-181

Kauppila A, Korpela H, Mäkilä UM, Yrjänheikki E (1987): Low serum selenium concentration and glutathione peroxidase activity in intrahepatic cholestasis of pregnancy. Br Med J (Clin Res Ed) 294: 150-152

Kauppila A, Tuimala R, Ylikorkala O, Reinilä M, Ylöstalo P (1979): Placental steroid synthesis from DHEAS during dexamethasone therapy. Obstet Gynecol 54: 39-42

Kenyon AP, Piercy CN, Girling J, Williamson C, Tribe RM, Shennan AH (2001): Pruritus may precede abnormal liver function tests in pregnant women with obstetric cholestasis: a longitudinal analysis. BJOG 108: 1190-1192

Korkeila K, Kivelä SL, Suominen S, Vahtera J, Kivimäki M, Sundell J, Helenius H, Koskenvuo M (2004): Childhood adversities, parent-child relationships and dispositional optimism in adulthood. Soc Psychiatry Psychiatr Epidemiol 39: 286-292

Korkeila K (2005): Epidemiological studies on psychosocial risk and protective factors of illness. Turun yliopiston julkaisuja Sarja D Medica-Odontologica

Korpimäki S, Sumanen M, Suominen S, Mattila K (2012): Self-reported rather than registered cancer is associated with psychosocial strain. BMC Fam Pract 13: 107-2296-13-107

Krakow D (2008): Medical and Surgical Complications of Pregnancy. In Danforth's Obstetrics and Gynecology, Gibbs R, Karlan B, Haney A and Nygaard I (eds) pp 305. Lippincott Williams & Wilkins: Philadelphia (Pa)

Kreek MJ, Sleisenger MH, Jeffries GH (1967): Recurrent cholestatic jaundice of pregnancy with demonstrated estrogen sensitivity. Am J Med 43: 795-803

Laatikainen T and Ikonen E (1975): Fetal prognosis in obstetric hepatosis. Ann Chir Gynaecol Fenn 64: 155-164

Laatikainen T and Tulenheimo A (1984): Maternal serum bile acid levels and fetal distress in cholestasis of pregnancy. Int J Gynaecol Obstet 22: 91-94

Laes E and Gissler M (2006): Health of pregnant women. In Health in Finland, Koskinen S, Aromaa A, Huttunen J and Teperi J (eds) pp 120-121. KTL, Stakes, Ministry of Social Affairs and Health: Vammala

Laifer SA, Stiller RJ, Siddiqui DS, Dunston-Boone G, Whetham JC (2001): Ursodeoxycholic acid for the treatment of intrahepatic cholestasis of pregnancy. J Matern Fetal Med 10: 131-135

Lammert F, Marschall HU, Glantz A, Matern S (2000): Intrahepatic cholestasis of pregnancy: molecular pathogenesis, diagnosis and management. J Hepatol 33: 1012-1021

Lang C, Meier Y, Stieger B, Beuers U, Lang T, Kerb R, Kullak-Ublick GA, Meier PJ, Pauli-Magnus C (2007): Mutations and polymorphisms in the bile salt export pump and the multidrug resistance protein 3 associated with drug-induced liver injury. Pharmacogenet Genomics 17: 47-60

Lee RH, Goodwin TM, Greenspoon J, Incerpi M (2006): The prevalence of intrahepatic cholestasis of pregnancy in a primarily Latina Los Angeles population. J Perinatol 26: 527-532

Leszczynska-Gorzelak B, Oleszczuk J, Marciniak B, Poreba R, Oszukowski P, Wielgos M, Czajkowski K, Zespol Ekspertow Polskiego Towarzystwa Ginekologicznego (2012): Clinical practice guidelines of the Team of Experts of the Polish Gynecological Society: management of the intrahepatic cholestasis of pregnancy. Ginekol Pol 83: 713-717

Leveno KJ, Cunningham FG, Roark ML, Nelson SD, Williams ML (1985): Prenatal care and the low birth weight infant. Obstet Gynecol 66: 599-605

Lo TK, Lau WL, Lam HS, Leung WC, Chin RK (2007): Obstetric cholestasis in Hong Kong--local experience with eight consecutive cases. Hong Kong Med J 13: 387-391

Locatelli A, Roncaglia N, Arreghini A, Bellini P, Vergani P, Ghidini A (1999): Hepatitis C virus infection is associated with a higher incidence of cholestasis of pregnancy. Br J Obstet Gynaecol 106: 498-500

Lyytinen H, Pukkala E, Ylikorkala O (2009): Breast cancer risk in postmenopausal women using estradiol-progestogen therapy. Obstet Gynecol 113: 65-73

Lyytinen H, Pukkala E, Ylikorkala O (2006): Breast cancer risk in postmenopausal women using estrogen-only therapy. Obstet Gynecol 108: 1354-1360

Marschall HU, Wikström Shemer EW, Ludvigsson JF, Stephansson O (2013): Intrahepatic cholestasis of pregnancy and associated hepatobiliary disease: A population-based cohort study. Hepatology 58:1385-1391

Martineau M, Raker C, Powrie R, Williamson C (2014): Intrahepatic cholestasis of pregnancy is associated with an increased risk of gestational diabetes. Eur J Obstet Gynecol Reprod Biol, doi:10.1016/j.ejogrb.2013.12.037

McCarthy A (2007): Miscellaneous medical disorders. In Dewhurst's Textbook of Obstetrics & Gynaecology, Edmonds D (ed) pp 282-288. Blackwell Publishing: Malden (Mass.)

Mishell DR,Jr (1991): Oral contraception: past, present, and future perspectives. Int J Fertil 36 Suppl 1: 7-18

Mossey JM and Shapiro E (1982): Self-rated health: a predictor of mortality among the elderly. Am J Public Health 72: 800-808

Müllenbach R, Bennett A, Tetlow N, Patel N, Hamilton G, Cheng F, Chambers J, Howard R, Taylor-Robinson SD, Williamson C 2005. ATP8B1 mutations in British cases with intrahepatic cholestasis of pregnancy. Gut 54 :829-834

Nicastri PL, Diaferia A, Tartagni M, Loizzi P, Fanelli M (1998): A randomised placebo-controlled trial of ursodeoxycholic acid and S-adenosylmethionine in the treatment of intrahepatic cholestasis of pregnancy. Br J Obstet Gynaecol 105: 1205-1207

Oude Elferink RP, Kremer AE, Beuers U (2011): Mediators of pruritus during cholestasis. Curr Opin Gastroenterol 27: 289-293

Paternoster DM, Fabris F, Palu G, Santarossa C, Bracciante R, Snijders D, Floreani A (2002): Intra-hepatic cholestasis of pregnancy in hepatitis C virus infection. Acta Obstet Gynecol Scand 81: 99-103

Pauli-Magnus C, Lang T, Meier Y, Zodan-Marin T, Jung D, Breymann C, Zimmermann R, Kenngott S, Beuers U, Reichel C, Kerb R, Penger A, Meier PJ, Kullak-Ublick GA 2004. Sequence analysis of bile salt export pump (ABCB11) and multidrug resistance p-glycoprotein 3 (ABCB4, MDR3) in patients with intrahepatic cholestasis of pregnancy. Pharmacogenetics 14: 91-102

Perreau P and Rouchy R (1961): Recurrent cholostatic jaundice of pregnancy. Gynecol Obstet (Paris) 60: 161-179

Prestwood KM, Kenny AM, Kleppinger A, Kulldorff M (2003): Ultralow-dose micronized 17beta-estradiol and bone density and bone metabolism in older women: a randomized controlled trial. JAMA 290: 1042-1048

Rainer PP, Primessnig U, Harenkamp S, Doleschal B, Wallner M, Fauler G, Stojakovic T, Wachter R, Yates A, Groschner K, Trauner M, Pieske BM,

von Lewinski D (2013): Bile acids induce arrhythmias in human atrial myocardium--implications for altered serum bile acid composition in patients with atrial fibrillation. Heart 99:1685–1692

Rannevik G, Jeppsson S, Kullander S (1972): Effect of oral contraceptives on the liver in women with recurrent cholestasis (hepatosis) during previous pregnancies. J Obstet Gynaecol Br Commonw 79: 1128-1136

Rathi U, Bapat M, Rathi P, Abraham P (2007): Effect of liver disease on maternal and fetal outcome--a prospective study. Indian J Gastroenterol 26: 59-63

Reyes H (1997): Review: intrahepatic cholestasis. A puzzling disorder of pregnancy. J Gastroenterol Hepatol 12: 211-216

Reyes H, Baez ME, Gonzalez MC, Hernandez I, Palma J, Ribalta J, Sandoval L, Zapata R (2000): Selenium, zinc and copper plasma levels in intrahepatic cholestasis of pregnancy, in normal pregnancies and in healthy individuals, in Chile. J Hepatol 32: 542-549

Reyes H, Gonzalez MC, Ribalta J, Aburto H, Matus C, Schramm G, Katz R, Medina E (1978): Prevalence of intrahepatic cholestasis of pregnancy in Chile. Ann Intern Med 88: 487-493

Reyes H, Ribalta J, González-Cerón M (1976). Idiopathic cholestasis of pregnancy in a large kindred. Gut 17: 709-713

Reyes H, Taboada G, Ribalta J (1979): Prevalence of intrahepatic cholestasis of pregnancy in La Paz, Bolivia. J Chronic Dis 32: 499-504

Reyes H, Zapata R, Hernandez I, Gotteland M, Sandoval L, Jiron MI, Palma J, Almuna R, Silva JJ (2006): Is a leaky gut involved in the pathogenesis of intrahepatic cholestasis of pregnancy? Hepatology 43: 715-722

Riikonen S, Savonius H, Gylling H, Nikkilä K, Tuomi AM, Miettinen TA (2000): Oral guar gum, a gel-forming dietary fiber relieves pruritus in intrahepatic cholestasis of pregnancy. Acta Obstet Gynecol Scand 79: 260-264

Rioseco AJ, Ivankovic MB, Manzur A, Hamed F, Kato SR, Parer JT, Germain AM (1994): Intrahepatic cholestasis of pregnancy: a retrospective case-control study of perinatal outcome. Am J Obstet Gynecol 170: 890-895

Roger D, Vaillant L, Fignon A, Pierre F, Bacq Y, Brechot JF, Grangeponte MC, Lorette G (1994): Specific pruritic diseases of pregnancy. A prospective study of 3192 pregnant women. Arch Dermatol 130: 734-739

Roncaglia N, Arreghini A, Locatelli A, Bellini P, Andreotti C, Ghidini A (2002): Obstetric cholestasis: outcome with active management. Eur J Obstet Gynecol Reprod Biol 100: 167-170

Rook M, Vargas J, Caughey A, Bacchetti P, Rosenthal P, Bull L (2012): Fetal outcomes in pregnancies complicated by intrahepatic cholestasis of pregnancy in a Northern California cohort. PLoS One 7: e28343, doi:10.1371/journal.pone.0028343

Ropponen A, Sund R, Riikonen S, Ylikorkala O, Aittomäki K (2006): Intrahepatic cholestasis of pregnancy as an indicator of liver and biliary diseases: a population-based study. Hepatology 43: 723-728

Sadler LC, Lane M, North R (1995): Severe fetal intracranial haemorrhage during treatment with cholestyramine for intrahepatic cholestasis of pregnancy. Br J Obstet Gynaecol 102: 169-170

Savander M, Ropponen A, Avela K, Weerasekera N, Cormand B, Hirvioja ML, Riikonen S, Ylikorkala O, Lehesjoki AE, Williamson C, Aittomäki K

(2003): Genetic evidence of heterogeneity in intrahepatic cholestasis of pregnancy. Gut 52: 1025-1029

Sepulveda WH, Gonzalez C, Cruz MA, Rudolph MI (1991): Vasoconstrictive effect of bile acids on isolated human placental chorionic veins. Eur J Obstet Gynecol Reprod Biol 42: 211-215

Serrano MA, Brites D, Larena MG, Monte MJ, Bravo MP, Oliveira N, Marin JJ (1998): Beneficial effect of ursodeoxycholic acid on alterations induced by cholestasis of pregnancy in bile acid transport across the human placenta. J Hepatol 28: 829-839

Shaw D, Frohlich J, Wittmann BA, Willms M (1982): A prospective study of 18 patients with cholestasis of pregnancy. Am J Obstet Gynecol 142: 621-625

Sigurdsson JA (2003). The GP's role in maternity care. Scand J Prim Health Care 21: 65

Steel R and Parker ML (1973): Jaundice in pregnancy. Med J Aust 1: 461

Stefanovic V and Ylikorkala O (2011): Raskaushepatoosi ja muut maksasairaudet raskausaikana. In Naistentaudit ja synnytykset, Ylikorkala O and Tapanainen J (eds) pp 422-427. Kustannus Oy Duodecim: Hämeenlinna

Svanborg A (1954). A study of recurrent jaundice in pregnancy. Acta Obstet Gynecol Scand 33: 434-444

THL 2013 FINRISKI-tutkimus. http://www thl fi/fi_FI/web/fi/tutkimus/hankkeet/ finriski Accessed Nov 19th 2013

Thomassen PA (1979): Urinary bile acids during development of recurrent cholestasis of pregnancy. Eur J Clin Invest 9: 417-423

Thorling L (1955). Jaundice in pregnancy; a clinical study. Acta Med Scand Suppl 302: 1-12

Tuomikoski P, Aittomäki K, Mikkola TS, Ropponen A, Ylikorkala O (2008): Effect of oral and transdermal hormone therapy on hyaluronic acid in women with and without a history of intrahepatic cholestasis of pregnancy. Am J Obstet Gynecol 198:375.e1-375.e5.

Tuomilehto J, Lindström J, Eriksson JG, Valle TT, Hämäläinen H, Ilanne-Parikka P, Keinänen-Kiukaanniemi S, Laakso M, Louheranta A, Rastas M, Salminen V, Uusitupa M, Finnish Diabetes Prevention Study Group (2001): Prevention of type 2 diabetes mellitus by changes in lifestyle among subjects with impaired glucose tolerance. N Engl J Med 344: 1343-1350

Turunen K, Mölsa A, Helander K, Sumanen M, Mattila KJ (2012): Health history after intrahepatic cholestasis of pregnancy. Acta Obstet Gynecol Scand 91: 679-685

Turunen K, Sumanen M, Haukilahti RL, Kirkinen P, Mattila K (2010): Good pregnancy outcome despite intrahepatic cholestasis. Scand J Prim Health Care 28: 102-107

Vainiomäki S, Kuusela M, Vainiomäki P, Rautava P (2008): The quality of electronic patient records in Finnish primary healthcare needs to be improved. Scand J Prim Health Care 26: 117-122

Viisainen Kea (1998): Ketkä eivät käy äitiysneuvolassa?: tutkimus riittämättömän raskaudenseurannan esiintyvyydestä ja syistä. 53: 2529-2534

WHO (2010): International Classification of Diseases (ICD). http://www.who.int /classifications/icd/en/ Accessed Nov 19th 2013

Wikström Shemer E and Marschall HU (2010): Decreased 1,25-dihydroxy vitamin D levels in women with intrahepatic cholestasis of pregnancy. Acta Obstet Gynecol Scand 89: 1420-1423

Williamson C, Miragoli M, Sheikh Abdul Kadir S, Abu-Hayyeh S, Papacleovoulou G, Geenes V, Gorelik J (2011): Bile acid signaling in fetal tissues: implications for intrahepatic cholestasis of pregnancy. Dig Dis 29: 58-61

Wojcicka-Jagodzinska J, Kuczynska-Sicinska J, Czajkowski K, Smolarczyk R (1989): Carbohydrate metabolism in the course of intrahepatic cholestasis in pregnancy. Am J Obstet Gynecol 161: 959-964

APPENDICES

Appendix 1   Information to the recipient

                     Translated from Finnish by Kristiina Helander, MA.

Appendix 2   Questionnaire

                     Translated from Finnish by Kristiina Helander, MA.

68
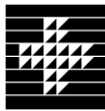
PIRKANMAAN
SAIRAANHOITOPIIRIN
KUNTAYHTYMÄ

September 6, 2010

TAMPEREEN
YLIOPISTO

INFORMATION TO THE RECIPIENT

Survey on the later life health of the mothers who gave birth and the children born to them in Tampere university hospital in the period 1969 - 1988

> We are asking you to participate in **a survey** investigating the health history and current health of the women who gave birth and the children born to them in Tampere university hospital between the years 1969 – 1988.
>
> Address source: Population information system, Population Register Centre, PB 70, 00581 Helsinki.

Purpose of this survey

> The purpose of this survey is to investigate whether factors related to mother's pregnancy and delivery have any associations with her and her child's later health and quality of life.
>
> The Ethics Committee of Pirkanmaa Health Care District, Finland, has reviewed the research plan and given its approval to it.

Implementation of the survey

> The survey questionnaire will be received by approximately 1 800 women and their children.
>
> In addition to the questionnaire, medical registers will be used in the survey. These include hospital discharge registers, the cancer registry and health insurance registers of the Social Insurance Institution of Finland (Kela).
>
> If you consent to your register data being accessed in the survey, please sign the consent form at the end of the questionnaire. If you don't sign the consent form, your register data will not be used.
>
> We kindly ask you to fill in the enclosed survey questionnaire and to post it in the enclosed return envelope by September 22, 2010. The postage fee of the return envelope has been prepaid for you.

Benefits associated with the survey

Participating in the survey will neither harm you nor be of immediate benefit to you. With the help of the survey, data is collected regarding the effects of the mother's health status during pregnancy and child birth on the later life health of both the mother and the child. Survey results will be useful for future mothers in follow-up of their pregnancies and childbirths.

Confidentiality, data processing and storage

All collected data and survey results will be handled with confidentiality in accordance to the guidelines stated in the [Finnish] personal data act. Individual survey participants will be given a code number, and all data will be stored in a coded format in the research data file. Final results will be reported at group level, and no individual participants can be identified. Research data will be stored in a locked storage facility at the department of medicine at the University of Tampere for 10 years after which time it will be destroyed.

Voluntariness

Participation is entirely voluntary but we hope that you will agree to complete the survey questionnaire.

Additional information

If you have any questions with regard to the survey, please contact Kaisa Turunen via contact information below.

Kaisa Turunen, Researcher
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Research supervisors:

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Professor, Chief Physician	Professor (Emeritus)
General Practice	Obstetrics and Gynecology
University of Tampere	University of Tampere
Pirkanmaa Hospital District	

Appendix 2

SURVEY 2010
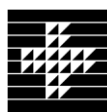
PIRKANMAAN
SAIRAANHOITOPIIRIN
KUNTAYHTYMÄ

TAMPEREEN
YLIOPISTO

MOTHERS

SURVEY ON THE LATER LIFE HEALTH OF THE MOTHERS WHO GAVE BIRTH AND THE CHILDREN BORN TO THEM IN TAMPERE UNIVERSITY HOSPITAL IN THE PERIOD 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 22 of this questionnaire** and include the number of the question at the beginning of your answer.

Please answer those 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 of value 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. Do you receive disability pension?

