Mother's intrahepatic cholestasis does not affect her daughter's health^{*}

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ABSTRACT

Objective: To establish whether a mother's intrahepatic cholestasis of pregnancy (ICP) has connections to her daughter's health. Design: A retrospective study of daughters to ICP mothers. Setting: The region of Tampere University Hospital in Finland. Subjects: The study population comprised 575 women diagnosed with ICP during at least one pregnancy in the obstetric department of Tampere University Hospital in the period 1969-1988, and two controls chosen for each. Questionnaires were sent to these women and to their daughters: 305 daughters to ICP mothers and 642 to controls in autumn 2010. Eventually 187 daughters to ICP mothers responded (61.3%) and 373 to controls (58.1%). Main Outcome Measures: Evaluated health, symptoms and complaints, diagnosed diseases, mental health and use of medicines. Results: Only minor differences were detected between the two groups regarding the majority of items inquired. The only prominent difference between daughters to ICP mothers and those to controls concerned epilepsy, which was significantly more frequent among ICP mothers' daughters, the prevalence being fourfold (3.2% vs 0.8%, p = 0.033). Conclusion: A mother's ICP does not generally affect her daughter's health. This can be considered an encouraging new finding for mothers with ICP in primary health care.

Keywords: Intrahepatic Cholestasis of Pregnancy; Inheritance; Epilepsy; Maternity Clinics; Primary Health Care

1. INTRODUCTION

Intrahepatic cholestasis of pregnancy (ICP) is a liver disorder which usually manifests in the third trimester of gestation as skin itching especially on the palms and soles and as increased serum bile acids and transaminases [1]. Shortly after delivery the itching attenuates and abnormal laboratory values normalize, but the disease nonetheless recurs in future pregnancies in about 40% - 60% of patients [2]. The incidence of ICP varies geographically; in Finland and in Europe in general the figure is approximately 1% of pregnancies [3].

The ultimate cause of ICP remains unknown but the condition appears to be related to increased sex hormone synthesis and metabolism during pregnancy [1,4]. In addition to this hormonal component there would also appear to be heritable and environmental factors [5-7]. ICP is more common in multiple pregnancies [8] and with a positive family history [9]. Advanced maternal age has been identified as a risk factor [10]. Selenium deficiency may be implicated in the pathogenesis of ICP [11].

ICP has no significant maternal effects during pregnancy (albeit itching can be intensive), but may have severe consequences for the fetus, including fetal distress, premature deliveries and intrauterine fetal death [1,12]. Active management such as early delivery by induced labor at 37 - 38 weeks gestation has been commonly recommended to prevent especially intrauterine fetal death [13]. Although delivery often occurs at earlier weeks of gestation, the newborns' Apgar scores are only slightly lower than normally [14].

In the Nordic countries, maternity care is organized in primary health care [15]. Serum aminotransferase levels are routinely measured for early detection of ICP if a pregnant woman has experienced itching, has a history of ICP or in cases of a multiple pregnancy [9]. In Finnish maternity care ICP is generally detected and appropri-

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ately managed, being thus only a minor risk for mothers and their children, good pregnancy outcome normally being attained [14].

A positive correlation has been discovered between the severity of ICP and fetal complication rates; when maternal serum bile acids exceed 40 µmol/L, the incidence of fetal complications begins to increase significantly [16]. Currently the best pharmacologic treatment for the condition seems to be ursodeoxycholic acid (UDCA) [17]. In severe ICP, treatment with UDCA improves all biochemical markers of cholestasis in the mother, itching included. Dexamethasone is also sometimes used. However, it remains unknown whether fetal complications could be reduced by pharmacologic treatment.

Approximately one out of six ICP patients has a positive family history, and in such cases the levels of serum transaminases are higher than in sporadic cases and the recurrence rate in subsequent pregnancies is 92% [9]. In addition, the widely varying prevalence of ICP between different countries and ethnic groups [3,13] indicates a genetic basis for the disease.

