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

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Conflicts of interest

None

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ABSTRACT

Introduction: Intrahepatic cholestasis of pregnancy (ICP) is a reversible liver disorder occurring during pregnancy. It has a typical genetic background with known genetic mutations and can be considered as an expression of this genetic predisposition. The objective of this study was to determine whether ICP is associated with specific long-term co-morbidity. **Material and methods:** The study population comprised 571 women with ICP in at least one pregnancy who were compared with 1333 pregnant women without ICP during the years 1969-1988 at Tampere University Hospital, Finland. The cohort's follow-up time was 44 years. All ICD-10 classification discharge diagnoses were examined for the women in the ICP group from 1998 to 2013 and ICD-10 diagnoses from outpatient care from 1969 to 2013. **Results:** At least one disease of the digestive system had been diagnosed in 50.4% (288/571) of the ICP mothers compared with 34.4% (459/1333) of the reference group ($p<0.001$). In a more detailed analysis women with a history ofICP had an increased risk for cholelithiasis and/or cholecystitis (odds ratio (OR) 2.88, 95% confidence interval (Cl) 2.17 to 3.84), diseases of the pancreas (OR 2.26, 95% CI 1.20 to 4.27), and hypothyroidism (OR 2.38, 95% CI 1.27 to 4.46) compared with the reference group. Arterial diseases were less common in the ICP mothers compared to the reference group (OR 0.38, 95% CI 0.15 to 0.99). Regarding other diseases, there were no statistically significant differences between the ICP mothers and reference group. **Conclusions:** Half of the women with a history ofICP have been diagnosed with at least one disease of the digestive system compared with a third in the reference group. The risk of cholelithiasis, cholecystitis, diseases of the pancreas and hypothyroidism is increased compared with the reference group. These are important facts when counselling women after a pregnancy with ICP. Also, this is of importance for the general practitioners and other physicians who take care of these women.

Keywords:
intrahepatic cholestasis of pregnancy, co-morbidity, hypothyroidism, diseases of the pancreas, diseases of the digestive system, cholelithiasis, cholecystitis, women's health issues

Abbreviations:
ICP, intrahepatic cholestasis of pregnancy
OR odds ratio
CI confidence interval

Key Message:
The study investigates the cohort's long-term co-morbidity over a 44-year follow-up. Hypothyroidism and diseases of the digestive system were found to be associated with cholestasis of pregnancy. The cohort and the controls had no other significant differences in co-morbidity.

INTRODUCTION

Intrahepatic cholestasis of pregnancy (ICP) is a liver disorder during pregnancy. The incidence of ICP varies geographically from 0.2% to 2%, being the most common in South America and northern Europe (1). It typically manifests at the late second or third trimester of the pregnancy. The diagnosis requires itching as a symptom and elevated liver enzymes and/or increased bile acids when measured in maternal serum. The diagnosis ofICP is by exclusion, when no other explanation is found for maternal symptoms and the elevated liver enzymes and/or bile acids. ICP mothers' deliveries are more likely to be complicated, with preterm delivery, fetal distress, and intrauterine fetal death (1). The biochemical abnormalities and itching resolve quickly after delivery (2).

Non-alcoholic cirrhosis with liver fibrosis, hepatitis C and nonspecific hepatitis are more common in ICP mothers than they are in controls from the Finnish population. The same is true for cholelithiasis and cholecystitis, biliary system disorders and non-alcoholic pancreatitis (3). In the study by Ropponen and colleagues the follow-up time started from the first ICP pregnancy. It has been observed that ICP is associated with later diabetes, psoriasis, inflammatory polyarthropathies and thyroid disease (4). An association between ICP and self-

repmied hypothyroidism and hepatobiliary diseases has been found (5). Self-reported breast cancer was higher in women with ICP compared to controls (5) but this association was not found in a registry-based study (6). In our study, the cohort was the same as reported in the studies by Turunen (2012) and Hamalainen (2017) (5,6).