   1   no

   2   yes, part-time pension

   3   yes, fixed-term pension or rehabilitation subsidy

   4   yes, permanent pension

5. How tall are you? _____ centimeters

6. What is your current weight?_____ kilograms

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

8. What was your highest weight during pregnancy or breast-feeding? Approximately _____ kilograms

9. What is your highest weight ever excluding pregnancy and breast-feeding periods? Approximately _____ kilograms

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

MENSTRUATION, PREGNANCIES, CONTRACEPTION, HORMONAL TREATMENTS

---

11. How old where you when you had your first period? _____years old

---

12. Have you ever used any form of birth control?

    1   no

    2   yes *Please circle any of the following methods you have used or at least tried once.*

a	oral contraceptives (the pill)	j	spermicide (contraceptive foam, cream, vaginal suppository or sponge)
b	minipills	k	safe period, i.e. rhythm method
c	subdermal contraceptive implants	l	coitus interruptus
d	contraceptive patch	m	emergency contraceptive pills (ECPs), i.e. the morning-after pill
e	vaginal ring	n	intrauterine device (IUD) for emergency contraception
f	intrauterine device (IUD/ coil) with progestogen	o	other method, which
g	regular IUD (coil)		_____
h	condom		_____
i	diaphragm		

---

13. Have you been sterilized?

    1   no

    2   yes, when I was _____years old

---

14. Has your partner had a vasectomy?

    1   no

    2   yes

---

15. Have you had a hysterectomy?

    1   no

    2   yes, when I was _____years old

16. Have you ever had any problems with birth control?

    1   no

    2   yes, what kind of problems?   *Please circle one or more of the following.*

        a   a disease or side effect that prevents the use of contraceptive pills

        b   adverse effects that led to removal of IUD (such as pain, discharge, infection)

        c   rubber latex allergy

        d   the regular contraceptive method failed

        e   disagreement with partner over contraceptive method

        f   other, what

            _____

---

17. Have oral contraceptive pills caused you

		no	yes
a	rise in liver function test	☐	☐
b	rise in blood pressure	☐	☐
c	weight gain	☐	☐
d	depression or other changes in mood	☐	☐
e	reduced sexual drive	☐	☐
f	migraine or worsening of migraine	☐	☐
g	blood clot	☐	☐
h	acne	☐	☐

    i   other, what _____

---

18. Have you ever used any treatment for **premenstrual symptoms** (such as swelling, irritability, melancholy, sleep disorders)?

    1   no

    2   yes, what?   *Please circle one or more of the following.*

        a   hormone therapy

        b   diuretics for fluid retention

        c   antidepressants

        d   sleeping pills

        e   vitamin, which? _____

        f   health food store product or similar

        g   other, what? _____

19. Have you ever used hormone therapy for **menstrual disorders** (such as irregular periods)?
Please note that we are not referring to menopausal hormone replacement therapy here.

1   no

2   yes, once or a few times

3   yes, all in all for about _____ years

20. If you answered **yes** to the previous question, do you remember what hormone you were given?
If you do, please write down, in the space below, the type of hormone or the brand name(s) of
the medicine(s).

_____

_____

21. How many times have you been pregnant?   _____ times

22. How many times have you given birth? _____times

How many living children do you have?   _____ child/children

23. Have you ever had a miscarriage?

1   no

2   yes, how many _____

24. Have you ever had an abortion?

1   no

2   yes, how many _____

If yes, why?

Please circle one or more of the following.

a   regular contraceptive method failed,
     what method?

     _____

b   because of my life situation

c   because of the life situation of my family

d   because of my disease

e   because of the disease or developmental
     disorder of the fetus

f   other reason, what?

     _____

25. Have you ever had an ectopic pregnancy?

    1   no

    2   yes, how many _____

---

26. Have you ever had a cesarean section (c-section)?

    1   no

    2   yes, _____ times

---

27. Have you ever given birth to twins or triplets?

    1   no

    2   yes, _____ times

---

28. Has your twin or triplet pregnancy ended in a miscarriage?

    1   no

    2   yes, _____ times

---

29. Have you ever been treated for infertility?

    1   no

    2   yes

---

30. Have you limited the number of children you have due to reasons concerning your **health**?

    1   no

    2   yes, for what reason? _____

---

31. Have you experienced any of the following problems **during your pregnancy**?

Please mark down all the times you remember regardless of whether the pregnancy ended in delivery or was terminated for some reason earlier.

		no	yes
a	rise in blood pressure	☐	☐
b	protein in urine	☐	☐
c	itching combined with rise in liver function test	☐	☐
d	rise in blood sugar	☐	☐
e	urinary tract infection	☐	☐
f	blood clot	☐	☐

32. Have you ever been hospitalized for **nausea and vomiting** during pregnancy?

    1   no

    2   yes, date(s) _____

---

33. Have you ever been hospitalized for **some other reason** during pregnancy?

    1   no

    2   yes, date(s) _____

         Why where you hospitalized _____

---

34. Has a doctor ever prescribed you **alcohol as a medication to stop contractions** during pregnancy?

    1   no

    2   yes, date(s) _____

---

35. Have you ever had any disease or symptom **during pregnancy** that prevented you from using hormones (such as oral contraceptive pills, other hormonal medication, menopausal hormone replacement therapy) after the pregnancy?

    1   no

    2   yes, what disease or symptom?_____

---

36. Have you ever been told that because of **a liver problem** you cannot use oral contraceptive pills or be treated with hormone therapy?

    1   no

    2   yes

---

37. Do you have a hormonal IUD/IUS (coil) now?

    1   no

    2   yes

---

38. Do you still have periods?

    1   yes, regularly

    2   yes, irregularly

    3   no

39. If you no longer have periods, why did they stop?   *Please circle only one answer*

    1   naturally due to menopause when I was _____ years old

    2   due to hysterectomy (ovaries were not removed or only one ovary was removed) when I was _____ years old

    3   due to hysterectomy and removal of both ovaries when I was _____ years old

    4   due to radiation therapy or some other reason when I was _____ years old

    5   due to IUD with progestogen when I was _____ years old

    6   due to some other reason, what? _____

40. Have you ever had a dilation and curettage (D&C) due to **abnormal uterine bleeding**? *Please note that we are not referring here to a* D&C *performed after a miscarriage or abortion, or to an evacuation* D&C *performed after a pregnancy.*

    1   no

    2   yes, _____ times

41. Have you ever experienced **menopausal symptoms**?

    1   no

    2   yes, they started when I was _____years old

MENOPAUSE AND MENOPAUSAL HORMONE REPLACEMENT THERAPY

Questions 42–51 are related to menopause. If the questions do not apply to you, do not answer them and move onto question 52.

---

42. Have you ever used **hormone replacement therapy (HRT)** in the past?

    1   no   *Move onto question 50*

    2   yes, how old were you when you started the therapy for the first time? _____years old

---

43. Are you **currently** using HRT? (Note that w*e are not referring here to vaginal suppositories or tablets, or creams that are applied vaginally or locally to outer vaginal area.)*

    1   no

    2   yes, in tablet form

    3   yes, through skin (hormone patch or gel)

    4   hormonal IUD / IUS (coil)

---

44. Have you ever used Livial tablets for the treatment of menopausal symptoms?

    1   no

    2   yes

    3   I don't know

---

45. Did you still have regular periods when HRT was first started?

    1   my periods were still relatively regular

    2   my periods had become irregular or the bleeding lasted longer

    3   my periods had stopped

---

46. How many years altogether have you taken HRT? _____ years

---

47. Have you had **unexpected** vaginal bleeding while taking HRT?

    1   no

    2   yes

48. Has HRT caused you such **side or adverse effects** that you had to stop taking it?

    1   no

    2   yes, what _____

49. Have you ever had any such **symptom, laboratory test result or disease** because of which you have been told you cannot use HRT?

    1   no

    2   yes, what _____

50. Have you had uterine bleeding after the menopause? *This question is intended for women who have never used HRT.*

    1   no

    2   yes

51. Apart from hormones, have you used any other medications for the treatment of menopausal symptoms or have you used other methods (such as physical activity, diet and so on)?

    1   no

    2   yes

        Please circle one or more of the following. If you don't know which group the product you have used belongs to, please write the name of the product in section g

a	sedative	e	vitamin
b	antidepressant	f	health food store products or similar
c	sleeping pills	g	other, what
d	medicine for heart arrhythmia and palpitations		_____

QUESTIONS ABOUT CLOSE RELATIVES

---

52. Has **your mother** ever had liver dysfunction during pregnancy?

1   no

2   yes

3   I don't know

---

53. Has **your mother** ever had a bone fracture?

1   no

2   yes, once

3   yes, at least twice

4   I don't know

---

54. Do you have any **sisters**?

1   no

2   yes, how many?_____   How many of your sisters have given birth? _____

    Have they ever had liver dysfunction during pregnancy?

a   no

b   yes, how many of them?_____

---

55. Do you have any **daughters**?

1   no

2   yes, how many?_____   How many of your daughters have given birth? _____

    Have they ever had liver dysfunction during pregnancy?

a   no

b   yes, how many of them?_____

---

56. Please assess how your oldest child did during the first year of his/her life. *Tick a box on every row*. (Note that 3 stands for average in the scale.)

	1	2	3	4	5	
ate very poorly	☐	☐	☐	☐	☐	ate very well
slept very poorly	☐	☐	☐	☐	☐	slept very well
was very often sick	☐	☐	☐	☐	☐	was very healthy
was very difficult to take care of	☐	☐	☐	☐	☐	was very easy to take care of

(Please write any additional information on p. 22.)

INTIMATE RELATIONSHIP AND SEXUALITY

Sexuality is partly related to hormonal factors. Therefore we want to survey issues related to the sexual life. If you, however, find questions 57-59 too personal, please note that you can leave them blank and continue to question 60.

---

57. 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 |

---

58. How satisfied are you with your sex life?

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

---

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

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

CURRENT HEALTH AND PHYSICAL CONDITION

---

60. 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

---

61. 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

62. 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 menstrual pain		☐	☐
10 vaginal and vulvar dryness	☐	☐	21 nausea		☐	☐
			22 insomnia		☐	☐
11 itching of palms and soles	☐	☐	23 nervousness		☐	☐
			24 depression		☐	☐

---

63. In the past 12 months, have you seen a doctor for some other reason than pregnancy or delivery?

Please count all the times you have seen a doctor at health centers, occupational health care centers, 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

---

64. In the past 12 months, have you been hospitalized for some other reason than pregnancy or delivery?

      1   no

      2   yes   about_____ days

65. Has a doctor ever told you that you have 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 (except during pregnancy)	☐	☐
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 (treatment 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

		no	yes
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	☐	☐

Gynecological diseases

		no	yes
38	endometriosis	☐	☐
39	polycystic ovary syndrome (PCOS)	☐	☐
40	breast cancer	☐	☐
41	gynecologic cancers (womb, cervix, ovaries, Fallopian tubes, vagina, vulva) – *please underline which*)	☐	☐
42	precancerous stage of cervical cancer, caused by HPV virus	☐	☐
43	precancerous stage of cervical cancer, cause is unknown to me	☐	☐

Lung diseases

		no	yes
44	asthma	☐	☐
45	chronic bronchitis	☐	☐
46	chronic obstructive pulmonary disease (COPD)	☐	☐
47	tuberculosis	☐	☐

Other diseases and conditions

		no	yes
48	other cancer, what _____	☐	☐
49	anemia (other than during pregnancy)	☐	☐
50	migraine	☐	☐
51	epilepsy	☐	☐
52	hives that lasted at least a month (urticaria)	☐	☐
53	some significant injury, what _____	☐	☐
54	some other significant, longstanding or often recurring disease, what _____	☐	☐

---

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

1   no

2   yes, to which? _____

---

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

1   no

2   yes, to which? _____

---

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

1   no

2   yes, what? _____

69. Have you had any of the following surgeries?

   1   gallbladder surgery

   2   gastric or duodenal ulcer surgery

   3   other bowel surgery

   4   coronary artery balloon dilatation

   5   coronary artery bypass surgery

   6   joint replacement surgery

   7   bone fracture surgery

   8   benign tumour surgery

   9   malignant tumour surgery

   10   other, what _____

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

   1   hip fracture, _____ times

   2   wrist fracture, _____ times

   3   spinal or vertebrae fracture, _____ times

MEDICINES

71. 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

---

72. 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? _____

---

73. 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? _____

---

74. 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

---

75. Have you ever smoked during your life?

    1   no   *Go to question 80*

    2   yes

---

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

    1   no

    2   yes, altogether for _____years

---

77. 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

---

78. 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

---

79. 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

80. 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 84*

    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

81. 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)

82. 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

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

    a   no

    b   yes

DIET

---

84. 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

---

85. 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 of the questions on the previous pages, please include the number of the question at the beginning of your comment.

ORIGINAL PUBLICATIONS

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ORIGINAL ARTICLE

Good pregnancy outcome despite intrahepatic cholestasis

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Abstract

Objective. Pregnant women complaining of itching are screened for intrahepatic cholestasis (ICP) by laboratory tests in primary healthcare. Cases of ICP are referred to specialist care. In Finland, ICP occurs in 1% of pregnancies. The aim was to study the outcome of deliveries. *Design.* Retrospective study of ICP pregnancies. Data were collected from the hospital discharge register, patient records, and the labour register. *Setting.* The region of Tampere University Hospital in Finland. *Subjects.* Altogether 687 ICP cases from 1969 to 1988 and two controls for each. *Main outcome measures.* ICP patients were compared with controls in terms of mother's age, pregnancy multiplicity, weeks of gestation at delivery, frequency of induction and Caesarean section, length of ward period, child's weight, Apgar scores, and stillbirth. *Results.* For ICP patients, the risk for hospital stay of 10 days or more was eightfold (OR 8.41), for gestational weeks less than 37 at delivery sevenfold (OR 7.02), for induction threefold (OR 3.26), for baby's low weight at birth almost twofold (OR 1.86), and for Caesarean section one and a half fold (OR 1.47). The possibility of the incidence of multiple pregnancy was two and a half fold (OR 2.49, 95%). ICP was not associated with mother's age, the baby's risk of stillbirth, or low Apgar scores. *Conclusion.* ICP mothers are found and taken care of appropriately, and thus ICP is only a minor risk for mothers and their children.

Key Words: *Caesarean section, intrahepatic cholestasis, length of stay, pregnancy outcome, primary healthcare*

In the Nordic countries maternity care is organized almost exclusively within a primary healthcare setting [1]. Deliveries are carried out mainly in hospitals [2]. In Finland midwives or nurses qualified in health nursing and midwifery are the principal staff of maternity clinics in health centres [3,4]. Midwives work with GPs, who are responsible for maternity clinics in health centres. Usually the referral system is organized with hospital maternity outpatient clinic, the same hospital where the delivery will be carried out.

Intrahepatic cholestasis of pregnancy (ICP) usually manifests in the third trimester of pregnancy as skin itching and as elevation of the serum levels of bile acids and liver enzymes [5,6]. The incidence of ICP in Finland and Sweden is 0.54–1.5% [7,8,9]. ICP may recur in 40–60% of subsequent pregnancies [5,10]. In 16% of cases ICP is familial, and in those cases ICP recurs in 92% [11]. ICP is more common

with mother's age over 35 years [9] and in multiple pregnancy [12,13]. The ultimate reason for ICP is unknown. ICP is thought to be the result of insufficient

> Intrahepatic cholestasis of pregnancy (ICP) contains risks for the foetus. It is important that ICP cases are detected in primary healthcare.
> - ICP mothers' ages did not differ significantly from others.
> - Childbirth happened at earlier weeks of gestation in ICPs, but Apgar scores were only slightly lower.
> - In ICP cases labour induction and Caesarean section were more common and hospital stay was significantly longer.

liver capacity to metabolize high amounts of placental hormones during pregnancy [5,14], and symptoms fade and laboratory tests normalize quickly after the delivery. ICP increases the risk of preterm birth (12–44%) [13,15,16], fetal distress during labour (10-44%) [7,13,15,17], and intrauterine fetal death (1–3%) [7,15,17] may ensue. Bile acids have been shown to induce vasoconstriction of human placental chorionic veins, and myometrial sensitivity to oxytocin [18,19]. In clinical practice, mode and timing of labour and delivery are managed individually to reduce risks for the foetus. ICP is a minor problem for the mother during pregnancy, delivery, and postpartum. It has been stated that women with a history of ICP are more prone to several liver and biliary disorders including non-alcoholic cirrhosis, nonspecific hepatitis, hepatitis C, cholelithiasis, and pancreatitis in their life, even before the first occurrence of ICP [20].

According to current guidelines, the GP or midwife in the health centre maternity clinic verifies ICP with laboratory tests if a pregnant woman in her last trimester of pregnancy complains of itching, especially on her palms and soles [21]. When a woman is diagnosed with ICP, she is referred to the hospital maternity outpatient clinic. If itching is intensive and ICP is evident, the patient must be urgently referred to an obstetric clinic even without laboratory tests.

The aim was to study certain characteristics of deliveries with ICP and the outcome of the pregnancies.

Material and methods

ICP pregnancies during 1969–1988 are our focus, because from these data we wanted to study whether ICP has any long-term effects on the lives of mothers and children. The hospital discharge register, labour register, and patient records of Tampere University Hospital (TUH) were available for the study. There were 4000 deliveries yearly on average in the hospital during these 20 years.

ICP patients were searched for from the hospital discharge register according to diagnosis codes. ICD-8 was used in TUH during 1969–1986. Because ICD-8 did not include a precise code for ICP, we observed all the obstetric code numbers that might contain ICP, that is, 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 number, and if it referred to ICP we included the case for further selection. ICD-9 was used in 1987–1988 and it contained appropriate codes 6467A Hepatosis gravidarum and 6467X Hepatopathia alia. Finally, the diagnosis was verified from each patient

record with the presence of the main symptom of itching and laboratory tests. At least one of the following was required: ASAT > 35 U/l, ALAT > 40 U/l, or bile acids 6 μmol/l or more.

In the hospital discharge register, 971 cases were found with appropriate diagnoses. Of those, 284 cases were dismissed (Figure 1). We found 575 women who had had ICP at least once. When repeated deliveries were included, we had 687 ICP cases in our study material.

For each ICP case, two controls were taken from the labour register, namely the previous and the next woman in the labour register. The outcome measures were mother's age, ongoing week of gestation (e.g. 36+1 was noted as 37 weeks), labour induction, Caesarean section, multiple pregnancy, length of ward period, child's weight at birth, Apgar scores, and stillbirth. In multiple pregnancy matters concerning the child only indicate the first-born child. To avoid selection of outcome measures sought from the labour register, data were collected systematically in the same structured form for ICP cases and controls.
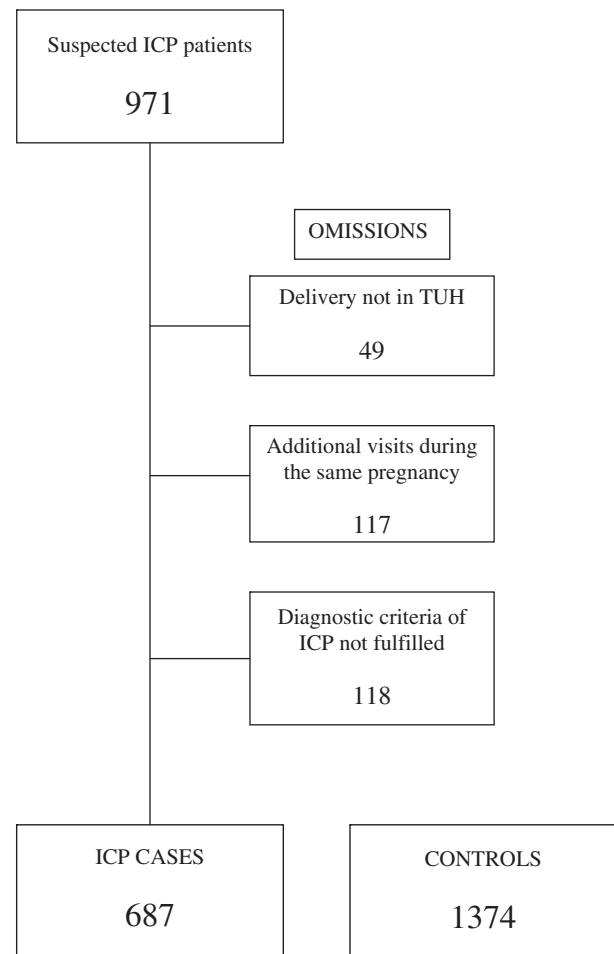

Figure 1. Flow chart of ICP patients and controls in Tampere University Hospital (TUH) during 1969–1988.