ICP would appear to have some long-term effects on women's health. There is an increased occurrence of a number of liver, biliary and pancreatic diseases among women with a history of ICP [18]. In addition, a higher frequency of breast cancer and hypothyreosis has recently been discovered [19]. Conversely, the frequency of hypertension, high cholesterol and cardiac arrhythmia is lower.

It has been proposed that the dominant mode of inheritance of ICP is either autosomal or X-chromosome-linked [20-22]. Several different cholestatic genes are evidently associated with the pathogenesis [23-25]. In view of the genetic predisposition to the disease, the aim of this study was to investigate whether a mother's ICP has connections to her daughter's health.

2. MATERIAL AND METHODS

To assess the health history of women who had suffered from ICP, a postal survey was conducted among ICP patients and control women in autumn 2010. The cohort comprised 575 women who had been diagnosed with ICP during at least one pregnancy in the obstetric department of Tampere University Hospital in the period 1969-1988, and two control women chosen for each [19].

At the same time, a slightly different questionnaire was sent to the daughters of these women. Postal addresses were obtained from the Population Register Centre in Finland. After excluding 11 stillborn and seven deceased daughters as well as 60 whose addresses could not be obtained, the questionnaire was sent to 947 daughters (305 to ICP and 642 to control mothers' daughters); 187 daughters to ICP mothers (61.3%) and 373 to controls (58.1%) responded (**Figure 1**).

While categorizing the respondents' age, 30 years was set as a cut-off point. Education was classified as "high" for those who had taken the matricular examination (gymnasium/grammar school) and "low" for those who had not. Concerning respondents' BMI, 25 kg/m² was set as a cut-off point. With respect to age, educational level and body mass index (BMI) the two groups were comparable (**Table 1**).

The two groups received identical questionnaires. The questionnaire comprised 65 items and the main aspects pertinent to this study were present health, symptoms and complaints, diseases diagnosed by a doctor, use of medicines and mental health.

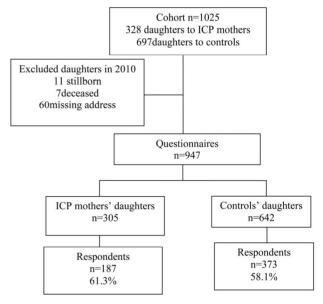


Figure 1. Flow chart of the survey population.

Table 1. Characteristics of daughters to ICP mothers and to controls.

	ICP group n = 187	Controls $n = 373$	Dif	ference
_	%	%	% units	Significance (p-value)
Age (years)				0.196
<30	48.7	42.9	5.8	
≥30	51.3	57.1	-5.8	
Education				0.136
Low	28.6	34.9	-6.3	
High	71.4	65.1	6.3	
Body Mass Index				0.431
BMI < 25.0	61.7	58.2	3.5	
BMI ≥ 25.0	38.3	41.8	-3.5	

Respondents were asked to evaluate their current health by choosing one of the following alternatives: good, fairly good, moderate, fairly poor and poor [19]. They were also asked whether any of 24 common symptoms or complaints had bothered them during the past year. Further, they were asked whether a doctor had ever diagnosed any of the diseases listed in the questionnaire, including gastrointestinal, endocrinological, urological, gynecological, oncological, bone- and articulation-related, respiratory and cardiovascular diseases. A few separate disorders were also listed, for example migraine, epilepsy and anemia. Respondents were further asked whether they had ever undergone any major medical surgery, and a history of hip, wrist and vertebral fractures was inquired after.

Respondents' mental health was estimated by two mental health-related questions and the Depression Scale. The two questions were devised to establish whether a respondent had ever suffered from a mental disorder and been treated for a mental disorder. The Depression Scale

is a validated Finnish test screening for the risk of present clinical depression [26].

Use of medicines, natural health drugs as well as vitamins and trace elements during the last 12 months were inquired after. Three options were given for the mode of use: non-use, occasional use and regular use.