ICP is associated with an increased risk for preeclampsia and gestational diabetes (7), both of which are risk factors for cardiovascular disease later in life (8,9). In a questionnaire study, women with a history ofICP reported less cardiac arrhythmia than the reference group, as well as high cholesterol and high blood pressure requiring medication (5).
Genetic predisposition, immune response, gestational hormones, and environmental factors are suggested to influence ICP's pathogenesis (2). The hepatic phospholipid transporter (MDR3/ABCB4), the aminophospholipid transpmier (ATP8Bl/FIC1), and the bile salt export pump (BSEP/ABCB11) have been found to include mutations in patients with ICP (2).

The development ofICP can be considered an expression of this genetic predisposition but what triggers the disease, other than pregnancy itself, is unknown. The aim of this study is to investigate whether ICP is associated with a specific co-morbidity later in life, by tracking ICD-10 diagnostic codes from medical records from hospitals and out-patient clinics.

MATERIAL AND METHODS

The cohort comprised all ICP pregnancies from the medical records of Tampere University Hospital (TUH) during the years 1969-1988. Diagnosis codes were used to identify patients with ICP in the hospital discharge registry. ICD-8 disease classification system was used at TUH from 1969 to 1986, and because ICD-8 did not include a precise code for ICP, we checked all the obstetric codes that might contain ICP: 637.9 Toxicosis NUD, 639.00 Pruritus, 639.01 Icterus gravis, 639.09 Necrosis acuta et subacuta hepatis, and 639.98 Aliae definitae. Thereafter, we checked the handwritten diagnosis behind the code, and if it referred to ICP, we included the case for further selection. ICD-9 disease classification system was used at TUH between 1987 and 1988, and it contained the appropriate codes: 6467A Hepatosis gravidarum and 6467X Hepatopathia alia. ICD-10 disease classification system has been used from the year 1996. The diagnosis was verified in each patient record by the presence of the main symptom of itching and abnormal laboratory test results. At least one of the following was required: ASAT >35 U/1, ALAT >40 U/1, or bile acids 2':6 μmol/1(10).

The study population comprised 687 ICP deliveries and 1374 women without ICP which served as a control group. The data included some women with separated ICP deliveries during the years 1969-1988, and each of these women was studied as an individual case, hence the rep· group contained a total of 575 women. None of the controls was twice as a control and none of the women was in both groups. The previous and following subjects in the maternity ward diary were taken as controls for each ICP case, so initially there were twice as many controls as ICP women. None of the controls had been diagnosed with ICP. There were no other exclusion criterions. In a questionnaire study with the same cohort the groups were comparable in terms of age, educational level, and body mass index (5). The groups did not differ regarding mean age at the time of delivery (28.0 years in the ICP group and 27.6 in the reference group). Four women from the ICP cases and 41 from the references were ruled out because of missing personal identity codes. The final cohort comprised 571 women with ICP and 1333 controls. The analyses were made comparing these two groups, not in a case-control manner.

The diagnoses were gathered from the Finnish Hospital Discharge Register. Everyone in Finland who has been admitted to specialized inpatient care, undergone outpatient surgery, or visited specialized outpatient care is included in the statistics (11). The data contain all the cohort's hospital discharge diagnoses from 1969 to 2013, including diagnoses made in specialized outpatient care from 1998 to 2013. The data from the Finnish Hospital Discharge Register included the diagnosis according to ICD-8 during the years 1969-1986 and ICD-9 during the years 1987-1995. ICD-10 classification system has been used from the year 1996 (12).

Statistical Analyses

The data were analysed using the SPSS for Windows, Version 23.0. The results are presented as frequencies and percentages. Statistical significance was tested with the chi-squared test, and p-values <0.05 are considered statistically significant. Binary logistic regression was used to achieve odds ratios (OR) and 95% confidence intervals (CI), with the dependent variable being 'ICP or not'.

Ethical approval

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

RESULTS

Diseases of the digestive system (K00-K99, ICP not included) were diagnosed in half of the ICP mothers (50.4%) and in a third of the control group (34.4%) ($p<0.001$). For the occurrence of other diagnoses as classified by the ICD-10 classification groups, there was not a statistically significant difference between ICP women and controls. Common diagnoses for both ICP mothers and the control group were from the genitourinary system (51.0% and 51.5%), the musculoskeletal system (47.6% and 43.6%) and the cardiovascular system (44.0% vs 40.7%). Neoplasia had occurred in 41.5% of the ICP mothers and 36.9% of the women in the control group. **(Table 1)**