Tampere University Hospital (TUH) takes care of all deliveries in its area. We consider that the control group represents all the almost 80 000 deliveries in TUH during the 20 years from 1969 to 1988. We wanted to compare the pregnancy outcome of the ICP group with the control group, rather than considering individual case-control pairs. Matching of controls to cases is based on coincidence (previous and next in the temporal register in the same hospital), which makes diagnostics and management in the two groups comparable.

The analyses were undertaken using the SPSS System for Windows, release 16.0. The results were presented as frequencies and mean values. The associations between ICP and matters concerning delivery, mother, and the newborn were analysed with logistic regression analyses (OR with 95% CI). Statistical significance was tested by t-test and chi-squared test.

Results

There were about 40 cases of ICP pregnancies during the study period every year (mean 38.6, range 25–59), except for the first three years when the numbers were lower (Figure 2). The incidence of ICP (n = 687) was 0.9% of all deliveries (n = 79508).

ICP deliveries were compared with controls. In the ICP group, hospital stay was significantly longer (Table I). Mothers' ages did not differ from controls. Babies' weights were lower. Apgar scores did not differ in practice.

Labour induction was carried out for almost half of the ICP patients and for one-fifth of the controls, and Caesarean section was more common in ICP cases (Table II). The percentage value of multiple pregnancies was two and a half fold and that of stillbirth almost twofold for ICP pregnancies. Proportion of mothers 35 years or older was slightly lower for ICP mothers.

In the logistic regression analyses mother's age was not associated with ICP (Table III). The risk of premature delivery was sevenfold among ICP patients compared with controls. The risk of induction was threefold and the risk of Caesarean section was one and a half fold. The possibility of the incidence of multiple pregnancies was two and a half fold. The risk of child's low weight at birth was twofold. Low Apgar scores and stillbirth were not associated with ICP. The risk of the duration of hospital stay being at least 10 days was more than eightfold.

Discussion

Mothers with ICP stayed longer in hospital and more often had labour induction and Caesarean section than controls. Children were born at earlier weeks, but Apgar scores did not differ significantly either at
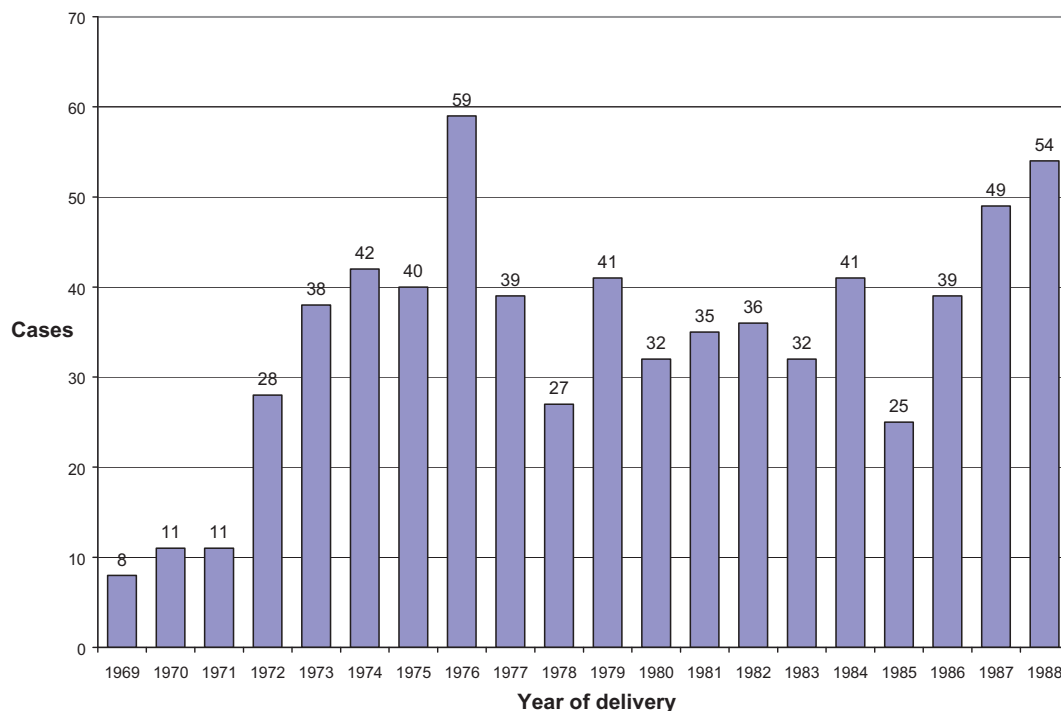

Figure 2. ICP patients in Tampere University Hospital during 1969–1988.

Table I. Comparison of ICP patients and controls in Tampere University Hospital during 1969–1988: Mean difference in variables.

Variables	Means		Mean difference	Significance p
	ICP patients (n = 687)	Controls (n = 1374)		
Weight at birth, grams	3 225	3 486	261	< 0.001
Apgar scores 1 min	8.1	8.3	0.2	0.019
Apgar scores 5 min	8.8	8.9	0.1	0.006
Hospital stay, days	18	10	8	< 0.001
Age of mother, years	27.5	27.2	0.3	0.196

one minute or at five minutes, the latter being more important for the prognosis of the child. Logistic regression analysis showed no significant risk growth in stillbirth, confidence intervals being wide. Stillbirth occurred in 1.2% of ICP cases, which fits with earlier studies (1–3%). In means, the difference in stillbirths was statistically significant. In any case, stillbirth was so infrequent that no ultimate conclusion can be drawn from these data. Power calculation shows that the number of ICP cases should have been 6000 to make conclusions of any significant difference.

Bile acids have been suspected in the case of fetal arrhythmia. In our study the number of stillbirths in which abnormal bile acid levels had been measured in mothers' blood was very low and showed no systematic trend. Normal bile acid levels were not systematically recorded.

In an earlier study [9], Heinonen and Kirkinen stated that ICP risk was increased by mother's age. In our study the association was not found. We analysed the measured variables using mother's age as continuous variant, and we found no changes in any of the risks.

The material is comprehensive, consisting of ICP cases in a university hospital over a 20-year period. The number of ICP cases found corresponds to the known 0.54–1.5% incidence of ICP. During 1969–1988 the incidence of ICP was 0.9% in Tampere University Hospital. ICP frequencies differed year by year during 1969–1988. In the first three years the explanation for lower frequencies might be implementation of ICD-8, but from 1972 onwards, we suggest that frequencies fit the normal variation.

The labour register, the source of data for the principal outcome of our study, is formally structured like "an account book", and may be considered reliable. In verifying ICP diagnoses we used paper patient records. Paper records include sources of error, as also do the present electronic patient records [22]. As to laboratory results, the electronic system is probably more reliable than paper records.

It may be that we overlooked some ICP cases because of the strict inclusion criteria, i.e. symptoms of itching and abnormal laboratory tests. On the other hand, applying the strict criteria we assume that we have found the correct positive ICP cases. In ICP, pruritus is relieved in a couple of days and laboratory tests return to normal in 7–21 days after delivery. The definition of ICP also includes absence of other diseases that cause these signs. In our study, we presume that at the time of confirmation of diagnosis, that is the day of getting home from hospital, itching would be relieved and other diseases would practically be excluded. We checked systematically that none of our controls was included in the ICP group. Laboratory tests for checking ICP were not routinely undertaken for asymptomatic women.

During the 20 years of our study, diagnostics have changed to some extent. Itching has been a constant diagnostic criterion. In the early years of the era, laboratory tests, such as a thymol test, iodine test, Schles, Meulengracht, or Ehrlich, were used, but they could not be interpreted as ICP criteria for our study. Ultrasound became a common means of assessing gestational age in the 1980s, supplementing menstrual history, pregnancy test, and clinical findings. Indications for induction and Caesarean

Table II. Comparison of ICP patients and controls in Tampere University Hospital during 1969–1988: Percentage values of variables.

Variables	ICP patients (n = 687)		Controls (n = 1374)		Significance p
	Number	%	Number	%	
Age of mother					
≥ 35	59	8.6	136	9.9	0.338
Induction	326	47.5	298	21.7	< 0.001
Caesarean section	102	14.8	146	10.6	0.005
Multiple pregnancy	35	5.1	29	2.1	< 0.001
Stillbirth	8	1.2	10	0.7	0.315

Table III. Risk for matters concerning delivery in ICP cases in the univariate logistic regression analyses.

	OR (95% CI)
Ongoing week of gestation at childbirth	
> 37	1.00
≤ 37	**7.02 (5.59–8.82)**
Induction	
No	1.00
Yes	**3.26 (2.68–3.97)**
Age of mother	
< 35	1.00
≥ 35	0.86 (0.62–1.18)
Caesarean section	
No	1.00
Yes	**1.47 (1.12–1.92)**
Multiple pregnancy	
No	1.00
Yes	**2.49 (1.51–4.11)**
Duration of hospital stay	
< 10 days	1.00
≥ 10 days	**8.41 (6.83–10.36)**
Stillbirth	
No	1.00
Yes	1.61 (0.63–4.09)
Apgar 1 min	
≥ 7	1.00
< 7	1.12 (0.77–1.63)
Apgar 5 min	
≥ 7	1.00
< 7	1.23 (0.66–2.32)
Weight at birth	
≥ 2500 g	1.00
< 2500 g	**1.86 (1.31–2.64)**

Note: Statistically significant ORs are shown in bold.

section have changed in ICP cases as well as in normal pregnancies.

Some false-positive ICP cases might be included, because itching is quite a common symptom during pregnancy, and slightly abnormal laboratory tests might occur for other reasons or without any clinical relevance. Hepatitis may also appear during pregnancy, but differential diagnosis can usually be made clinically and by additional laboratory tests. Symptomatic gallstones can raise laboratory values whereas itching is not typical of gallstones. Neither for ICP patients nor for controls did we exclude eclampsia, where hepatobiliary laboratory tests may rise, especially in HELLP (hemolysis, elevated liver enzymes, low platelet count) syndrome. We suggest that HELLP cases are not a significant group in these data.

Tampere University Hospital (TUH) deals with all normal deliveries in its area. In addition, the management of at-risk pregnancies and deliveries from a larger area is allocated to TUH. In that respect, our material is not quite equivalent to an unselected population. The university hospital selection can be seen for example in gemini frequency: in Finland, gemini frequency was 1.1% [2], and in our material it was 2.1% in controls and 5.1% in ICP cases.

In our study the risk of adverse outcome in ICP pregnancies seems smaller than stated in earlier studies [7,13,15,17]. The role of primary healthcare is important in finding ICP mothers. The system for referring ICP cases from primary healthcare to specialist care was already well established in the 1970s and 1980s.

Little is known about associations of ICP with other aspects of the health of mothers and their children. It has been stated that women with a history of ICP are more prone to gallstones, and some other hepatobiliary diseases are more common in women with a history of ICP [20]. In one study dyslipidemia during pregnancy was associated with ICP [23]. Women with ICP have been reported to present greater glucose concentrations in serum samples collected two hours after breakfast and after supper, and in glucose tolerance tests [24]. As for children, we did not observe the need for care in a neonatal unit or the neonatal death rate. Birth weights of ICP mothers' children were lower than weights of controls. Some authors do not consider that ICP is associated with intrauterine growth retardation [16,25], but slightly or clearly different results have been apparent [9,26]. The risks of some medical and social disabilities in adulthood increased with decreasing gestational age at birth [27], and further study is needed to find out if ICP increases or decreases the adverse effects of preterm birth.

Practically all (99.7%) pregnant women take advantage of public maternity healthcare in Finland [2]. GPs are responsible for maternity clinics in health centres. The convention of screening itching women for ICP in primary healthcare, referring ICP patients to the obstetric clinic, and management in hospital seems to have contributed to the good outcome in Finland. Documented local guidelines for maternity care and referral instructions are essentially important for primary healthcare maternity clinics. They should be updated regularly in collaboration with GPs and obstetric clinics.

According to our findings, ICP mothers are found and taken care of appropriately, and thus ICP is only a minor risk for mother and child during pregnancy and delivery. The role of the GP is important in assessing risks in practice among women with ICP and their children.

Ethical approval

Ethical approval was received from the Ethics Committee for Pirkanmaa Hospital District (R02149).

Declaration of interest: The authors report no conflicts of interest.

References

[1] Sigurdsson J. The GP's role in maternity care. Scand J Prim Health Care 2003;21:65.

[2] Statistics, registers and population studies. National Institute for Health and Welfare. Finland. http://www.thl.fi/en_US/web/en/research/statistics (accessed 11 February 2010).

[3] Laes E, Gissler M. Health of pregnant women. In: Koskinen S, Aromaa A, Huttunen J, Teperi J, editors. Health in Finland. Vammala: KTL, Stakes, Ministry of Social Affairs and Health; 2006:120–1.

[4] Maternity and child health clinics. Ministry of Social Affairs and Health. http://www.stm.fi/en/social_and_health_services/health_services/primary_health/maternity_clinics (accessed 9 March 2010).

[5] Reyes H. Intrahepatic cholestasis: A puzzling disorder of pregnancy. J Gastroenterol Hepatol 1997;12:211–16.

[6] Lammert F, Marshall HU, Glantz A, Matern S. Intrahepatic cholestasis of pregnancy: Molecular pathogenesis, diagnosis and management. J Hepatol 2000;33:1012–21.

[7] Laatikainen T, Tulenheimo A. Maternal serum bile acid levels and fetal distress in cholestasis of pregnancy. Int J Gynaecol Obstet 1984;22:91–4.

[8] Berg B, Helm G, Petersohn L, Tryding N. Cholestasis of pregnancy. Acta Obstet Gynecol Scand 1986;65:107–13.

[9] Heinonen S, Kirkinen P. Pregnancy outcome with intrahepatic cholestasis. Obstet Gynecol 1999;94:189–93.

[10] Germain AM, Carvajal JA, Glasinovic JC, Kato C S, Williamson C. Intrahepatic cholestasis of pregnancy: An intriguing pregnancy-specific disorder. J Soc Gynecol Investig 2002;9:10–14.

[11] Savander M, Ropponen A, Avela K, Weerasekera N, Cormand B, Hirvioja M-L, et al. Genetic evidence of heterogeneity in intrahepatic cholestasis of pregnancy. Gut 2003;52:1025–9.

[12] Gonzales MC, Reyes H, Arrese M, Figueroa D, Lorca B, Andresen M, et al. Intrahepatic cholestasis of pregnancy in twin pregnancies. J Hepatol 1989;9:84–90.

[13] Glantz A, Marshall HU, Mattson LÅ. Intrahepatic cholestasis of pregnancy: Relationships between bile acid levels and fetal complication rates. Hepatology 2004;40:467–74.

[14] Davidson KM. Intrahepatic cholestasis of pregnancy. Semin Perinatol 1998;22:104–11.

[15] Fisk NM, Storey GN. Fetal outcome in obstetric cholestasis. Br J Obstet Gynaecol 1988;95:1137–43.

[16] Rioseco AJ, Ivancovic MB, Manzur A, Hamed F, Kato SR, Parer JT, et al. Intrahepatic cholestasis of pregnancy: A retrospective case-control study of perinatal outcome. Am J Obstet Gynecol 1994;170:890–5.

[17] Alsulyman OM, Ouzounian JG, Ames-Castro M, Goodwin TM. Intrahepatic cholestasis of pregnancy: Perinatal outcome associated with expectant management. Am J Obstet Gynecol 1996;175:957–60.

[18] Sepúlveda WH, González C, Cruz MA, Rudolph MI. Vasoconstrictive effect of bile acids on isolated human placental chorionic veins. Eur J Obstet Gynecol Reprod Biol 1991;42:211–15.

[19] Germain AM, Kato S, Carvajal JA, Valenzuela GJ, Valdes GL, Glasinovic JC. Bile acids increase response and expression of human myometrial oxytocin receptor. Am J Obstet Gynecol 2003;189:577–82.

[20] Ropponen A, Sund R, Riikonen S, Ylikorkala O, Aittomäki K. Intrahepatic cholestasis of pregnancy as an indicator of liver and biliary diseases: A population based study. Hepatology 2006;43:723–8.

[21] Evidence-based medicine guidelines. Obstetrics. Duodecim. Finland. http://www.terveysportti.fi/ebmg/ltk.koti (accessed 8 April 2009).

[22] Vainiomäki S, Kuusela M, Vainiomäki P, Rautava P. The quality of electronic patient records in Finnish primary healthcare needs to be improved. Scand J Prim Health Care 2008;26:117–22.

[23] Dann AT, Kenyon AP, Wierzbicki AS, Seed PT, Shennan AH, Tribe RM. Plasma lipid profiles of women with intrahepatic cholestasis of pregnancy. Obstet Gynecol 2006;107:106–14.

[24] Wójcicka-Jagodzińska J, Kuczyńska-Sicińska J, Czajkowski K, Smolarczyk R. Carbohydrate metabolism in the course of intrahepatic cholestasis in pregnancy. Am J Obstet Gynecol 1989;161:959–64.

[25] Zimmermann P, Koskinen J, Vaalamo P, Ranta T. Doppler umbilical artery velocimetry in pregnancies complicated by intrahepatic cholestasis. J Perinat Med 1991;19:351–5.

[26] Vega J, Sáez G, Smith M, Agurto M, Morris NM. Risk factors for low birth weight and intrauterine growth retardation in Santiago, Chile (in Spanish). Rev Med Chil 1993;121:1210–19.

[27] Moster D, Lie RT, Markestad T. Long-term medical and social consequences of preterm birth. N Engl J Med 2008;359:262–73.

Health history after intrahepatic cholestasis of pregnancy

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Abstract

Objective. To establish whether intrahepatic cholestasis of pregnancy (ICP) is associated with other diseases during a woman's lifetime. *Design.* Prospective controlled cohort study. *Setting.* University Hospital in Finland. *Population.* A total of 575 women with ICP and 1374 control women, all having delivered in 1969–1988. Questionnaires were sent to 544 ICP patients and 1235 control women. Responses were received from 1178 (66.4%). *Methods.* Questionnaire survey in autumn 2010. *Main outcome measures.* Perceived health, symptoms and complaints, diseases diagnosed by a doctor and use of medicines. *Results.* No statistically significant differences were detected in perceived health. Differences in recent symptoms and complaints were small. Diagnoses made by a doctor showed higher frequencies in the ICP group than in control women for other hepatobiliary diseases, breast cancer and hypothyreosis. Diagnosed hypertension and high cholesterol requiring medication as well as cardiac arrhythmia were less frequent in the ICP group. Women in this group used antacid medicines more often than control women. *Conclusions.* There were few differences between the ICP patients and control women except for a higher frequency of later hepatobiliary disease, breast cancer and hypothyreosis. Women with a history of ICP should be screened for hypothyreosis more readily than those without. The higher frequency of breast cancer warrants further research.

Abbreviations: ICP, intrahepatic cholestasis of pregnancy.

Introduction

Intrahepatic cholestasis of pregnancy (ICP) usually manifests in the third trimester as skin itching, especially on the palms and soles, and as an elevation of the serum levels of bile acids and liver enzymes (1,2). The incidence of ICP in Finland is 0.54–1.5% of pregnancies (3–5). The figure varies from country to country, being at its lowest less than 0.5%, but for example in Chile it is 16%, and among the Araucanos Indians in Chile 28% (6). Intrahepatic cholestasis of pregnancy recurs in almost half of subsequent pregnancies (1,7). In one of six cases ICP is familial, and in such cases it almost always recurs (8).

Intrahepatic cholestasis of pregnancy is thought to be the result of an insufficient liver capacity to metabolize large amounts of placental hormones during pregnancy (1,9). The ultimate cause of the condition is unknown, but is thought to be multifactorial, involving genetic, hormonal and envi-

ronmental factors. The severity of ICP varies between subsequent pregnancies (10). More severe ICP cases occur in the winter (11). Nutritional factors, for example selenium deficiency, may also have a role in ICP (10). Interestingly, a theory of "leaky gut" has been suggested to explain a part of the pathogenesis of ICP, namely enhancement of the absorption of bacterial endotoxins (12). Cytokines might favor this absorption to initiate a hepatic inflammatory cascade.