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

3. RESULTS

The two groups did not differ in respect of respondents' own evaluation of their current health status. Of ICP mothers' daughters 87.1% and of controls' daughters 86.0% assessed their health as good or fairly good. Symptoms and complaints are shown in **Table 2** and diagnosed diseases in **Table 3**.

There were only minor differences between the two

Table 2. Symptoms and complaints during the past 12 months among daughters to ICP mothers and to controls.

	ICP mothers' daughters n = 187	Controls' daughters n = 373		Difference	
	%	%	% units	Significance (p-value)	
Arthralgia, joint pain	21.9	16.1	5.8	0.090	
Recurring stomach problems	26.2	22.3	3.9	0.299	
Dizziness	26.2	22.8	3.4	0.372	
Dyspnea	13.9	10.5	3.4	0.230	
Heart palpitation	19.3	16.1	3.2	0.349	
Vaginal and vulvar dryness	18.2	15.0	3.2	0.336	
Headache	53.5	50.7	2.8	0.531	
Nervousness	25.7	23.1	2.6	0.494	
Nausea	19.3	16.9	2.4	0.490	
Foot and/or leg swelling	16.0	13.9	2.1	0.507	
Depression	19.3	17.4	1.9	0.596	
Urinary problems	10.7	8.8	1.9	0.481	
Backache	44.9	43.2	1.7	0.693	
Dysmenorrhea	32.6	31.6	1.0	0.814	
Coughing	34.2	33.5	0.7	0.866	
General itching of skin	24.6	23.9	0.7	0.847	
Neck and shoulder pain	61.0	60.9	0.1	0.981	
Rheumatic pains	3.7	4.3	-0.6	0.759	
Itching of palms and soles	9.6	10.7	-1.1	0.688	
Dryness of eyes and mouth	11.8	13.1	-1.3	0.645	
Blushing	15.0	17.4	-2.4	0.462	
Chest pain	5.9	8.3	-2.4	0.303	
Sweating	19.3	22.0	-2.7	0.455	
Insomnia	25.1	28.4	-3.3	0.411	

Table 3. Diseases diagnosed by a doctor among daughters to ICP mothers and to controls.

	ICP mothers' Controls' daughters (n = 187) daughters (n = 373)) I	Difference	
	%	%	% units	Significance (p-value)	
Diseases of the digestive system					
Cholelithiasis	4.8	3.2	1.6	0.349	
Rise in liver function test results (except during pregnancy)	7.5	5.9	1.6	0.470	
Acute hepatitis	1.6	0.8	0.8	0.386	
Chronic choledochitis	1.1	0.3	0.8	0.220	
Fatty liver	1.6	0.8	0.8	0.386	
Helicobacter pylori infection	1.1	0.5	0.6	0.480	
Gastric catarrh, gastric or duodenal ulcer	6.4	5.9	0.5	0.808	
Crohn's disease	0.5	0.3	0.2	0.618	
Chronic hepatitis	0.5	0.5	0.0	0.998	
Pancreatitis	0.0	0.0	0.0	-	
Liver cirrhosis	0.0	0.3	-0.3	0.479	
Celiac disease	0.5	1.6	-1.1	0.281	
Colitis ulcerosa	0.0	1.1	-1.1	0.155	
Endocrine and metabolic diseases					
Hypothyreosis	5.3	3.8	1.5	0.380	
Goiter	1.6	0.5	1.1	0.205	
Diabetes on medication	2.1	2.1	0.0	0.996	
Hyperthyreosis	2.1	2.1	0.0	0.996	
Diabetes on diet therapy	3.2	4.0	-0.8	0.633	
Gynecological diseases					
Polycystic ovary syndrome (PCOS)	7.0	4.3	2.7	0.180	
Breast cancer	0.0	0.0	0.0	-	
Gynecologic cancers	0.0	0.5	-0.5	0.316	
Endometriosis	2.1	4.6	-2.5	0.155	
Diseases of the respiratory system					
Asthma	12.8	9.9	2.9	0.296	
Diseases of the circulatory system					
High blood pressure on medication	3.7	2.7	1.0	0.490	
Pulmonary embolus	0.5	0.0	0.5	0.157	
Cardiac failure	0.0	0.3	-0.3	0.479	
High cholesterol on medication	1.1	1.9	-0.8	0.474	
Cardiac arrhythmia	4.8	7.2	-2.4	0.270	
Other diseases					
Migraine	25.7	21.4	4.3	0.262	
Epilepsy	3.2	0.8	2.4	0.033	
Any other than breast or gynegologic cancer	1.1	0.3	0.8	0.220	
Anemia (except during pregnancy)	9.6	10.5	-0.9	0.759	