When taking a closer look at individual diagnoses from the ICD- IO classification groups a statistically significant difference was found in the occurrence of thyroid (7.0% vs 4.6%; $p=0.03$) disorders among ICP women and controls. Arterial diseases were more common in controls (0.9% vs 2.3%; $p=0.04$; OR 0.38, 95% CI 0.15 to 0.99). Regarding occurrence of other disease groups there were no differences. **(Table 2).**

The occurrence of different thyroid diseases in the ICP mothers and references are presented in **Table 3.** Hypothyroidism was diagnosed in 3.5% (n=20) of the ICP mothers and in 1.5% (n=20) of the references (OR 2.38, 95% CI 1.27 to 4.46). Five of the ICP mothers and none of the control group had two different diagnoses among the disorders of thyroid gland: of the ICP mothers, three had been diagnosed with hypothyroidism and thyrotoxicosis and two with hypothyroidism and goiter.

Hepatobiliary diseases (ICP not included) were diagnosed in 35.2% (n=201) of the ICP mothers and in 11.6% (n=155) of the references ($p<0.001$). Diseases of the digestive system other than hepatobiliary diseases were diagnosed in 28.4% (n=162) of the ICP mothers and in

27.5% (n=366) of the reference group (p=0.68). **Table 4** shows that cholelithiasis and/or cholecystitis (OR 2.88, 95% CI 2.17 to 3.84) and diseases of the pancreas (OR 2.26, 95% CI 1.20 to 4.27) were found significantly more often in the ICP mothers than in the reference group. Five hepatitis cases were diagnosed in the cohort up to 2013, and two of them being hepatitis C.

DISCUSSION

Hepatobiliary diseases were overrepresented in women with a history ofICP. Moreover, there was a higher occurrence of thyroid gland diseases in the mothers with ICP, especially goiter and hypothyroidism. In contrast, the occurrence of arterial diseases was lower in the ICP group. Cholelithiasis and/or cholecystitis and diseases of the pancreas were more common in the ICP mothers than in the reference group. Regarding other disease groups, there were no statistically significant differences between the ICP mothers and controls. Genitourinary, musculoskeletal and cardiovascular diseases were the most common diseases among both groups.

The strength of our study is the extensive cohort including all ICP cases diagnosed at TUH from 1969 to 1988. Another strength of the study is the long follow-up time of 44 years. In addition, our data include all diagnoses made in specialized health care. The Finnish Hospital Discharge Register is one of the oldest national hospital discharge registers in the world. The completeness and accuracy of the register seem to vary from satisfactory to very good (13). The data can thus be considered reliable and valid.

The weakness of our study is that the data do not contain diagnoses made in primary health care. Hypothyroidism, asthma, and high blood pressure, for example, are usually followed-up and treated in primary healthcare in Finland. We do not have records of parity for either the ICP group or the reference group. A few of the women may have had a delivery even before 1969, when the follow-up started. Our aim in this study was to compare morbidity between women with ICP and the reference group, and we did not analyze the time from ICP to the diagnosis of a hypothyroid condition. In futiher studies, the period from ICP to the diagnosis of various diseases might be of great interest. The threshold values of laboratory tests for ICP diagnosis were lower in 1969-1988 than at present. Nevertheless, the ICP diagnosis was

made at TUH according to the custom of the time and the diagnosis can be regarded as adequate. The upper limit of normal bile acids can be reduced to between 6 and 10 μmol/1 in fasted women although many studies use an upper limit of normal between 10 and 14 μmol/1 (2). In our study, the results can be considered similar, even though the diagnostic criterion for ICP was a bile acid concentration ?.6 μmol/1 instead of?.l O μmol/1.

The diagnoses were extrapolated to ICD-10 as in a previous Swedish study (4). More accurate analyses were made with diagnosis codes that had not been used in previous ICP studies. If the code in ICD-8 or -9 was less accurate than in ICD-10, the diagnostic classification was made by the superior code heading. The possibility of misdiagnosis may be considered low.