Key Message

Women with a history of intrahepatic cholestasis of pregnancy had only a few differences in lifelong health compared with control women. They had a higher frequency of hepatobiliary diseases, breast cancer and hypothyreosis and a lower frequency of hypertension, high cholesterol and cardiac arrhythmia.

In Finland, ICP is usually detected in primary healthcare maternity clinics, and patients are referred to hospital obstetric clinics for follow-up in view of the risks for the fetus. Intrahepatic cholestasis of pregnancy increases the risk of preterm birth (13–15), fetal distress during labor (3,13,14,16) and intrauterine death (3,14,16). For the mothers, ICP is a minor problem during pregnancy and delivery, although it is associated with an increased incidence of induction of labor and cesarean section (17). Itching may be intense and particularly disturbing, but rapidly fades postpartum. Moreover, women with a history of ICP are more prone to several liver and biliary disorders, including hepatitis C, non-alcoholic liver cirrhosis, gallstones and cholecystitis, and non-alcoholic pancreatitis, even before the first occurrence of ICP (18).

Liver function in the human body is so fundamental and complex that we must envisage conditions and diseases other than hepatobiliary conditions as being associated with ICP. We studied associations of ICP with perceived health, specific symptoms and complaints, diseases diagnosed by a doctor and the women's later use of medicines.

Material and methods

To assess the health history of women who had suffered from ICP, we conducted a postal survey among ICP patients and control women in autumn 2010. Research approval was obtained from the Ethics Committee of the Pirkanmaa Hospital District (R02149).

The study population comprised 575 women who had been diagnosed with ICP during at least one pregnancy (a total of 687 cases of ICP) in the obstetric department of Tampere University Hospital in the period 1969–1988. From the hospital discharge register, we chose all the patients who had a diagnosis code that referred to ICP. The diagnosis was then verified from each patient record with the presence of the main symptom of itching, and laboratory tests. At least one of the following was required: aspartate aminotransferase >35 U/L, alanine aminotransferase >40 U/L or bile acids ≥6 μmol/L. Two control women were selected for each woman who had ICP. Postal addresses were obtained from the Population Register Centre in Finland. In the ICP group, 22 women (3.8%) and in the control group 71 (5.2%) had died by August 2010. Postal addresses were available for 1779 (95 and 90%) women. With one reminder, we received 1178 acceptable responses, which corresponds to 66.4% of all the questionnaires sent (see Figure 1).

There were no statistically significant differences between the ICP group and the control group regarding age, educational level or present body mass index (Table 1). At the end of the year 2010, the mean age of women in the ICP group was 58.5 years and in the control group 58.3 years. Education was classified as "high" for those who had taken the matric-
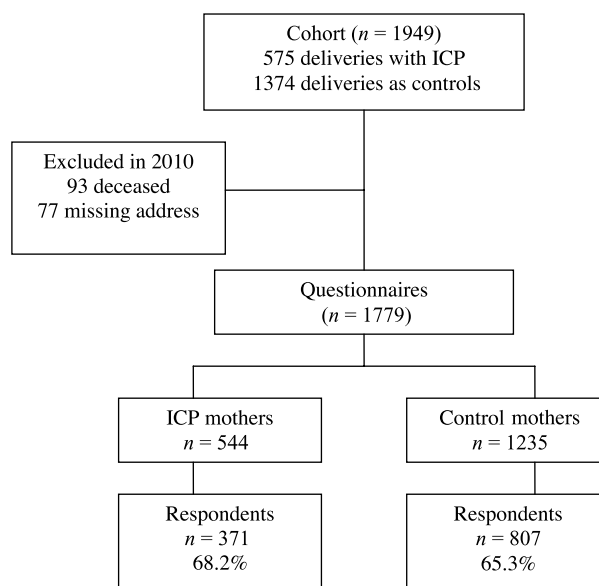
Figure 1. Flow chart of the study population. ICP, intrahepatic cholestasis of pregnancy.

ular examination (gymnasium/grammar school) and "low" for those who had not.

The questionnaire consisted of 85 items and covered the following main aspects: health in general; symptoms and complaints; diseases diagnosed by a doctor; health habits; use of medicines; and gynecological obstetric history. The ICP women and the control women received identical questionnaires. In this survey, the focus was on lifelong health history. Women's general health conditions before the index pregnancies were not charted. The questionnaire included internationally validated questions, and also questions that were originally constructed for this study (the questionnaire is available as Appendix S1).

The respondents were asked to describe their present health, regardless of any diseases they might have, by choosing one of five options: good, fairly good, moderate, fairly poor and poor. In the analysis, we combined the response categories "good" and "fairly good" into "good" and "moderate", "fairly poor" and "poor" into "poor". The respondents were also asked whether any of 24 common symptoms or complaints had bothered them during the past 12 months. Furthermore, they were asked whether a doctor had ever told them they had one or more of the diseases listed in the questionnaire, among them gastroenterological, hepatobiliary, endocrinological, urological, gynecological, oncological, bone- and articulation-related, respiratory and cardiovascular diseases. A few separate disorders, such as migraine, epilepsy and anemia, were also listed. Respondents were further asked whether they had ever undergone any major medical surgeries, and a history of hip, wrist and vertebral fractures was inquired upon.

Table 1. Characteristics of the respondents in the intrahepatic cholestasis of pregnancy (ICP) and control groups.

	ICP group (n = 371) (%)	Control group (n = 807) (%)	Difference	
			(% units)	Significance (p-value)
Age (years)				0.742
40–49	8.6	7.8	0.8	
50–59	45.3	48.9	−3.6	
60–69	42.0	39.0	3.0	
70–89	4.0	4.1	−0.1	
Education level				0.961
Low	67.0	67.2	−0.2	
High	33.0	32.8	0.2	
Body mass index (kg/m²)				0.265
≤25.0	40.0	38.3	1.7	
25.0–29.9	33.7	38.4	−4.7	
≥30.0	26.3	23.3	3.0	

Two basic mental health-related questions and the Depression Scale sought to assess the mental health of the respondents. The questions were: "Have you ever suffered from a mental disorder?" and "Have you ever been treated for a mental disorder?" The Depression Scale is a validated Finnish test screening for the risk of present clinical depression (19).

Use of medicines, natural health drugs as well as vitamins and trace elements during the last 12 months were inquired about. Three options were given for the mode of use: non-use, occasional use and regular use. In the analyses, we combined the categories of regular and occasional use to compare with "non-use".

Statistical analyses were made using the SPSS System for Windows, release 16.0 (SPSS Inc., Chicago, IL, USA). Results are presented as frequencies. Statistical significance was tested by the chi-squared test.

Results

Good or fairly good health was reported by 70.7% of the respondents in the ICP group and 72.7% in the control group, the difference being not significant. Responses concerning symptoms and complaints are shown in Table 2. Itching on the palms and soles was less frequent among women with a history of ICP. One in seven women in the ICP group had suffered chest pain and one in 10 control women, the difference not being significant.

Details of diagnoses made by a doctor are presented in Table 3. The most marked differences between the two groups pertained to hepatobiliary diseases, which were significantly more frequent in the ICP group. There was a slight but insignificant difference in pancreatitis. Regarding the prevalence of diabetes, there was a slight but not statistically significant difference in favor of the ICP group.

Compared with control women, there was a higher frequency of breast cancer and hypothyreosis in the ICP group, whereas cardiac arrhythmia, high cholesterol and high blood pressure requiring medication were less frequent.

Cholecystectomy (32.8 vs. 9.8%, $p < 0.001$) and surgery for malignant tumors (8.9 vs. 5.1%, $p = 0.012$) were more common in the ICP than the control group. Wrist fracture had occurred in 11.1% of women in the ICP group and in 8.8% among control women. The numbers of hip and vertebral column fractures were less than five in both groups. Differences in respect of bone fractures were not statistically significant. Likewise, there were no major differences in mental health history or risk of present clinical depression between the two groups.

Use of gastric acid reducers was more frequent in the ICP group (Table 4). Painkiller use was more common in the ICP group, but the difference was not significant. Medicines for mental disorders did not distinguish the groups, which was in line with the reports on mental health.

Discussion

Differences between the ICP and control groups were minor with respect to perceived health, symptoms and complaints, diseases and use of medicines. The higher frequency of gallstones and other hepatobiliary diseases was the most significant factor characterizing the ICP group, as anticipated on the basis of previous studies. Higher frequencies of breast cancer and hypothyreosis in the ICP group are major new findings.

This study involved a comprehensive cohort of ICP patients and control women from 22–41 years ago. Postal addresses were available for the majority of the study population, and the response rate (66.4%) is high for a postal survey in international terms. The two large groups did not differ regarding

Table 2. Symptoms and complaints during the past 12 months in the ICP and control groups.

	ICP group (n = 345–361) (%)	Control group (n = 753–780) (%)	Difference	
			(% units)	Significance (*p*-value)
Chest pain	13.7	9.8	3.9	0.054
Neck and shoulder pain	65.1	61.8	3.3	0.283
Headache	40.0	37.2	2.8	0.364
Heart palpitation	31.8	29.5	2.3	0.438
Arthralgia, joint pain	50.6	49.0	1.6	0.633
Blushing	22.9	21.9	1.0	0.689
Rheumatic pains	19.5	18.6	0.9	0.725
Nausea	5.7	5.1	0.6	0.665
Nervousness	21.7	21.1	0.6	0.829
Vaginal and vulvar dryness	36.5	36.1	0.4	0.884
Recurring stomach problems	18.3	18.3	0.0	0.988
Insomnia	41.5	42.0	−0.5	0.883
Dryness of eyes and mouth	36.7	37.3	−0.6	0.855
Dizziness	22.0	22.8	−0.8	0.771
Dysmenorrhea	3.5	4.8	−1.3	0.318
Foot and/or leg swelling	31.2	33.0	−1.8	0.564
Dyspnea	15.7	17.6	−1.9	0.425
General itching of skin	20.7	23.0	−2.3	0.406
Urinary problems	14.4	16.9	−2.5	0.295
Sweating	45.4	48.4	−3.0	0.345
Backache	43.8	47.0	−3.2	0.325
Depression	16.0	19.4	−3.4	0.173
Itching of palms and soles	5.7	9.4	−3.7	0.039
Coughing	26.5	32.3	−5.8	0.050

age, educational level or body mass index. Ethnically, the Finnish population is and has always been relatively homogeneous. We therefore consider ethnicity not to be a confounding factor in the results of this survey and believe the findings of this study to be applicable to the whole of Finland as well as to the rest of Scandinavia, where the population and incidence of ICP are similar to ours.

Although most people in Finland take a positive attitude to research and questionnaires, there has recently been a notable slight decrease in response rates. An on-line survey might have increased the response rate among the youngest women. The youngest respondent was 42 years old, while the oldest was 81. On the whole, the postal survey provided us with abundant information on the respondents' personal perceptions, which would not have been revealed by searches in national disease registers.

The higher incidence of breast cancer among the women in the ICP group is a new finding. The major risk factors for breast cancer are age, family history of breast cancer, proliferative changes and atypical hyperplasia of the breast, early menarche, late menopause, long menses duration, nulliparity, late maternal age at first pregnancy and, presumably, exogenous hormones (20). One explanation for the biological mechanism responsible for the association between ICP and

breast cancer noted by us might be deduced from differences in estrogen metabolism. In addition, the number of eventual full-term pregnancies may be lower among women who have suffered from ICP as an obstetric complication, which might also increase the risk of breast cancer. Postmenopausal hormone therapy for five years or more is considered to increase the risk of breast cancer (21). However, hormone replacement therapy has hitherto been considered at least relatively contraindicated for women with a history of ICP and, consequently, presumably less used. Liver transaminase activities have nonetheless been proved to remain within normal ranges on postmenopausal hormone therapy (22), and this treatment mode will thus presumably be more common than previously among women with a history of ICP.

Another new finding was the higher frequency of hypothyreosis in the ICP group. Links between ICP and hypothyreosis may be of viral or autoimmune origin. Recent research has brought out an association between choledocholithiasis and hypothyreosis (23). In our study, ICP was associated with both. Hypothyreosis is probably an underdiagnosed disorder in the Finnish population. In a study from the UK, subclinical hypothyroid status was detected in 4% of otherwise healthy women at the age of 65 years or more (24). We may speculate whether women with a history

Table 3. Diseases diagnosed by a doctor in the ICP and control groups.

	ICP group (n = 353–370) (%)	Control group (n = 741–796) (%)	Difference (% units)	Significance (p-value)
Diseases of the digestive system				
Cholelithiasis	37.2	12.1	25.1	<0.001
Rise in liver function test results (except during pregnancy)	16.8	9.2	7.6	<0.001
Gastric catarrh, gastric or duodenal ulcer	17.3	13.6	3.7	0.099
Chronic choledochitis	5.0	1.5	3.5	0.001
Helicobacter pylori infection	8.3	7.5	0.8	0.633
Pancreatitis	1.9	1.1	0.8	0.294
Fatty liver	4.9	4.2	0.7	0.555
Acute hepatitis	1.9	1.3	0.6	0.389
Crohn's disease	0.8	0.3	0.5	0.174
Celiac disease	2.2	2.0	0.2	0.861
Chronic hepatitis	0.5	0.4	0.1	0.686
Liver cirrhosis	0.0	0.1	−0.1	0.497
Colitis ulcerosa	1.4	2.2	−0.8	0.361
Endocrine, nutritional and metabolic diseases				
Hypothyreosis	17.2	11.6	5.6	0.011
High cholesterol on medication	21.1	26.6	−5.5	0.041
Diabetes on medication	7.4	8.9	−1.5	0.390
Diseases of the genitourinary system				
Endometriosis	12.1	8.9	3.2	0.091
Malignant neoplasms				
Breast cancer	6.3	3.7	2.6	0.047
Any cancer other than breast or gynegological cancer	4.2	3.1	1.1	0.354
Gynecological cancers	1.9	1.4	0.5	0.512
Diseases of the respiratory system				
Chronic obstructive pulmonary disease	1.7	0.8	0.9	0.171
Asthma	9.1	10.3	−1.2	0.558
Diseases of the circulatory system				
Thrombophlebitis in lower extremity	8.5	8.0	0.5	0.778
Deep venous thrombosis in lower extremity	2.2	3.3	−1.1	0.292
Myocardial infarction	0.5	1.7	−1.2	0.124
Cardiac arrhythmia	15.2	21.8	−6.6	0.008
High blood pressure on medication	31.6	38.3	−6.7	0.027

Table 4. Regular and occasional use of medicines during the past 12 months in the ICP and control groups.

	ICP group (n = 312–363) Regular or occasional use (%)	Control group (n = 672–770) Regular or occasional use (%)	Difference (% units)	Significance (p-value)
Gastric acid reducers	40.4	32.5	7.9	0.014
Natural health drugs	51.9	45.9	6.0	0.078
Dermatological drugs	20.6	16.8	3.8	0.149
Painkillers	93.7	90.3	3.4	0.057
Sleeping pills	23.3	20.4	2.9	0.291
Vitamins or trace elements	80.7	78.2	2.5	0.326
Medicines for asthma or allergy	29.0	27.2	1.8	0.553
Sedatives	8.3	6.7	1.6	0.356
Heart medicine	10.5	12.9	−2.4	0.282
Eye drops	33.6	36.7	−3.1	0.344
Antidepressants	10.8	14.9	−4.1	0.075
Medicine for high cholesterol	22.1	27.1	−5.0	0.088
Medicine for high blood pressure	35.5	41.2	−5.7	0.078

of ICP are more aware of their health status and more alert to any symptoms and signs by themselves, and are thus not left underdiagnosed as regards hypothyreosis.

We assumed that the three prominent intestinal diseases, celiac disease, Crohn's disease and colitis ulcerosa, might be representative of "the leaky gut" (12) and thus be connected with ICP occurrence. Frequencies of these diseases did not, however, distinguish the two study groups.

As the liver contributes to vitamin D metabolism, it is conceivable that there might be disturbances in bone transformation among women in the ICP group. At delivery, women with ICP have been reported to have significantly lower levels of 1,25-dihydroxyvitamin D_3 in their serum than healthy women (25). We therefore expected to find differences in osteoporosis and, more clearly, in the incidence of bone fractures between the ICP and control groups. The overall number of fractures was, however, low, and we found no differences between the two groups. Considering that the mean age of our study population was 58 years, it is possible that our women were too young to have reached an age at which women are prone to osteoporotic fractures.

Dyslipidemia during pregnancy has been shown to be associated with ICP (26). Women with ICP have been reported to present greater glucose concentrations in serum samples collected two hours after breakfast and after supper, and in glucose tolerance tests (27). The possible associations of ICP with thromboembolism can be attributed to the liver's complex role in the blood clotting cascade. Consequently, we anticipated evidence of ICP associations with obesity, diabetes and cardiovascular diseases. Surprisingly, however, none of these proved to be more frequent among women with a history of ICP. In contrast, cardiac arrythmia diagnosed by a doctor was significantly less frequent in the ICP group. The reason for this is unclear. Differences in health habits between the two groups might explain the finding, for example, in postponing the end-points of cardiovascular diseases.

Regular or occasional use of gastric antacids was more frequent in the ICP group, although there were no differences in gastroduodenal diseases. The explanation for this might be biliary dyspepsia. Surprisingly, our findings show that fewer women with a history of ICP had suffered from "itching of palms and soles" during the past 12 months. The reason for this might be that ICP women know what the symptom indicates, and when they are certain that they have no symptoms suggestive of ICP at present, they report no bothersome itching, whereas control women would be ignorant of the ICP disease and thus might report itching, for example due to fungal infections.

According to our findings, in some respects women with a history of ICP lead even healthier lives than control women, although bile stones and other hepatobiliary diseases were common among the ICP group. We suggest that instances of ICP constitute an additional reason to screen women for

hypothyreosis, especially those who have suffered from choledocholithiasis. In addition, the increased frequency of breast cancer following previous ICP warrants further research. In general, however, after an episode of ICP, women do not need to be concerned about their health or singled out for special follow-up for the rest of their lives.

Funding

References

1. Reyes H. Review: intrahepatic cholestasis. A puzzling disorder of pregnancy. J Gastroenterol Hepatol. 1997;12:211–6.

2. Lammert F, Marschall HU, Glantz A, Matern S. Intrahepatic cholestasis of pregnancy: molecular pathogenesis, diagnosis and management. J Hepatol. 2000;33:1012–21.

3. Laatikainen T, Tulenheimo A. Maternal serum bile acid levels and fetal distress in cholestasis of pregnancy. Int J Gynaecol Obstet. 1984;22:91–4.

4. Berg B, Helm G, Petersohn L, Tryding N. Cholestasis of pregnancy. Clinical and laboratory studies. Acta Obstet Gynecol Scand. 1986;65:107–13.

5. Heinonen S, Kirkinen P. Pregnancy outcome with intrahepatic cholestasis. Obstet Gynecol. 1999;94:189–93.

6. Reyes H, Gonzalez MC, Ribalta J, Aburto H, Matus C, Schramm G, *et al*. Prevalence of intrahepatic cholestasis of pregnancy in Chile. Ann Intern Med. 1978;88:487–93.

7. Germain AM, Carvajal JA, Glasinovic JC, Kato CS, Williamson C. Intrahepatic cholestasis of pregnancy: an intriguing pregnancy-specific disorder. J Soc Gynecol Investig. 2002;9:10–4.

8. Savander M, Ropponen A, Avela K, Weerasekera N, Cormand B, Hirvioja ML, *et al*. Genetic evidence of heterogeneity in intrahepatic cholestasis of pregnancy. Gut. 2003;52:1025–9.