groups. Chronic choledochitis, cholelithiasis, rise in liver function test results (other than during pregnancy), acute hepatitis and fatty liver were all more common among daughters to ICP mothers. Hypothyreosis and goiter were likewise more frequent among ICP mothers' daughters. Polycystic ovary syndrome was more frequent among ICP mothers' daughters, whereas endometriosis was less frequent. Cancers other than breast or gynecologic were more common among daughters to ICP mothers than among the controls' daughters. None of these differences were statistically significant. Concerning bone fractures, mental health, medication allergies and use of medicines there were no differences between the two groups, either.

A prominent difference between daughters of ICP mothers and those of controls concerned epilepsy, which was significantly more frequent among ICP mothers' daughters, the prevalence being fourfold (3.2% vs 0.8%, p = 0.033).

4. DISCUSSION

There were only minor differences between the two groups regarding most of the survey questions. The main finding was a higher frequency of epilepsy among daughters to ICP mothers, the difference being fourfold.

Postal addresses were found for the majority of the study population. Response rates did not differ markedly between the groups (61.3% and 58.1%) and they were relatively high for a postal survey. Data were collected by a questionnaire to be filled in at home. As most of the respondents were relatively young, a better response rate might have been achieved by an online survey.

Since we only studied daughters we cannot generalize the findings to apply also to the sons of ICP mothers. However, the majority of the diseases observed in this study were not gender-dependent. Antenatal corticosteroids are sometimes administered in ICP [17], and also to women expected to deliver preterm because they reduce the newborn's respiratory and cardiac problems [27]. However, corticosteroids have increased the risk of epilepsy especially among male infants. Neuro-sensory development seems to be more sensitive to external factors in the fetal life of boys than of girls.

Although higher frequencies of several liver, biliary and pancreatic diseases, breast cancer and hypothyreosis have been discovered among women with a history of ICP, this was not the case regarding their daughters. However, by reason of the considerable age difference between mothers and daughters at the time of the postal survey, the two groups cannot be compared with each other as to the incidence of the above-mentioned conditions. On the other hand, at least hypothyreosis often emerges at a relatively young age.

It may be speculated that epilepsy can be the result of fetal distress or premature delivery, though there are contradictory study results concerning such a hypothesis. Recently it has been noted that very premature birth and perinatal distress have associations with epilepsy [28] and that preterm infants have higher rates of seizures than full-term infants [29]. Conversely, it has been also claimed that low birth weight and fetal distress do not cause epilepsy [30].

To our knowledge this is the first study to explore the association between mothers' ICP and their daughters' health in later life. Based on our findings a mother's ICP will not affect her daughter's health. It has recently been reported that women with a history of ICP have, in most cases unnecessarily, limited their number of children for health reasons more often than women without ICP, and they also more often have a single child compared to controls [31].

Pregnancy follow-up and screening ICP takes place at maternity clinics in primary health care. Based on the findings here, our conclusion is that healthcare professionals can reassure mothers with ICP that the condition does not generally have any long-term adverse effects on their daughters' health in later life.

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