A population-based study observed a diagnosis of cardiovascular diseases more often in women with ICP than in the controls (4). In the aforementioned study, the occurrence of cardiovascular diseases in the ICP group was nearly 11%, which is lower than in our study. In a questionnaire study on the same cohort, cardiac arrhythmia, high cholesterol, and high blood pressure requiring medication were reported less frequently in the ICP group (5). Furthermore, in the present study there was a lower incidence of arterial diseases in the ICP group than in the reference group. The same population-based study did not find any difference regarding arterial diseases between women with ICP and their controls (4). The older age of our cohort might explain why the differences were found in the present study.

The association between ICP and the increased risk for hepatobiliary diseases is well known (3,5,14). In our study, over half of the women with a history ofICP had been diagnosed with diseases of the digestive system, which is significantly greater compared to the diagnosis rate in the reference women. The risk for cholecystitis and cholelithiasis in women with ICP was remarkably higher than it was in the references. The findings are in agreement with previous research.

Diseases of the pancreas were more common in the ICP group compared to the reference group. Prior to this study, non-alcoholic pancreatitis was found to be more common in ICP patients than in controls (3). Our study found an increased risk for cholecystitis and cholelithiasis in the ICP mothers. Patients with pancreatitis may also have cholecystitis, and it

is plausible that only one of the diagnoses had been noted down in the medical records. However, the records of women with ICP presumably have the same weakness as the records of the references.

Hypothyroidism was more commonly diagnosed in the women with ICP than in the reference group. It is commonly noted that autoimmune pathogenesis has a remarkable effect on hypothyroidism (15). It can be speculated that there might also be an autoimmune aspect in the pathogenesis ofICP. However, it should be noted that there might be overdiagnosis of hypothyroidism but this can be regarded similar in both groups (16).

To cross-validate our results, we repeated the study using the patient records of our cohort members from the Finnish Cancer Registry. Slightly more of the ICP mothers were diagnosed with breast cancers compared to the controls. (6). However, such a difference between the groups was not found in the present study. The explanation for the difference between these two studies might be that the Cancer Registry data (6) had a longer follow-up time.

ICP has been linked with various genetic mutations, and the genetic background has an effect on the pathogenesis of ICP (2). Although differences regarding the co-morbidity in the ICP and the reference groups were found, the explanation might be the genetic predisposition rather than the history of ICP itself. The shared risk factors, such as mutations in particular genes, might influence the pathogenesis ofICP and also other diseases of the digestive system. Both ICP and gallstone diseases are associated with the ABCB4 gene (17-19).

CONCLUSION

Half of the women with a history ofICP have been diagnosed with at least one disease of the digestive system compared with a third in the reference group. The risk of cholelithiasis, cholecystitis, diseases of the pancreas and hypothyroidism was increased compared with the reference group. These are imp01iant facts when counselling women after a pregnancy with ICP. Also, this is of impo1iance for the general practitioners and other physicians who take care of these women.

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Table 1. The incidence(%) of specific ICD 10 disease groups in the intrahepatic cholestasis of pregnancy (ICP) women and the control group.

	ICD-lOcode	ICP N=571		Controls N=l333		Difference	
		n	%	n	%	% units	p-value
Diseases of the digestive system (ICP not included)	K00-K99	288	50.4	459	34.4	16.0	**<0.001**
Neoplasms	C00-D48	237	41.5	492	36.9	4.6	0.06
Diseases of the musculoskeletal system and connective tissue	M0O-M99	272	47.6	581	43.6	4.0	0.10
Diseases of the cardiovascular system	IO0-I99	251	44.0	542	40.7	3.3	0.18
Endocrine, nutritional, and metabolic diseases	E00-E90	103	18.0	215	16.1	1.9	0.31
Diseases of the nervous system and sense organs	G00-H95	232	40.6	526	39.5	1.1	0.63
Symptoms, signs, and abnormal clinical and laboratory findings not elsewhere classified	R00-R99	294	51.5	682	51.2	0.3	0.90
Diseases of the genitourinary system	N00-N99	291	51.0	687	51.5	-0.5	0.82
Diseases of the blood and blood-forming organs and certain disorders involving the immune mechanism	D50-D89	15	2.6	43	3.2	-0.6	0.49
Diseases of the respiratory system	JO0-J99	146	25.6	356	26.7	-1.1	0.61
Infectious and parasitic diseases	A00-B99	62	10.9	164	12.3	-1.4	0.37
Mental and behavioral disorders	F00-F99	89	15.6	228	17.1	-1.5	0.42
Injury, poisoning, and certain other consequences of external causes	S00-T98	203	35.6	497	37.3	-1.7	0.47