9. Davidson KM. Intrahepatic cholestasis of pregnancy. Semin Perinatol. 1998;22:104–11.

10. Reyes H, Baez ME, Gonzalez MC, Hernandez I, Palma J, Ribalta J, *et al*. Selenium, zinc and copper plasma levels in intrahepatic cholestasis of pregnancy, in normal pregnancies and in healthy individuals, in Chile. J Hepatol. 2000;32:542–9.

11. Hay JE. Liver disease in pregnancy. Hepatology. 2008;47:1067–76.

12. Reyes H, Zapata R, Hernandez I, Gotteland M, Sandoval L, Jiron MI, *et al*. Is a leaky gut involved in the pathogenesis of intrahepatic cholestasis of pregnancy? Hepatology. 2006;43:715–22.

13. Glantz A, Marschall HU, Mattsson LA. Intrahepatic cholestasis of pregnancy: Relationships between bile acid levels and fetal complication rates. Hepatology. 2004;40:467–74.

14. Fisk NM, Storey GN. Fetal outcome in obstetric cholestasis. Br J Obstet Gynaecol. 1988;95:1137–43.

15. Rioseco AJ, Ivankovic MB, Manzur A, Hamed F, Kato SR, Parer JT, *et al*. Intrahepatic cholestasis of pregnancy: a retrospective case-control study of perinatal outcome. Am J Obstet Gynecol. 1994;170:890–5.

16. Alsulyman OM, Ouzounian JG, Ames-Castro M, Goodwin TM. Intrahepatic cholestasis of pregnancy: perinatal outcome associated with expectant management. Am J Obstet Gynecol. 1996;175:957–60.

17. Turunen K, Sumanen M, Haukilahti RL, Kirkinen P, Mattila K. Good pregnancy outcome despite intrahepatic cholestasis. Scand J Prim Health Care. 2010;28:102–7.

18. Ropponen A, Sund R, Riikonen S, Ylikorkala O, Aittomaki K. Intrahepatic cholestasis of pregnancy as an indicator of liver and biliary diseases: a population-based study. Hepatology. 2006;43:723–8.

19. Salokangas RK, Poutanen O, Stengard E. Screening for depression in primary care. Development and validation of the Depression Scale, a screening instrument for depression. Acta Psychiatr Scand. 1995;92:10–6.

20. DiSaia PJ, Creasman WT. Breast diseases. In: DiSaia PJ, Creasman WT (eds). Clinical gynecologic oncology, 6th edn. St. Louis, MO: Mosby, 2002. pp. 399–402.

21. Lyytinen H, Pukkala E, Ylikorkala O. Breast cancer risk in postmenopausal women using estradiol-progestogen therapy. Obstet Gynecol. 2009;113:65–73.

22. Ropponen A, Aittomäki K, Vihma V, Tikkanen MJ, Ylikorkala O. Effects of oral and transdermal estradiol administration on levels of sex hormone-binding globulin in postmenopausal women with and without a history of intrahepatic cholestasis of pregnancy. J Clin Endocrinol Metab. 2008;90:3431–4.

23. Laukkarinen J, Kiudelis G, Lempinen M, Räty S, Pelli H, Sand J, *et al*. Increased prevalence of subclinical hypothyroidism in common bile duct stone patients. J Clin Endocrinol Metab. 2007;92:4260–4.

24. Wilson S, Parle JV, Roberts LM, Roalfe AK, Hobbs FD, Clark P, *et al*. Prevalence of subclinical thyroid dysfunction and its relation to socioeconomic deprivation in the elderly: a community-based cross-sectional survey. J Clin Endocrinol Metab. 2006;91:4809–16.

25. Wikström Shemer E, Marshall H-U. Decreased 1,25-dihydroxy vitamin D levels in women with intrahepatic cholestasis of pregnancy. Acta Obstet Gynecol Scand. 2010;1420–3.

26. Dann AT, Kenyon AP, Wierzbicki AS, Seed PT, Shennan AH, Tribe RM. Plasma lipid profiles of women with intrahepatic cholestasis of pregnancy. Obstet Gynecol. 2006;107:106–14.

27. Wójcicka-Jagodzińska J, Kuczyńska-Sicińska J, Czajkowski K, Smolarczyk R. Carbohydrate metabolism in the course of intrahepatic cholestasis in pregnancy. Am J Obstet Gynecol. 1989;161:959–64.

Supporting Information

Additional supporting information may be found in the on-line version of this article.

Appendix S1. Survey on the later life health of the mothers who gave birth and the children born to them in Tampere University Hospital in the period 1969–1988.

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Health behavior after intrahepatic cholestasis of pregnancy[*]

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ABSTRACT

Background: Pregnancy is an opportunity to adopt favorable health behaviors. We studied whether intrahepatic cholestasis of pregnancy (ICP) promotes favorable health behavior in later life. Design: A prospective controlled cohort study. The method was a questionnaire survey in 2010 among 575 women with ICP and 1374 controls, all having delivered between the years 1969 and 1988 in Tampere University Hospital in Finland. Questionnaires were sent to 544 ICP patients and 1235 controls. Responses were received from 1178 (response rate 66.2%). The main outcome measures concerning recent or current health behavior were smoking, alcohol consumption, physical activity, body mass index (BMI) and special diet. Results: Current smoking was less common in the ICP group than among controls (10.5% vs 15.7%, p = 0.017). Assessed by smoking pack years there was a similar difference: in the ICP group 11.7% of women had at least 10 smoking pack years compared to 18.0% of the controls (p = 0.006). Recent alcohol consumption did not separate the two groups. The groups did not differ as to reported physical activity assessed in MET units. Fewer ICP women had had BMIs of 30 or more during pregnancy compared with controls (18.8% vs 25.1%, p = 0.023). In other points of life the BMI differences were not statistically significant. Weight-loss diet and gallbladder diet were more common in the ICP group (6.3% vs 3.6%, p = 0.044, and 3.0% vs 1.3%, p = 0.038). Conclusions: Having developed ICP two to four decades earlier seemed to constitute an effective intervention for smoking habits but not for other aspects of health behavior.

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Keywords: Health Behavior; Intrahepatic Cholestasis of Pregnancy; Smoking; Alcohol Risk Use; Physical Activity; Body Mass Index

1. INTRODUCTION

In female life, pregnancy is an opportunity to adopt health behaviors favorable for later life. Finnish primary care maternity clinics monitor and treat any problems emerging during pregnancy, and also contribute to general health promotion in encouraging pregnant mothers and their families to revise their health behaviors. The free services of the mother health clinics are popular. According to the official birth register 99.8% of pregnant women attend maternity clinics during their pregnancies [1].

Intrahepatic cholestasis of pregnancy (ICP) usually manifests in the third trimester as skin itching especially on the palms and soles, and as an elevation of serum levels of bile acids and liver enzymes [2,3]. The incidence of ICP in Finland is 0.54% - 1.5% of pregnancies [4-6]. The condition recurs in almost half of subsequent pregnancies [2,7]. In one out of six cases it is familial, and in such cases almost always recurs [8].

ICP is thought to be the result of insufficient liver capacity to metabolize high amounts of placental hormones during pregnancy [2,9]. In Finland, ICP is usually detected in primary health care maternity clinics, and patients are referred to hospital obstetric clinics for follow-up in view of the risks for the fetus. ICP increases the risk of preterm birth [10-12], fetal distress during labor [4,10,11,13] and intrauterine death [4,11,13].

For the mothers, ICP is a minor problem during pregnancy and delivery except in being associated with an increased incidence of induction and cesarean section [14]. Itching may be intensive and disturbing but rapidly fades postpartum. Moreover, women with a history of ICP are more prone to a number of liver and biliary disorders, including hepatitis C, nonalcoholic liver cirrhosis, gallstones and cholecystitis, and nonalcoholic pancreati-

tis during their life time, even before the first occurrence of ICP [15].

Our hypothesis was that ICP induced women to lower alcohol consumption, since sufferers are aware of the hepatic origin of the disorder. It is moreover generally known that the liver is responsible for alcohol metabolism. Since cholelithiasis is significantly more common among women with an ICP history, we presumed they would make certain dietary choices, which might also lead to a lowering in weight.

We inquired whether these women had considered their ICP episode to have been so serious that they had adopted favorable health habits for the rest of their lives. We assessed differences in self-reported alcohol use, smoking, physical activity, body mass index (BMI) and in adherence to any special diet between the ICP and control groups.

2. MATERIAL AND METHODS

To assess the health history of women who had suffered from ICP, we conducted a mail survey among ICP patients and controls in autumn 2010. Research approval was obtained from the Ethics Committee of the Pirkanmaa Hospital District (R02149).

The study population comprised 575 women who had been diagnosed with ICP at least during one pregnancy (altogether there were 687 cases of ICP) in the obstetric department of Tampere University Hospital in the period 1969-1988. Two controls were selected for each ICP case, *i.e.* the case previous to and immediately following the ICP case in the maternity ward diary [16]. Mail addresses were obtained from the Population Register Centre in Finland. In the ICP group, 22 women (3.8%) and in the control group 71 (5.2%) had died by August 2010. Mail addresses were available for 1779 (95% and 90%) women. With one reminder, we received 1178 acceptable responses, which corresponds to 66.2% of all questionnaires sent (**Figure 1**).

There were no statistically significant differences between the ICP group and the controls regarding age or educational level (**Table 1**). At the end of the year 2010, the mean age in the ICP group was 58.5 and in the control group 58.3 years. Education was classified as "high" for those who had taken the matriculation examination, and "low" for those who had not.

The main outcome measures concerning women's health behavior were recent alcohol consumption, smoking history, recent physical activity and body mass index (BMI). We also assessed proportions of those maintaining special diets.

Smoking was asked after in several questions: "Have you ever smoked during your life?", "Have you ever smoked regularly (daily or almost daily for at least a
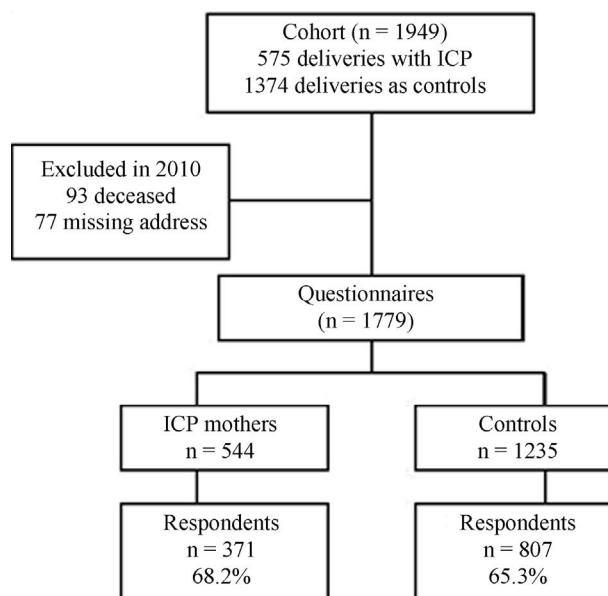

Figure 1. Flow chart of the survey population. ICP, intrahepatic cholestasis of pregnancy.

Table 1. Characteristics of respondents in the ICP and control groups.

	ICP group (n = 371)	Controls (n = 807)	Difference	
	%	%	% units	Significance (p-value)
Age (years)				0.724
40 - 49	8.6	7.8	0.8	
50 - 59	45.3	48.9	−3.6	
60 - 69	42.0	39.0	3.0	
70 - 89	4.0	4.1	−0.1	
Education				0.961
Low	67.0	67.2	−0.2	
High	33.0	32.8	0.2	

year)?" and "Do you currently smoke (cigarettes, cigars or pipe tobacco)?". To ascertain smoking pack years, the number of cigarettes per day and the yearly count of smoking were also asked. A smoking pack year corresponds to one pack of 20 cigarettes per day during one year. Alcohol consumption was inquired after by the three-question version of the Alcohol Use Disorders Identification Test (AUDIT-C).

To assess the intensity and average duration of weekly physical exercise the respondents had performed in the past 12 months we used a battery of four questions. Responses were converted into a metabolic equivalent of task units (MET) [17], one MET unit corresponding to the oxygen use of a resting person, which is approximately 3.5 ml/kg/min. Furthermore, a MET value of two or more was classified as "active" and less than two as "passive".

Women's weights at different points of time in their lives were inquired after as well as their present heights, and BMIs were calculated. In the analysis we used 30

kg/m² as the cut-off point. The questionnaire also included a list of special diets.

Finally, a sum variable of four health behaviors was built. Current non-smoking, alcohol use corresponding to less than 5 points on the AUDIT-C scale, being physically active (MET ≥ 2) and not being obese (BMI < 30) were considered favorable health habits, and all of them were encoded with the value one. All other behaviors were given a value of two. The sum variable score thus varied from four to eight, the value 4 signifying good and 8 bad health habits.

Statistical analyses were made using the SPSS System for Windows; release 20.0. Results were presented as frequencies and percentages. Statistical significance was tested by chi-squared test.

3. RESULTS

The ICP group women here included fewer current smokers than the control group (10.5% vs 15.7%, p = 0.017). A lower proportion of ICP women also had a smoking history involving ten or more smoking pack years (11.7% vs 18.0%, p = 0.006) (**Table 2**). There was no statistically significant difference between the ICP and control groups in respect of alcohol risk use (**Table 2**). There was, in contrast, a difference in the proportion of women who had not used any alcohol during the last 12 months (18.3% vs 14.9%), the difference however not being statistically significant.

Physical activity showed no statistically significant difference between the two groups when all respondents were divided into two groups, "active" and the "passive"

group (**Table 2**). A 6.3% units lower proportion of BMIs of 30 or more during pregnancy was noted in the ICP group (18.8% vs 25.1%, p = 0.023). The proportion of women with a current or ever BMI value of at least 30 was three per cent units higher in the ICP group, but the difference was not statistically significant (**Table 3**). Only half of the women reported knowing their own birth weight. Of these, women in the ICP group were somewhat lighter at birth: birth weight proportions less than 2500 grams were 8.0% vs 5.7% for ICP and controls respectively, and birth weight proportions of 4500 grams or more were 1.6% and 5.2% respectively, the difference not being statistically significant.

The sum variable of the four aspects of health behavior brought out no marked differences between the two groups, only the score eight (=bad health habits) producing a difference of 0.3% (ICP) vs 1.8% (controls) (p = 0.037) in favor of the ICP women.

Among the ICP women 3.0% and in the control group 1.3% (p = 0.038) reported maintaining a gallbladder diet, and 6.3% vs 3.6% (p = 0.044) followed a weight-loss diet (**Table 4**). None in the ICP group and only 1.4% in the control group reported adherence to a vegetarian diet (p = 0.024).

4. DISCUSSION

Current smoking was less common in the ICP than the control group, and this also pertained to smoking pack years. Recent use of alcohol showed no marked differences. As to physical activity and obesity the groups did not differ significantly.

Table 2. Alcohol use*, smoking and physical activity in the ICP and control groups.

	ICP group (n = 371) %	Controls (n = 807) %	Difference	
			% units	Significance (p-value)
Alcohol use/Audit C score				0.652
0 - 4	81.0	82.1	−1.1	
≥5	19.0	17.9	1.1	
Current smoking				**0.017**
Smoking	10.5	15.7	−5.2	
Non-smoking	89.5	84.3	5.2	
Smoking pack years				**0.006**
<10 years	88.3	82.0	6.3	
≥10 years	11.7	18.0	−6.3	
Physical activity				0.765
Passive (MET/day < 2)	29.5	30.4	−0.9	
Active (MET/day ≥ 2)	70.5	69.6	0.9	

*Audit-C; the cut-off point for high risk alcohol use for women is 5 or more.

Table 3. Proportions of body mass index (BMI kg/m^2) at different points of life in the ICP and control groups.

	ICP group (n = 336 - 365)[*] %	Controls (n = 722 - 792)[*] %	Difference	
			% units	Significance (p-value)
BMI in 2010				0.257
BMI < 30	73.7	76.8	−3.1	
BMI ≥ 30	26.3	23.2	3.1	
BMI at 20 years				0.071
BMI < 30	100.0	99.1	0.9	
BMI ≥ 30	0.0	0.9	−0.9	
Highest BMI during pregnancy				**0.023**
BMI < 30	81.2	74.9	6.3	
BMI ≥ 30	18.8	25.1	−6.3	
Highest BMI ever				0.279
BMI < 30	65.2	68.5	−3.3	
BMI ≥ 30	34.8	31.5	3.3	

[*]The number of respondents varies because respondents chose not to answer all questions.

Table 4. Special diets (%) among women in the ICP and control groups.

Special diet	ICP group (n = 366) %	Controls (n = 795) %	Difference	
			% units	Significance (p-value)
Lactose-free or low-lactose diet	16.7	17.2	−0.5	0.812
Gluten-free diet	2.5	2.9	−0.4	0.675
Gallbladder diet	3.0	1.3	1.7	**0.038**
Low-fat or low-cholesterol diet	14.8	13.6	1.2	0.593
Weight-loss diet	6.3	3.6	2.7	**0.044**
Vegetarian diet	0.0	1.4	−1.4	**0.024**
Other special diet	7.9	6.0	1.9	0.230

The study population, which comprised diagnosed ICP cases and controls who had all delivered in Tampere University Hospital in 1969-1988, was comprehensive. The two groups did not differ significantly in respect of age or educational level. The answers concerning maintenance of a lactose-free or low-lactose diet (17%) corresponded to the known prevalence of lactose intolerance in the Finnish adult population [18], which also confirms the comparability of the groups.

In international terms, the response rate (66.2%) can be regarded as high for a mail survey [19]. One explanation for this might be that we designed the questionnaire to be as practical as possible so that respondents could fill it in at one sitting. An e-mail survey might have resulted in a higher response rate among younger women. As a whole, the mail survey provided us with abundant information on individual health habits which would not have been revealed by searches in national disease registers.

A Finnish study from 2004 showed that working-aged coronary heart disease patients persisted in smoking and being obese more often than controls, which would imply that secondary prevention in this disease is disappointing [20]. Based on our responses, an ICP episode during a pregnancy seems to act for certain individuals as some kind of intervention, as the number of smokers was lower among the ICP women compared to the controls. One explanation for this might be that smokers in the ICP group may have quit smoking because of dyspepsia which is more common among smokers than non-smokers. Quitting smoking alleviates gastroesophageal reflux symptoms [21]. Our recent study among the same population showed that women in the ICP group had used antacid drugs more often than the controls [16].

We considered it likely that alcohol use would be markedly lower among former ICP sufferers compared to controls, but this was not the case. It is possible that ICP women consider the disorder to be connected solely with pregnancy and hence see no need to maintain alcohol restrictions later in life. As hepatobiliary diseases were more common among ICP women than controls [16], a moderate restrictive recommendation for alcohol use might be useful after an ICP episode.

The lower proportion of ICP women with a BMI of 30 or more during pregnancy might be explained by their having had earlier deliveries than the controls [14].

In our recent study, breast cancer and hypothyreosis were more common in the ICP than the control group [16]. These diseases cannot ultimately be avoided by favorable health habits. Of cardiovascular disorders, high blood pressure on medication, high cholesterol on medication and cardiac arrhythmia were less common in the ICP than in the control group. These are all conditions which can be influenced by favorable health habits.

According to our findings, there were few long-term associations between ICP and subsequent health behaviors. ICP had no marked effect on respondents' alcohol consumption, although in view of the hepatobiliary origins of the condition a connection with reduced alcohol use might have been expected. On the other hand, our findings showed that ICP was associated with lower smoking frequency compared to controls. This is a new result which warrants further research.

REFERENCES

[1] National Institute for Health and Welfare (2012) Finland. http://www.thl.fi/fi_FI/web/kasvunkumppanit-fi/palvelut/neuvolat/aitiysneuvola

[2] Reyes H. (1997) Review: Intrahepatic cholestasis. A puzzling disorder of pregnancy. *Journal of Gastroenterology and Hepatology*, **12**, 211-216. doi:10.1111/j.1440-1746.1997.tb00410.x

[3] Lammert, F., Marschall, H.U., Glantz, A. and Matern, S. (2000) Intrahepatic cholestasis of pregnancy: Molecular pathogenesis, diagnosis and management. *Journal of Hepatology*, **33**, 1012-1021. doi:10.1016/S0168-8278(00)80139-7

[4] Laatikainen, T. and Tulenheimo, A. (1984) Maternal serum bile acid levels and fetal distress in cholestasis of pregnancy. *International Journal of Gynecology & Obstetrics*, **22**, 91-94. doi:10.1016/0020-7292(84)90019-5

[5] Berg, B., Helm, G., Petersohn, L. and Tryding, N. (1986) Cholestasis of pregnancy. Clinical and laboratory studies. *Acta Obstetricia et Gynecologica Scandinavica*, **65**, 107-113. doi:10.3109/00016348609158363

[6] Heinonen, S. and Kirkinen, P. (1999) Pregnancy outcome with intrahepatic cholestasis. *Obstetrics & Gynecology*, **94**, 189-193. doi:10.1016/S0029-7844(99)00254-9

[7] Germain, A.M., Carvajal, J.A., Glasinovic, J.C., Kato, C.S. and Williamson, C. (2002) Intrahepatic cholestasis of pregnancy: An intriguing pregnancy-specific disorder. *Journal of the Society for Gynecologic Investigation*, **9**, 10-14. http://rsx.sagepub.com/content/9/1/10.full.pdf

[8] Savander, M., Ropponen, A., Avela, K., Weerasekera, N., Cormand, B., Hirvioja, M.L., *et al*. (2003) Genetic evidence of heterogeneity in intrahepatic cholestasis of pregnancy. *Gut*, **52**, 1025-1029. doi:10.1136/gut.52.7.1025

[9] Davidson, K.M. (1998) Intrahepatic cholestasis of pregnancy. *Seminars in Perinatology*, **22**, 104-111. doi:10.1016/S0146-0005(98)80042-6

[10] Glantz, A., Marschall, H.U. and Mattsson, L.A. (2004) Intrahepatic cholestasis of pregnancy: Relationships between bile acid levels and fetal complication rates. *Hepatology*, **40**, 467-474. doi:10.1002/hep.20336

[11] Fisk, N.M. and Storey, G.N. (1988) Fetal outcome in obstetric cholestasis. *British Journal of Obstetrics and Gynaecology*, **95**, 1137-1143. doi:10.1111/j.1471-0528.1988.tb06791.x

[12] Rioseco, A.J., Ivankovic, M.B., Manzur, A., Hamed, F., Kato, S.R., Parer, J.T., *et al*. (1994) Intrahepatic cholestasis of pregnancy: A retrospective case-control study of perinatal outcome. *American Journal of Obstetrics & Gynecology*, **170**, 890-895.

[13] Alsulyman, O.M., Ouzounian, J.G., Ames-Castro, M. and Goodwin, T.M. (1996) Intrahepatic cholestasis of pregnancy: Perinatal outcome associated with expectant management. *American Journal of Obstetrics & Gynecology*, **175**, 957-960. doi:10.1016/S0002-9378(96)80031-7

[14] Turunen, K., Sumanen, M., Haukilahti, R.L., Kirkinen, P. and Mattila, K. (2010) Good pregnancy outcome despite intrahepatic cholestasis. *Scandinavian Journal of Primary Health Care*, **28**, 102-107. doi:10.3109/02813431003784001

[15] Ropponen, A., Sund, R., Riikonen, S., Ylikorkala, O. and Aittomaki, K. (2006) Intrahepatic cholestasis of pregnancy as an indicator of liver and biliary diseases: A population-based study. *Hepatology*, **43**, 723-728. doi:10.1002/hep.21111

[16] Turunen, K., Mölsä, A., Helander, K., Sumanen, M. and Mattila, K.J. (2012) Health history after intrahepatic cholestasis of pregnancy. *Acta Obstetricia et Gynecologica Scandinavica*, **9**, 679-685. doi:10.1111/j.1600-0412.2012.01403.x

[17] Wilson, W.F., Paffenbarger, R.S., Morris, J.N. and Havlik, R.J. (1986) Assessment methods for physical activity and physical fitness in population studies: Report of NHLBI workshop. *American Heart Journal*, **111**, 1177-1192. doi:10.1016/0002-8703(86)90022-0

[18] Rasinperä, H. (2006) Adult-type hypolactasia: Genotype-phenotype correlation. Thesis, University of Helsinki. http://www.doria.fi/bitstream/handle/10024/1389/adulttyp.pdf?sequence=1

[19] Asch, D.A., Jedrziewski, M.K. and Christakis, N.A. (1997) Response rates to mail surveys published in medical journals. *Journal of Clinical Epidemiology*, **50**, 1129-1136. doi:10.1016/S0895-4356(97)00126-1

[20] Sumanen, M., Koskenvuo, M., Immonen-Räihä, P., Suo-minen, S., Sundell, J. and Mattila, K. (2004) Secondary prevention of coronary heart disease is disappointing among patients of working age. *Family Practice*, **21**, 304-306. doi:10.1093/fampra/cmh315

[21] Nakajima, K., Nagahara, A., Kurosawa, A., Seyama, K., Asaoka, D., Osada, T., Hojo, M. and Watanabe, S. (2011) Quit smoking improves gastroesophageal reflux symp-toms and quality of life. *Health*, **3**, 677-683. doi:10.4236/health.2011.311114

Intrahepatic cholestasis of pregnancy is common among patients' first-degree relatives

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Abstract

Intrahepatic cholestasis of pregnancy has been shown to have a genetic predisposition. We studied whether Finnish women who had suffered from the disorder reported their first-degree relatives to have had liver dysfunction during their pregnancies. Questionnaires were sent in autumn 2010 to a total of 544 former intrahepatic cholestasis of pregnancy patients and 1235 controls, all having delivered during 1969–1988. The response rate was 66.2%. The incidence of intrahepatic cholestasis is 0.5–1.5% of pregnancies in Finland. In our survey, altogether 12.8% of mothers (odds ratio 9.2), 15.9% of sisters (odds ratio 5.3) and 10.3% of daughters (odds ratio 4.8) of women who had suffered from intrahepatic cholestasis of pregnancy had had liver dysfunction during pregnancy. Our findings strengthen the earlier knowledge of the genetic component in intrahepatic cholestasis of pregnancy. We suggest that all pregnant women are asked about their family history regarding liver dysfunction during pregnancy.

Abbreviations: ICP, intrahepatic cholestasis of pregnancy.

Introduction

Having a positive family history of certain conditions may lead to targeted risk assessment, screening and preventive information, care or surgery. This could pertain also to intrahepatic cholestasis of pregnancy (ICP). In Scandinavia the incidence of ICP is 0.5–1.8% of pregnancies (1,2). In 16% of cases, the condition is hereditary (3). In singleton pregnancies, risk of ICP per delivery has proved to be 6% in the first-degree relatives (4). It has been proposed that the disease may be transmitted as a predisposing trait by individuals of either gender (5). The inheritance of ICP has been presumed to run in a dominant mode, in either an autosomal or X-chromosome-linked fashion (1,6). Several different cholestatic genes have been suggested to transmit the metabolic disorder (7–9).

When a pregnant woman complains of itching of healthy skin, she will be screened for ICP. This is also done in cases of multiple pregnancy and with a history of ICP pregnancy (3). Detection of the condition is important because of the risks for the fetus (10).

As genetic factors play a role in the appearance of ICP, we aimed at exploring the heredity of this condition in the Finnish population. We inquired about the occurrence of ICP among women's close relatives in a large postal questionnaire survey.

Material and methods

The original study population comprised 575 women with ICP during one or more pregnancies (altogether 687 pregnancies) and two controls for each case with ICP (11). All the women delivered in Tampere University Hospital during the period 1969–1988. The diagnoses in the hospital discharge register that referred to ICP were verified. Criteria for ICP diagnosis were the main symptom, itching, and abnormal laboratory tests (at least one of the following: aspartate aminotransferase >35 U/L, alanine aminotransferase >40 U/L or bile acids ≥6 μmol/L). Two controls were selected for each ICP case, i.e. the previous and the next woman at the delivery ward diary. Postal addresses for sending the questionnaires in autumn 2010 were available for 544 women in the ICP group and 1235 in the control group, and the response rate was 66.2%. Research approval was obtained from the Ethics Committee of the Pirkanmaa Hospital District (R02149).

There were no statistically significant differences between the ICP and control groups regarding age, education or present body mass index. In this survey, the focus was on the heredity of ICP. The respondents were asked whether their mothers, sisters or daughters had ever suffered from liver dysfunction during their pregnancies.

The analyses were undertaken using the SPSS System for Windows, release 20.0. Statistical significance was tested by the chi-squared test. The associations between the prevalence of ICP among ICP mothers and their relatives were analyzed with logistic regression analyses (odds ratio with 95% confidence interval). Of sisters and daughters, only those who had delivered were included in the analysis.

Results

In the ICP group, 12.8% of mothers, 15.9% of sisters and 10.3% of daughters had ICP during pregnancy. In the control group, ICP was rare among close relatives. All the differences were statistically significant. In the logistic regression analysis the risk of own mother having had the same disorder was 9.2. The corresponding risk for sisters was 5.3 and for daughters 4.8 (Table 1).

Discussion

According to our findings ICP was relatively common among first-degree female relatives of women who had suffered from the disorder. It was especially common among sisters. Our findings thus support the notion of a genetic component being part of the ICP pathogenesis. The study population, which comprised diagnosed ICP cases and controls who had all delivered in Tampere University Hospital during two decades, was comprehensive. The two groups did not differ significantly with respect to age or educational level. The response rate (66.2%) can be regarded as high for a postal survey. ICP patients appeared to be aware of the ICP history of their relatives (4), and we believe this also pertains to our study population. An important weakness of the study, however, is that there is the risk the ICP women's mothers were not correctly diagnosed due to missing suitable laboratory tests.

Practically all pregnant women in Finland make use of the public maternity healthcare in health centers (12). It is probable that all ICP disorders during pregnancies will be found. We also consider the findings of this study to be applicable to the whole of Finland, as well as to other Nordic countries, where the population and incidence of ICP are similar to ours.

Our findings strengthen the earlier knowledge of the genetic component of ICP. Women with ICP are more likely to have a sister or mother with a history of the disorder. Likewise, their daughters bear a higher risk of suffering from ICP. To enable earlier detection and treatment of the condition, we recommend that all pregnant women in the health center maternity clinics should be asked about their family history regarding liver disorders.

Table 1. Appearance (%) and risk (OR with 95% CI) of liver dysfunction during pregnancy among first-degree relatives of ICP women and controls.

	ICP group % (n/N)	Controls % (n/N)	Difference		OR (95% CI)
			% Units	p-value	
Mothers	12.8 (27/211)	1.6 (8/511)	11.2	<0.001	9.2 (4.1–20.7)
Sisters*	15.9 (36/227)	3.1 (15/485)	12.8	<0.001	5.3 (3.7–7.6)
Daughters*	10.3 (15/145)	2.3 (8/343)	8.0	<0.001	4.8 (2.0–11.7)

N, total number of women; OR, odds ratio; CI, confidence intervals; ICP, intrahepatic cholestasis of pregnancy.
*Only those women who have delivered are included.

Funding

References

1. Hirvioja M-L, Kivinen S. Inheritance of intrahepatic cholestasis of pregnancy in one kindred. Clin Genet. 1993;43(6):315–7.

2. Berg B, Helm G, Petersohn L, Tryrding N. Cholestasis of pregnancy: clinical and laboratory studies. Acta Obst Gynecol Scand. 1986;65(2):107–13.

3. Savander M, Ropponen A, Avela K, Weerasekera N, Cormand B, Hirvioja ML, et al. Genetic evidence of heterogeneity in intrahepatic cholestasis of pregnancy. Gut. 2003;52(7):1025–9.

4. Eloranta M-J, Heinonen S, Mononen T, Saarikoski S. Risk of obstetric cholestasis in sisters of index patients. Clin Genet. 2001;60(1):42–5.

5. Reyes H, Ribalta J, Gonzales-Ceron M. Idiopathic cholestasis of pregnancy in a large kindred. Gut. 1976;17(9):709–13.

6. Holzbach RT, Sivac DA, Braun WE. Familial recurrent intrahepatic cholestasis of pregnancy: a genetic study providing evidence for transmission of a sex-limited, dominant trait. Gastroenterology. 1983;85(1):175–9.

7. Pauli-Magnus C, Lang T, Meier Y. Sequence analysis of bile salt export pump (ABCB11) and multidrug resistance p-glycoprotein 3 (ABCB4, MDR3) in patients with intrahepatic cholestasis of pregnancy. Pharmacogenetics. 2004;14(2):91–102.

8. Eloranta M-L, Häkli T, Hiltunen M, Helisalmi S, Punnonen K, Heinonen S. Association of single nucleotide polymorphisms of the bile salt export pump gene with intrahepatic cholestasis of pregnancy. Scand J Gastroenterol. 2003;38(6):648–52.

9. Müllenbach R, Bennett A, Tetlow N, Patel N. *ATP8B1* mutations in British cases with intrahepatic cholestasis of pregnancy. Gut. 2005;54(6):829–34.

10. Alsulyman OM, Ouzonian JG, Ames-Castro M, Goodwin TM. Intrahepatic cholestasis of pregnancy: perinatal outcome associated with expectant management. Am J Obstet Gynecol. 1996;175(4 Pt 1):957–60.

11. Turunen K, Mölsä A, Helander K, Sumanen M, Mattila KJ. Health history after intrahepatic cholestasis of pregnancy. Acta Obstet Gynecol Scand. 2012;91(6): 679–85.

12. Maternity and child health clinics. Ministry of Social Affairs and Health. Available online at: http://www.stm.fi/en/social_and_health_services/health_services/primary_health/maternity_clinics (accessed 26 May, 2013).

Contraception

Original research article

Unnecessary confusion about family planning after intrahepatic cholestasis of pregnancy[☆],[☆☆]

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Abstract

Background: As conceptions have changed regarding the suitability of oral contraceptives for women with a history of intrahepatic cholestasis of pregnancy (ICP), we studied whether the contraindications formerly in force had affected family planning decisions and mode of contraception among women with such a history.

Study Design: ICP women and their controls who gave birth in 1969–1988 in Tampere University Hospital, Finland, were sent a questionnaire in 2010. The inquiry covered items concerning contraception, deliveries, menstruation and sex life.

Results: ICP women had limited their number of children for health reasons more often than the controls. They also more often had a single child compared to the controls. The use of oral contraceptives was less common among ICP women. Deliveries were equally successful in both groups.

Conclusion: Physicians should provide sufficient and accurate information on ICP to the patients. Proper introduction of suitable contraception methods and successful communication with the patients would also reduce unnecessary problems and confusion regarding future family planning practices.

1. Introduction

Intrahepatic cholestasis of pregnancy (ICP) usually manifests in the third trimester as skin itching, especially on the palms and soles, and as an elevation of serum levels of bile acids and liver enzymes [1,2]. The incidence of ICP in Finland is 0.54%–1.5% of pregnancies [3–5], which is the same as that in Europe on average [2]. ICP may recur in 40%–50% of subsequent pregnancies [1,6]. In almost one fifth of cases, ICP is familial and, in such cases, recurs in 92 % of subsequent pregnancies [7].

ICP is thought to be the result of insufficient liver capacity to metabolize high amounts of placental hormones during pregnancy [1,6]. The ultimate cause of the condition remains unknown but is thought to be multifactorial: genetic, hormonal and environmental. The severity of ICP varies in subsequent pregnancies [1]. More severe cases occur in winter [1], and nutritional factors, for example, selenium deficiency, may have a role in the etiology [8–10].

ICP has no major physical consequences except for higher frequencies of cesarean sections and induction [5,11]. Itching may be intensive and disturbing but fades quickly postpartum. Some liver and biliary diseases seem to be more frequent among women with a history of ICP [12]. For the fetus, consequences may be more severe: ICP increases the risk of preterm birth [13], fetal distress during labor [3,13] and intrauterine death [3].

Oral contraceptives (OCs) were first introduced in the United States in 1960 and in Finland 2 years later [14,15]. The first-generation pills contained a 150-mcg estrogen component and 9.85 mg of progestogen, but by 1970, the

amount of estrogen was reduced to 50 mcg on account of reported thromboembolic cases [16]. In 1974, low-dose OCs (containing 20–35 mcg of estrogen) were released, also in Finland, and in the same year, the former high-dose pills were withdrawn from the market [16,17]. Progestin-only OCs were first available in Finland in 1971, and copper-releasing intrauterine devices (IUDs) became available in 1972 [17].

Sexual behavior became more liberal [18,19] and the use of different contraceptive methods changed rapidly during the 1970s and 1980s, partly due to the new contraceptives introduced [20]. Whereas, in the early 1970s, the most popular contraception methods in Finland were the condom, OCs and withdrawal, by the end of the 1980s, IUDs had become the method most used [20]. IUDs were the most popular method especially among married women, whereas younger women preferred OCs [20]. Since 1982, the pill has been gaining in popularity among all Finnish women [20,21].

Cholestatic states during use of OCs have been reported in women who have developed ICP [22–24]. As the incapacity of the liver to metabolize the increased load of estrogen during pregnancy has been held to be implicated in ICP pathogenesis, it is possible that, by the same mechanism, the OCs can cause cholestasis [1,25]. Hence, OCs have been contraindicated or at least not advocated for women with a history of ICP [25,26]. According to a French study in 1997, low-dose OCs can be prescribed to ICP women once their liver function test results have normalized since OCs did not cause pruritus or major rise in liver function tests for most ICP women [24]. Checkups including liver function tests and providing information about the risk of cholestasis are still recommended [2]. However, contradiction between different viewpoints still occurs.

As the use of estrogen-containing contraceptives was formerly contraindicated after an ICP pregnancy, we here studied the contraceptive practices of ICP women and any complications they might have experienced regarding their choices. We also sought to establish whether ICP had affected women's attitudes towards their sex life and the possible impact of this on their family planning practices.

2. Material and methods

The focus in this study was on women who had developed ICP when giving birth in Tampere University Hospital in the period 1969–1988. Altogether, 575 women were diagnosed [11] as having ICP during that period. We selected two controls for each of their deliveries (687) from the hospital's labor register, chronologically the previous and the next parturient without ICP. In the autumn of 2010, we conducted a postal inquiry among the ICP patients and the controls. Addresses were obtained from the Population Register Centre in Finland. We sent the questionnaire to 1779 women with one reminder and received 1178 acceptable responses. The flowchart of the study population is shown in Fig. 1.
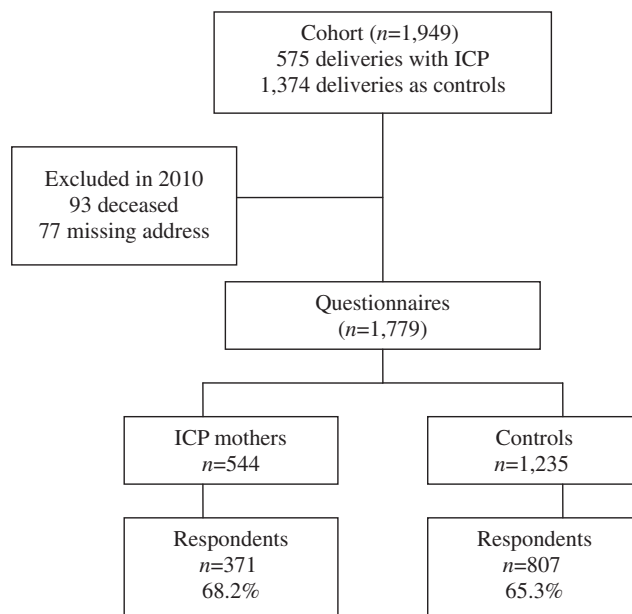

Fig. 1. Flowchart of the survey population.