Congenital malformations, deformations, and chromosomal abnormalities	Q00-Q99	13	2.3	54	4.1	-1.8	0.05
Diseases of the skin and subcutaneous tissues	L00-L99	80	14.0	221	16.6	-2.6	0.16

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

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

	ICD-10 code	**ICP N=571**		**Controls N=l333**		**Difference**	
		n	%	**n**	%	% **units**	*p*-**value**
Neoplasms							
Breast cancer	C50	36	6.3	66	5.0	1.3	0.30
Liver and biliary tract cancer	C22-C24	0	0.0	0	0.0	0.0	
Malignant diseases other than the aforementioned	C00-D48	216	37.8	458	34.4	3.4	0.15
Diseases of the thyroid gland	E00-E07	40	7.0	61	4.6	2.4	**0.03**
Immune-mediated diseases							
Diabetes mellitus	E10-E14	34	6.0	97	7.3	-1.3	0.30
Sarcoidosis	D86	2	0.4	5	0.4	0.0	0.94
Crohn's	K50	3	0.5	5	0.4	0.1	0.64
Ulcerative colitis	K51	6	1.1	10	0.8	0.3	0.51
Celiac disease	K90.0	6	1.1	13	1.0	0.1	0.88
Inflammatory polyarthropathies	M05-M09	20	3.5	46	3.5	0.0	0.96
Systemic connective tissue disorders	M32	1	0.2	3	0.2	0.0	0.83
Asthma	*145*	28	4.9	72	5.4	-0.5	0.66
Psoriasis	140	8	1.4	27	2.0	-0.6	0.35
Cardiovascular diseases							
Hype1iensive disease	110-115	67	11.7	178	13.4	-1.7	0.33

Coronary heart disease	121-125	27	4.7	65	4.9	-0.2	0.89
Pulmonary heart disease	126	8	1.4	18	1.4	0.0	0.93
Cerebrovascular disease	127-28 G4S	22	3.9	56	4.2	-0.3	0.73
Arterial diseases	170-179	5	0.9	30	2.3	-1.4	**0.04**
Pregnancy-associated diseases							
Preeclampsia	014.0-014.2	23	4.0	72	5.4	-1.4	0.21
Gestational diabetes	024.4	9	1.6	24	1.8	-0.2	0.73

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

Table 3. Risk (OR with 95% CI) for at least one disease of the thyroid gland in the intrahepatic cholestasis of pregnancy (ICP) mothers and the control group.

Disease of the thyroid gland	**ICD-10 code**		**n**	%	**OR**	**95%CI**
Thyroiditis	E06	Controls	4	0.3		
		ICP	3	0.5	1.76	0.39---7.87
Goiter	E0l.0-E0l.2 E04	Controls	22	1.7		
		ICP	17	3.0	0.55	0.29---1.04
Thyrotoxicosis	E05	Controls	14	1.1		
		ICP	4	0.7	1.51	0.49---4.60
Hypothyroidism	E0I.8 E02-E03	Controls	20	1.5		
		ICP	20	3.5	**2.38**	1.27-4.46
Other disorders of the thyroid gland	E00-E07 (excluding the aforementioned)	Controls	1	0.1		
		ICP	0	0.0	-	

* Five of the ICP mothers and none of the controls had two different diagnoses among diseases of the thyroid gland.

Table 4. Risk (OR with 95% CI) for at least one mentioned hepatobiliary disease or disease of the pancreas in the intrahepatic cholestasis of pregnancy (ICP) mothers and the control group.

Hepatobiliary disease	**ICD-10**		**n**	%	**OR**	**95%CI**
Cholecystitis and/or cholelithiasis	K80-K81	Controls	106	8.0		
		ICP	114	20.0	**2.88**	2.17-3.84
Diseases of the pancreas	K85-K86	Controls	20	1.5		
		ICP	19	3.3	**2.26**	1.20-4.27
Cirrhosis of the liver	K.70.2 K.76.1 K.70.3 P78.8 K.71.7 K.74	Controls	8	0.6		
		ICP	7	1.2	2.06	0.74-5.70