For the demographic characteristics of the study population, we considered age, educational level and body mass index (BMI). Ages were expressed in full years on the last day of 2010. Education was described by two classes: high, referring to those with the matriculation examination (Finnish equivalent of UK A-levels), and low, indicating education below this. BMI was calculated from the reported weight (kg) and height (m) and then classified into three categories: normal ($BMI<25.0$), overweight (BMI 25.0–29.9) and obese ($BMI\geq30.0$).

The questionnaire consisted of 85 items covering the following main aspects: health in general, symptoms and complaints, diseases or conditions diagnosed by a doctor, health habits and gyneco-obstetric history. The questionnaire was identical for the ICP women and the controls. The participants did not know the exact reason (history of ICP) for being selected to this study.

The questions dealt with contraception, sexual health, pregnancies and menstruation. Respondents were asked whether they had used contraception and, if so, which method; they selected one or more of the 15 alternatives offered. We also inquired after problems concerning contraception: a disease or side effect which had prevented the use of OCs, injurious effects which had led to the removal of an IUD, rubber latex allergy, failure of the contraceptive method used, disagreement with partner over contraceptive method or any "other problems they might have encountered." The questionnaire included a list of possible adverse effects OCs may have caused: rise in liver function test levels, rise in blood pressure, weight gain, depression or other mental symptoms, reduced sexual drive, migraine, blood clot (referring to embolus or thrombosis), acne or "other." Respondents were also asked if they or their

partners had been sterilized and whether they had had a hysterectomy. They were also asked whether they had been told that they could not use OCs or hormonal treatment in the future on account of a liver problem and if they had had any type of disease or had experienced any symptom during pregnancy which prevented them from using hormones.

Pregnancy- and family-planning-related questions concerned the lifelong number of pregnancies (also twin or triplet pregnancies), deliveries and children alive, the number of miscarriages, abortions and cesarean sections. The number of deliveries was classified into three categories: one delivery, two deliveries and three or more deliveries. We also asked whether the respondents had limited their number of children for health reasons or had had specific problems during pregnancy (rise in blood pressure, proteinuria, itching with rise in liver function test results, rise in blood sugar, urinary tract infections or blood clots). To establish the menstrual history, we asked the age at menarche and, if relevant, menopause.

The questions related to sexuality and relationship encompassed the following: "How important is sex to you?" "How satisfied are you with your sex life?" and "How satisfied are you with your current domestic partnership/marriage/relationship?" There were seven categories on a Likert-type scale, with 1 indicating *not at all important/very dissatisfied* and 7 indicating *very important/very satisfied*. The categories were divided into two classes for purposes of analysis: important/satisfied (categories 5–7) and not important/dissatisfied (1–4).

The data were analyzed with SPSS 16.0 for Windows. The results are presented as frequencies. Statistical significance was tested by χ^2 test.

3. Results

There were no statistically significant differences between the ICP group and controls in any demographic variable (age, educational level and BMI) (Table 1).

3.1. Contraception

There was a statistically significant difference in the use of combined OCs, with ICP patients having used this mode less than the controls (52.0% vs. 62.9%, p<.001). Otherwise, the use of the various methods did not differ between the two groups. Compared with the controls, there was a trend to use more progestin-only pills among the ICP patients (20.8% vs. 16.1%, p=.052) (Table 2). Sterilizations were equally common in both groups (32.3% vs. 31.4%, p=.733).

In general, there were no notable differences in the number of contraceptive complications (40.8% vs. 36.6%, p=.174). Causes for complications, however, varied between the groups. The ICP patients had more often had a disease preventing the use of OCs, whereas the controls had disagreed with their partners over the method used more

Table 1
Characteristics of the respondents in the ICP and control groups

	ICP group (n=371)	Controls (n=807)	Difference	
	%	%	% Units	Significance p
Age (years)				.742
40–49	8.6	7.8	0.8	
50–59	45.3	48.9	−3.6	
60–69	42.0	39.0	3.0	
70–89	4.0	4.1	−0.1	
Education				.961
Low	67.0	67.2	−0.2	
High	33.0	32.8	0.2	
BMI (kg/m²)				.265
BMI<25.0	40.0	38.3	1.7	
BMI 25.0–29.9	33.7	38.4	−4.7	
BMI≥30.0	26.3	23.3	3.0	

often than the ICP women. Otherwise, frequencies of causes of problems were similar (Table 3).

The adverse effects of OCs are shown in Table 4. More subjects had elevated liver function tests than controls (31.1% vs. 5.7%, p<.001). Other adverse effects did not differ statistically significantly between the groups.

In the ICP group, 27.5% of the women had had a disease or a symptom during pregnancy which subsequently prevented the use of OCs. In the control group, the proportion was 2.2%, the difference being statistically significant (p<.001). The reported diseases and symptoms were almost merely rises in liver function tests or itching in the ICP group, whereas controls mentioned sporadic cases of hypertension, migraine, diabetes, preeclampsia, epilepsy and embolus. Of the ICP women, 40.7% as opposed to 2.2% of

Table 2
Contraceptive methods used by the ICP and control group women

	ICP patients n=371 %	Controls n=807 %	Difference % Units	Significance p
Progestin-only pill	20.8	16.1	4.7	.052
Condom	68.7	66.5	2.2	.457
Interrupted intercourse	16.2	15.1	1.1	.642
Copper-releasing IUD	61.5	60.5	1.0	.748
Contraceptive patch	1.1	0.4	0.7	.143
Spermicide	7.5	6.8	0.7	.648
Emergency contraception, IUD	0.0	0.1	−0.1	.498
Other contraception	0.5	0.7	−0.2	.692
Vaginal ring	0.0	0.2	−0.2	.337
Diaphragm	0.3	0.6	−0.3	.433
Subdermal contraceptive implant	1.1	1.9	−0.8	.323
Rhythm method	5.9	6.9	−1.0	.518
Emergency contraception, pills	0.8	2.1	−1.3	.109
Progestin-releasing IUD	26.4	28.9	−2.5	.383
Contraceptive pill	52.0	62.9	−10.9	<.001
No method used	4.9	5.3	−0.4	.732

Table 3
Problems with contraceptive methods in the ICP and control groups

	ICP patients	Controls	Difference	
	n=371	n=807	% Units	Significance
	%	%		p
Disease or symptom during pregnancy preventing later use of OCs	27.5	2.2	25.3	<.001
Disease or side effect preventing the use of OCs	26.1	11.5	14.6	<.001
Disagreement with partner over contraceptive method	0.3	1.6	−1.3	.048
Other problems	1.3	3.0	−1.7	.094
Failure of the method	11.3	13.5	−2.2	.297

the control group had been told that they could not use OCs due to their liver complication (p<.001).

3.2. Deliveries

Cesarean sections and multiple pregnancies occurred more often among the ICP patients, and the differences were significant. There were no specific differences between the groups in figures for abortions, miscarriages or ectopic pregnancies. The ICP women had limited their number of children for health reasons notably more frequently than the controls, the significance being less than .001 (Table 5). There was a statistically significant difference (p=.001) in the classified number of deliveries: compared with controls, ICP women had had fewer children. They had finished their families more often after just one child (Fig. 2).

3.3. Menstruation

There was a slight difference between the ICP women and the controls in age at menarche, but this was not statistically significant, nor was the difference in age at menopause. There were no differences in the number of hysterectomies between the two groups.

Table 4
Adverse effects of oral contraceptives in the ICP and control groups among those having used OCs

	ICP patients	Controls	Difference	
	n=193	n=508	% units	Significance
	%	%		p
Rise in liver function test results	31.1	5.7	25.4	<.001
Migraine	10.9	8.3	2.6	.280
Other problems	6.7	6.7	0.0	.984
Embolism	1.0	1.6	−0.6	.591
Depression or other changes in mood	15.0	16.3	−1.3	.672
Rise in blood pressure	3.1	4.7	−1.6	.345
Weight gain	26.4	28.0	−1.6	.686
Acne	0.5	2.4	−1.9	.106
Decrease in sexual desire	7.3	11.4	−4.1	.105

Table 5
Obstetric characteristics of the ICP and control group women

	ICP patients (n=371)	Controls (n=807)	Difference	
	%	%	% Units	Significance p
Restriction of number of children for health reasons	17.3	7.7	9.6	<.001
Cesarean sections	21.8	15.5	6.3	.008
Twin or triplet pregnancies	6.5	3.2	3.3	.010
Abortions	25.1	21.8	3.3	.216
Ectopic pregnancies	6.7	5.5	1.2	.383
Miscarriages	24.8	26.0	−1.2	.655

3.4. Sexuality and relationship

Significantly more ICP patients than controls considered sex not important, the difference being 7.6 percentage units (p=.022). There were no statistically significant differences in ratings of satisfaction with sex life and current relationship (p=.355 and p=.543).

4. Discussion

The results reveal the ICP patients to have limited the number of their children for health reasons more often than the controls. They also more often had just one child in their families.

ICP would appear to be the reason for not having more children. In fact, however, many previous studies have shown that ICP does not markedly affect the outcome of pregnancy [11] and that ICP should not be a contraindication for future pregnancies [26]. ICP does not automatically recur or be more severe in subsequent pregnancies, and the risks
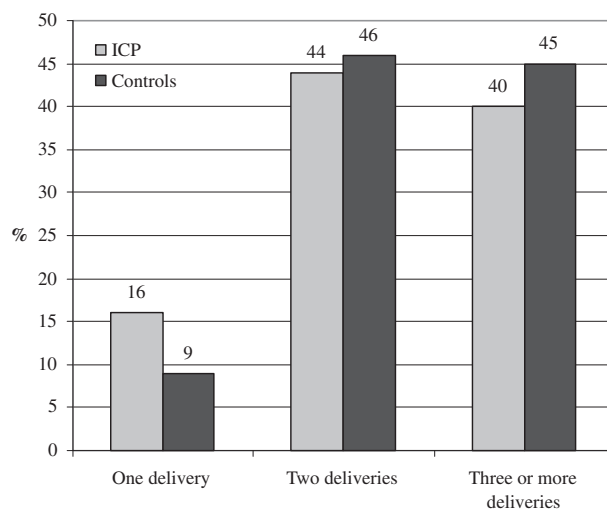

Fig. 2. Number of lifelong deliveries among the ICP and control group women (p value=.003).

for the fetus are minor in well-organized follow-up [5,11]. Our findings likewise show pregnancies to be equally successful in both groups; there were no significant differences in numbers of abortions, miscarriages and ectopic pregnancies. On the other hand, ICP was associated with an increased incidence of cesarean sections and inductions [5,11], which mothers may experience as frightening and uncomfortable situations. The symptoms of ICP can also be extremely disturbing, especially at night. The condition might have aroused uncertainty or fear for the baby's well-being, especially if communication with the doctor had been insufficient and details of ICP were not fully clear to the patient. Negative experiences of pregnancy and childbirth may diminish the desire to have more children.

In Finland, all women visit maternity clinics in primary health care several times during their pregnancies [27]. Liver function tests are taken if itching appears. If the tests are elevated, the mother will be referred to an obstetric clinic in secondary care for more detailed follow-up.

The body of data here was substantial (1178 respondents), and the response rate (66%) for the questionnaire was exceptionally good. The data can be regarded as a reliable and representative cross-section of Finnish women since all ICP patients giving birth in Tampere University Hospital in 1969–1988 were included and the number of controls was twice that of ICP cases.

The data were collected by a questionnaire which the participants filled in at home several years after the event. It is possible that some sections of the questionnaire were unclear, with the result that the respondents did not fully understand what was being inquired. It is also probable that a number of respondents were unable to remember particular details regarding matters arising several decades ago. Also, the conceptions, beliefs and assumptions of the participants may have affected their answers and rendered them medically imprecise. The respondents did not know they were selected to this study owing to their ICP history. Therefore, we do not know whether their answers concern the index pregnancy selected from the hospital's labor register or their other possible pregnancies. Hence, we have to consider the answers as a lifelong process.

Since the period covered in this study was fairly long, courses of action and guidelines for treatment may conceivably have differed from each other and from those currently applied, for example, in the diagnostics of ICP, the follow-up of pregnancy or the prescription of OCs.

The findings here show that oral contraceptives have raised liver function test results in women who have suffered from cholestasis of pregnancy. Some older studies have arrived at similar conclusions in the context of high-dose estrogen [22,23], but only a few have addressed the consequences of the low-estrogen-dose pills used today [24,28]. The majority of guidelines concerning the prescription of OCs are thus based on studies which are possibly outdated. It is probable that ICP women's liver values have been tested more often than the controls' because of their

background with cholestasis. This might have increased the number of elevated but harmless liver function test results. In Finland, according to the Evidence-Based Medicine Guidelines [29], an active hepatic disease is a contraindication for prescribing OCs. However, for some reason, a previous history of ICP has also been placed in the same category as active hepatic disease. Moreover, there are also discrepancies between textbooks of different specialties: according to one Finnish textbook of gynecology and obstetrics [30], OCs can be prescribed to women with an ICP history, while the textbook of hepatology [31] considers ICP a contraindication.

It emerged here that ICP patients had used OCs less than the controls, most likely because they had been told that a liver complication or symptom during pregnancy prevented their use. It is not certain whether they really had been told this or whether it was merely a conclusion they themselves had drawn, thus abandoning even a trial of the pills. It is possible that the pills caused more symptoms to the ICP women before the year 1974 when low-dose OCs were first introduced in Finland. This might have caused hesitation to provide OCs to ICP patients. Altogether, 48% of the ICP patients here had never tried OCs. This might explain the differences seen in disagreement with their partner over contraceptive method and appreciation of sex. Since the range of alternatives had been restricted for health reasons from ICP women, it may have been easier for the couples to settle for the remaining options. On the other hand, difficulties and frustration may have arisen about sex, as possibly the most desired option (OCs) had not been available, thus leading to undervaluation of sex.

Even though the OC users of the ICP group had had raised liver function tests, the respondents did not, however, report any serious complications. We hence agree with current international recommendations that women with a history of ICP can use OCs provided that their liver function tests are followed.

Doctors exert an influence on their patients, and even isolated random comments may leave a lasting impression and form a permanent notion for them. It would thus be extremely important for doctors in primary health care or those who otherwise take care of ICP patients to acquire adequate and especially accurate information regarding ICP and its consequences. It would also be important for them to pass on this information in a comprehensible way to ICP patients when consulting them about family planning and choices of contraception. Thus, unnecessary problems, confusion and restrictions to family size could be prevented.

5. Conclusions

It is probable that ICP women's liver values have been tested more often than the controls' because of their background with cholestasis. This might have increased the number of elevated but harmless liver function test results.

Even though the OC users of the ICP group had had raised liver function tests, the respondents did not, however,

report any serious complications. We hence agree with current international recommendations that women with a history of ICP can use OCs provided that their liver function tests are followed.

Acknowledgment

References

[1] Reyes H. Review: intrahepatic cholestasis. A puzzling disorder of pregnancy. J Gastroenterol Hepatol 1997;12:211–6.

[2] Bacq Y. Liver diseases unique to pregnancy: a 2010 update. Clin Res Hepatol Gastroenterol 2011;35:182–93.

[3] Laatikainen T, Tulenheimo A. Maternal serum bile acid levels and fetal distress in cholestasis of pregnancy. Int J Gynaecol Obstet 1984; 22:91–4.

[4] Berg B, Helm G, Petersohn L, Tryding N. Cholestasis of pregnancy. Clinical and laboratory studies. Acta Obstet Gynecol Scand 1986; 65:107–13.

[5] Heinonen S, Kirkinen P. Pregnancy outcome with intrahepatic cholestasis. Obstet Gynecol 1999;94:189–93.

[6] Trauner M, Boyer JL. Cholestatic syndromes. Curr Opin Gastroenterol 2002;18:314–29.

[7] Savander M, Ropponen A, Avela K, Weerasekera N, Cormand B, Hirvioja ML, et al. Genetic evidence of heterogeneity in intrahepatic cholestasis of pregnancy. Gut 2003;52:1025–9.

[8] Kauppila A, Korpela H, Makila UM, Yrjanheikki E. Low serum selenium concentration and glutathione peroxidase activity in intrahepatic cholestasis of pregnancy. Br Med J (Clin Res Ed) 1987; 17(294):150–2.

[9] Reyes H, Simon FR. Intrahepatic cholestasis of pregnancy: an estrogen-related disease. Semin Liver Dis 1993;13:289–301.

[10] Reyes H, Baez ME, Gonzalez MC, Hernandez I, Palma J, Ribalta J, et al. Selenium, zinc and copper plasma levels in intrahepatic cholestasis of pregnancy, in normal pregnancies and in healthy individuals, in Chile. J Hepatol 2000;32:542–9.

[11] Turunen K, Sumanen M, Haukilahti RL, Kirkinen P, Mattila K. Good pregnancy outcome despite intrahepatic cholestasis. Scand J Prim Health Care 2010;28:102–7.

[12] Ropponen A, Sund R, Riikonen S, Ylikorkala O, Aittomaki K. Intrahepatic cholestasis of pregnancy as an indicator of liver and biliary diseases: a population-based study. Hepatology 2006;43:723–8.

[13] Glantz A, Marschall HU, Mattsson LA. Intrahepatic cholestasis of pregnancy: relationships between bile acid levels and fetal complication rates. Hepatology 2004;40:467–74.

[14] Piper JM, Kennedy DL. Oral contraceptives in the United States: trends in content and potency. Int J Epidemiol 1987;16:215–21.

[15] Kosunen E. Adolescent reproductive health in Finland: oral contraception, pregancies and abortions from the 1980s to the 1990s. Academic dissertation. Acta Universitatis Tamperensis 1996.

[16] Mishell Jr DR. Oral contraception: past, present, and future perspectives. Int J Fertil 1991;36(Suppl 1):7–18.

[17] Hirvonen E, Idanpaan-Heikkila J. Cardiovascular death among women under 40 years of age using low-estrogen oral contraceptives and intrauterine devices in Finland from 1975 to 1984. Am J Obstet Gynecol 1990;163(1 Pt 2):281–4.

[18] Kontula O, Haavio-Mannila E. Finnish sex. Information about the change in Finnish sex life (Suomalainen seksi : tietoa suomalaisten sukupuolielämän muutoksesta); 1993 [In Finnish].

[19] United Nations. Adolescent reproductive behaviour. Evidence from developed countries. New York: United Nations; 1988.

[20] Makkonen K, Hemminki E. Different contraceptive practices: use of contraceptives in Finland and other Nordic countries in the 1970s and 1980s. Scand J Soc Med 1991;19:32–8.

[21] Kosunen E, Rimpelä M, Vikat A, Rimpelä A, Helakorpi S. Use of oral contraceptives in Finland in the 1990s. Finnish Medical Journal 1999;54:163–7.

[22] Kreek MJ, Sleisenger MH, Jeffries GH. Recurrent cholestatic jaundice of pregnancy with demonstrated estrogen sensitivity. Am J Med 1967; 43:795–803.

[23] Rannevik G, Jeppsson S, Kullander S. Effect of oral contraceptives on the liver in women with recurrent cholestasis (hepatosis) during previous pregnancies. J Obstet Gynaecol Br Commonw 1972;79:1128–36.

[24] Bacq Y, Sapey T, Brechot MC, Pierre F, Fignon A, Dubois F. Intrahepatic cholestasis of pregnancy: a French prospective study. Hepatology 1997;26:358–64.

[25] Connolly TJ, Zuckerman AL. Contraception in the patient with liver disease. Semin Perinatol 1998;22:178–82.

[26] Laatikainen T. Pregnancy, hormone therapy and the liver (Raskaus, hormonihoito ja maksa), 98. Duodecim; 1982, pp. 1470–7. [In Finnish].

[27] National Institute for Health and Welfare. Finland. Available at: , http://www.thl.fi/fi_FI/web/kasvunkumppanit-fi/palvelut/neuvolat/aitiysneuvola. Accessed February 24, 2012.

[28] Kascák P, Korbel' M. Hormonal contraception after intrahepatic cholestasis of pregnancy. [In Czech]. Ceska Gynekol 2011;76:374–8.

[29] Kunnamo I. Evidence-based medicine guidelines. Helsinki: Duodecim; cop; 2005.

[30] Ylikorkala O, Tapanainen J. Gynecology and obstetrics (Naistentaudit ja synnytykset). Helsinki: Duodecim; 2011 [In Finnish].

[31] Höckerstedt K, Aaltonen L. Gastroenterology and hepatology. (Gastroenterologia ja hepatologia). Helsinki: Duodecim; 2007 [In Finnish].

BRIEF REPORT

Menopause after a history of intrahepatic cholestasis of pregnancy

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Abstract

Objective: Intrahepatic cholestasis of pregnancy is a hormone-provoked disorder that fades quickly after parturition. The aim of this study was to establish whether a history of intrahepatic cholestasis of pregnancy reduces the use of hormone therapy for menopausal symptoms and, irrespective of hormone therapy, whether intrahepatic cholestasis is associated with other health aspects after menopause.

Methods: In 2010, questionnaires were sent to a cohort of women who delivered in Tampere University Hospital, Finland, from 1969 to 1988. The study population comprised postmenopausal women with a history of intrahepatic cholestasis of pregnancy (n = 189) and their controls (n = 416). The main outcome measures were the use of hormone therapy and other means of alleviating menopausal symptoms, and the diseases the women reported.

Results: There were no differences in the use of hormone therapy between the two groups. Of the diseases reported, breast cancer, hepatobiliary diseases, and hypothyroidism were more frequent among women with a history of intrahepatic cholestasis of pregnancy, whereas cardiac arrhythmia was less frequent. With respect to other diseases, there were no differences.

Conclusions: A history of intrahepatic cholestasis of pregnancy does not reduce the use of hormone therapy. However, when physicians prescribe hormone therapy for these women, a history of intrahepatic cholestasis of pregnancy calls for attention in view of its association with gallstones.

Key Words: Intrahepatic cholestasis of pregnancy – Hormone therapy – Menopause – Breast cancer – Gallstones – Hypothyroidism.

W hen a pregnant woman in her third trimester complains of itching on otherwise healthy skin, laboratory tests to detect intrahepatic cholestasis of pregnancy (ICP) are indicated. The incidence of ICP is 1% of pregnancies.[1] ICP is a minor complaint among mothers that abates quickly after parturition but calls for alterations in obstetric management because of fetal risks,[2,3] which result in increased induction of labor and cesarean section in these women.[4,5] With respect to the subsequent health of women with a history of ICP, our recent study showed higher frequencies of reported breast cancer, hypothyroidism, and hepatobiliary diseases, and lower frequencies of hypertension, elevated cholesterol level, and cardiac arrhythmia.[6]

ICP is familial in 16% of cases,[7] and pedigree structures show dominant inheritance. Different gene expression profiles may contribute to the complex pathogenesis of ICP.[8] It is possible that this condition, coinciding with the intense hormonal activity of pregnancy, might predispose women to changes in liver metabolism and to variations in hormonal changes, hormone-linked symptoms and diseases, or hormonal interventions.

Research has been performed to assess the risk-to-benefit ratio of hormone therapy (HT) in alleviating menopausal symptoms and in preventing or postponing certain diseases. Women with a history of ICP have previously been advised not to use hormonal medications. However, oral or transdermal HT does not affect the levels of hyaluronic acid and other liver markers in women with a history of ICP.[9]

After menopause, the risks for osteoporosis and osteoporotic fractures increase; it has been estimated that up to half of women develop a bone fracture during their postmenopausal life.[10] Estrogen increases bone mineral density, especially in older women, even at very low doses.[11] The Women's Health Initiative reported a decreased risk of bone fractures with estrogen or estrogen-progestin treatment.[12] Among postmenopausal women, small elevations in C-reactive protein—within the range not indicative of infection—predict cardiovascular risk.[13] Oral or transdermal HT does not affect C-reactive protein levels either in the presence or in the absence of ICP.[14] Some early evidence indicated that HT reduces the risk of

coronary heart disease events when started on healthy women within a few years of menopause,[15] but new research on these women is warranted. Estrogen use for less than 5 years is associated with a reduced risk of breast cancer, whereas estrogen use for 5 years or more leads to four to six extra breast cancers for every 10,000 woman-years.[16] Estrogen combined with progestin increases the risk of breast cancer even when used for less than 5 years.[17]

An episode of intrahepatic cholestasis in 1969-1988 reduced women's later use of hormonal contraception.[18] Our aim here was to test the hypothesis that a history of ICP reduces the use of HT for menopausal symptoms and—irrespective of HT—influences other health aspects after menopause.

METHODS

The basic study population comprised 575 women with ICP and 1,374 controls who all delivered in Tampere University Hospital, Finland, between 1969 and 1988.[6] The women with a diagnosis of ICP were selected from the hospital discharge register. The diagnosis was verified from patient records—with the main symptom being itching—together with at least one elevated liver test value. The parturient previous to and the parturient following each index woman in the delivery ward diary were chosen as controls. A postal survey was conducted in 2010. Questionnaires were sent to 544 women with ICP and 1,235 controls. Research approval was obtained from the Ethics Committee of the Pirkanmaa Hospital District (R02149).

Women in the ICP and control groups received similar questionnaires. They were asked for their age at menarche and their last period indicating menopause. The questions "Have you ever had any disease or symptom during pregnancy that has prevented you from using hormones (such as oral contraceptive pills, other hormonal medication, menopausal hormone therapy)?" and "Have you ever been told that because of a liver problem you cannot use oral contraceptive pills or be treated with hormonal medication?" were conceived to explore any problems regarding the use of contraception and HT.

A panel of 24 common symptoms and complaints was presented, and the question read as follows: "In the past 12 months, have you been bothered by any of the following symptoms or complaints?" Here, only those which might have been relevant to menopause or postmenopause are discussed. Furthermore, questions regarding HT read: "Have you ever used hormone therapy?" and "Do you currently use hormone therapy?" Tibolone use was later queried using a separate question. Respondents were also asked to indicate any alternative nonhormone medications or other methods they had used in managing menopausal symptoms. The question concerning diseases was "Has a doctor ever told you that you have or have had any of the following diseases or conditions?" Respondents were asked to tick boxes on a panel of 45 diseases and conditions, and to report any wrist, hip, and vertebral column fractures they had experienced. Of these conditions, breast cancer, cardiovascular diseases, osteoporosis, and hepatobiliary diseases were most relevant to menopause and a history of ICP.

Statistical analyses were performed using the SPSS System for Windows, release 20.0. Results are presented as frequencies, percentages, means, and medians. Statistical significance was tested with χ^2 test.

RESULTS

Acceptable responses to the questionnaire survey (with one reminder) were received from a total of 1,178 women, with the response rate being 66.2% (68.2% among women with ICP and 65.3% among control women). The two groups did not differ statistically significantly in age, education, or present body mass index. The study population, in keeping with the whole Finnish population in 1969-1988, was extremely homogeneous in ethnicity. The postmenopausal study population comprised 189 women with a history of ICP and 416 control women who had all reported that their menstruation had ceased naturally because of menopause. Age at menarche and age at menopause did not separate the ICP and control groups. The mean and median ages at menarche were 13 years in both groups. When menstruation ceased, the mean ages were 51.4 versus 51.5 years, and the median age was 52 years in both groups.

More women with a history of ICP than women without a history of ICP reported obstacles or prohibitions with respect to hormone use. Of the total respondents, 23.2% of the ICP group and 1.9% of the control group reported having had a disease or symptom during pregnancy that prevented them from using hormones, with the difference being statistically significant ($P < 0.001$). In the ICP group, 31% of those women who had been told not to use hormones had used HT, whereas 51% of those who did not report a denial of hormones had used HT. The difference was statistically significant ($P = 0.021$).

Altogether, 37.8% of the ICP group and 2.7% of the control group reported having been told not to use oral contraceptive pills or not to be treated with HT because of a liver problem ($P < 0.001$). Despite preconditions, however, there were no statistically significant differences in HT use between the groups. Among women with ICP and controls, 46.6% and 43.3% ($P = 0.450$), respectively, reported having used HT at some time (Table 1), whereas current use of HT was reported by 30.7% versus 34.4% ($P = 0.540$). All those who reported having used tibolone also reported having used HT, and tibolone use did not differ between the groups. HT was the most common means for alleviating menopausal symptoms. One of seven respondents had used health food store or similar products, but none of the nonhormonal methods brought out differences between the groups (Table 1).

The prevalences of common symptoms and complaints during the past 12 months, as well as diseases or conditions confirmed by a doctor as reported by the respondents, are presented in Table 2. There were no statistically significant between-group differences in the frequencies of recently experienced symptoms and complaints.

TABLE 1. *Use of hormone therapy, other medications, or treatments to alleviate menopausal symptoms in the ICP (n = 189) and control (n = 416) groups*

	ICP group (%)	Control group (%)	Difference % Units	P
Hormone therapy	46.6	43.3	3.3	0.450
Sleeping pills	6.9	5.3	1.6	0.438
Other medications and/or methods	8.5	7.7	0.8	0.744
Sedatives	1.1	0.7	0.4	0.671
Vitamins	6.9	7.0	−0.1	0.967
Health food store or similar products	15.3	15.6	−0.3	0.930
Medicine for heart arrhythmia and palpitations	1.1	3.4	−2.3	0.101
Antidepressants	1.6	4.1	−2.5	0.111

ICP, intrahepatic cholestasis of pregnancy.

Breast cancer was reported by 14 women (7.4%) in the ICP group and 8 women (1.9%) in the control group, with the difference being statistically significant (*P* = 0.001; Table 2). Among breast cancer patients, 7 of 14 in the ICP group and 3 of 8 in the control group had at some time used HT. Acute myocardial infarction was reported by no one in the ICP group and by eight women (2.0%) in the control group, with the difference, however, being not statistically significant (*P* = 0.054). Cardiac arrhythmia diagnosed by a doctor was less common in the ICP group than in the control group, but high cholesterol or blood pressure medication prescribed by a doctor showed no marked differences between the groups. Hepatobiliary and thyroid gland diseases showed increased frequencies among women with ICP. There were no differences in the occurrences of asthma, diabetes, gastrointestinal diseases, or rheumatoid arthritis. Likewise, the frequencies of osteoporosis or bone fractures (wrist, hip, or vertebral column) showed no statistically significant differences between the groups. Moreover, no woman reported having had a fracture of the vertebral column.

DISCUSSION

Our hypothesis that a history of ICP reduced women's use of HT was not confirmed. On the other hand, ICP was reflected in women's postmenopausal life, with a higher occurrence of breast cancer. Cardiac arrhythmia was more common in the control group than in the ICP group; however, with respect to other diseases or conditions and recent symptoms or complaints, there were no differences between the groups.

The original study population was comprehensive, including all verified ICP cases in Tampere University Hospital from 1969 to 1988, and the ICP and control groups did not differ significantly with respect to age, body mass index, or educational level. For a postal survey, the 66% response rate

TABLE 2. *Symptoms, complaints, and diseases of postmenopausal respondents in the ICP (n = 189) and control (n = 416) groups*

	ICP group (%)	Control group (%)	Difference % Units	P
Symptoms and complaints in the past 12 mo				
Vaginal and vulvar dryness	40.2	33.2	7.0	0.093
Chest pain	13.2	9.1	4.1	0.127
Blushing	21.2	19.7	1.5	0.680
Headache	33.9	32.7	1.2	0.777
Insomnia	38.6	37.5	1.1	0.792
Heart palpitations	27.5	27.9	−0.4	0.925
Nervousness	18.5	19.7	−1.2	0.731
Sweating	45.0	46.2	−1.2	0.787
Urinary problems	14.3	16.3	−2.0	0.519
Depression	13.2	16.1	−2.9	0.361
Current or past diseases of respondents (according to the doctor)				
Gallstones	39.2	12.0	27.2	<0.001
Rise in liver function test (except during pregnancy)	14.8	7.9	6.9	0.009
Hypothyroidism	15.9	9.9	6.0	0.033
Goiter	9.5	3.8	5.7	0.005
Breast cancer	7.4	1.9	5.5	0.001
Chronic choledochitis	6.3	1.2	5.1	<0.001
Bone fractures	11.1	9.1	2.0	0.448
Angina pectoris	4.2	3.4	0.8	0.597
Osteoporosis	4.8	6.5	−1.7	0.405
Myocardial infarction	0.0	1.9	−1.9	0.055
Cardiac arrhythmia	14.3	21.2	−6.9	0.046

ICP, intrahepatic cholestasis of pregnancy.

can be considered high. Thus, the data can be regarded as reliable, and the results can be considered generalizable.

Our questionnaire survey produced information with a focus on the respondents' own experience. It is conceivable that some of the answers may be objectively wrong, as they may have been derived from misremembered details, misunderstandings, or wrong interpretations, but this pertains to both the ICP group and the control group.

A higher occurrence of breast cancer among women with ICP in our study is a new finding. The association between ICP, HT, and breast cancer cannot be established based solely on our data because of the small number of breast cancer patients who used HT. A conspicuous weakness in our study was that we could not present the length of use of estrogen, progesterone, and/or tibolone. Future research will establish whether a history of ICP should be considered a contraindication for HT use in view of an increased risk of breast cancer. One explanation for the higher breast cancer occurrence among women with ICP might be that, compared with controls, they have fewer children,[18] which is a known risk factor for breast cancer.[19] In the short run, gene research of ICP may explain the genetics behind the pathophysiology of ICP and breast cancer.

According to previous research, hypothyroidism is associated with gallstones.[20] ICP is associated with a higher occurrence of hypothyroidism and hepatobiliary diseases such as gallstones.[6] Our study confirms prior findings. Caution is thus warranted in prescribing estrogen therapy for women with a history of ICP because estrogen is causally associated with gallbladder disease, and women with asymptomatic gallstones should not receive estrogens in view of the risk of cholecystitis.[21,22]

In this cohort, a history of ICP did not reduce the use of HT, which has probably been important for the quality of life of these women. The number of women who reported having been advised against the use of contraceptive hormones or HT because of a liver problem was higher than the number of women who reported having been told not to use hormones because of a liver problem during pregnancy. One explanation for this might lie in testing: Up to the 1990s, a few months after the introduction of oral contraceptive use, aminotransferases were commonly tested in Finnish health center family planning offices. We suggest that slight rises in aminotransferase values may have prevented hormone use unnecessarily. We cannot tell whether gallstones were diagnosed before or during HT. It is thus possible that, in some cases, HT has turned asymptomatic gallstones into symptomatic ones and even complicated them.

CONCLUSIONS

A history of ICP does not reduce the use of HT. However, a history of ICP calls for attention when physicians prescribe HT because ICP is associated with a higher occurrence of gallstones. Further research is needed before any conclusions can be drawn regarding associations between HT and an elevated breast cancer risk among women with a history of ICP.

REFERENCES

1. Lammert F, Marschall HU, Glantz A, Matern S. Intrahepatic cholestasis of pregnancy: molecular pathogenesis, diagnosis and management. *J Hepatol* 2000;33:1012-1021.
2. Laatikainen T, Tulenheimo A. Maternal serum bile acid levels and fetal distress in cholestasis of pregnancy. *Int J Gynaecol Obstet* 1984; 22:91-94.
3. Glantz A, Marschall HU, Mattsson LA. Intrahepatic cholestasis of pregnancy: relationships between bile acid levels and fetal complication rates. *Hepatology* 2004;40:467-474.
4. Heinonen S, Kirkinen P. Pregnancy outcome with intrahepatic cholestasis. *Obstet Gynecol* 1999;94:189-193.
5. Turunen K, Sumanen M, Haukilahti RL, Kirkinen P, Mattila K. Good pregnancy outcome despite intrahepatic cholestasis. *Scand J Prim Health Care* 2010;28:102-107.
6. Turunen K, Mölsä A, Helander K, Sumanen M, Mattila KJ. Health history after intrahepatic cholestasis of pregnancy. *Acta Obstet Gynecol Scand* 2012;9:679-685.
7. Savander M, Ropponen A, Avela K, et al. Genetic evidence of heterogeneity in intrahepatic cholestasis of pregnancy. *Gut* 2003;52:1025-1029.
8. Floreani A, Caroli D, Lazzari R, et al. Intrahepatic cholestasis of pregnancy: new insights into its pathogenesis. *J Matern Fetal Neonatal Med* 2013;26:1410-1415.
9. Tuomikoski P, Aittomäki K, Mikkola TS, et al. Effect of oral and transdermal hormone therapy on hyaluronic acid in women with and without a history of intrahepatic cholestasis of pregnancy. *Am J Obstet Gynecol* 2008;198:375.e1-375.e5.
10. Gallagher JC, Levine JP. Preventing osteoporosis in symptomatic postmenopausal women. *Menopause* 2011;18:109-118.
11. Prestwood KM, Kenny AM, Kleppinger A, Kulldorff M. Ultra low-dose micronized 17β-estradiol and bone density in older women: a randomized controlled trial. *JAMA* 2003;290:1042-1048.
12. Cauley JA, Robbins J, Chen Z, et al. Effects of estrogen plus progestin on risk of fracture and bone mineral density: the Women's Health Initiative randomized trial. *JAMA* 2003;290:1729-1738.
13. Ridker PM, Hennekens CH, Buring JE, Rifai N. C-reactive protein and other markers of inflammation in the prediction of cardiovascular disease in women. *N Engl J Med* 2000;342:836-843.
14. Ropponen A, Aittomäki K, Tikkanen MJ, Ylikorkala O. Levels of serum C-reactive protein during oral and transdermal estradiol in postmenopausal women with and without a history of intrahepatic cholestasis of pregnancy. *J Clin Endocrinol Metab* 2005;90:142-146.
15. Harman SM, Vittinghoff E, Brinton EA, et al. Timing and duration of menopausal hormone treatment may affect cardiovascular outcomes. *Am J Med* 2011;124:199-205.
16. Lyytinen H, Pukkala E, Ylikorkala O. Breast cancer risk in postmenopausal women using estrogen-only therapy. *Obstet Gynecol* 2006;108: 1354-1360.
17. Lyytinen H, Pukkala E, Ylikorkala O. Breast cancer risk in postmenopausal women using estradiol-progestogen therapy. *Obstet Gynecol* 2009;113:65-73.
18. Mölsä A, Turunen K, Mattila KJ, Sumanen M. Unnecessary confusion about family planning after intrahepatic cholestasis of pregnancy. *Contraception* 2012;86:639-644.
19. DiSaia PJ, Creasman WT. Breast diseases. In: DiSaia PJ, Creasman WT, eds. *Clinical Gynecologic Oncology*, 6th ed. St Louis, MO: Mosby, 2002: 399-402.
20. Laukkarinen J, Kiudelis G, Lempinen M, et al. Increased prevalence of subclinical hypothyroidism in common bile duct stone patients. *J Clin Endocrinol Metab* 2007;92:4260-4264.
21. Hart AR, Luben R, Welch A, Bingham S, Khaw KT. Hormone replacement therapy and symptomatic gallstones—a prospective population study in the EPIC-Norfolk cohort. *Digestion* 2008;77:4-9.
22. Dhiman RK, Chawla YK. Is there a link between oestrogen therapy and gallbladder disease? *Expert Opin Drug Saf* 2006;5:117-129.