Research Article

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Intrahepatic cholestasis of pregnancy and cancer, immune-mediated and cardiovascular diseases: A population-based cohort study

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Background & Aims: Intrahepatic cholestasis of pregnancy (ICP) is the most common liver disease in pregnancy. It is associated with hepatobiliary diseases that might predispose to cancer and also with gestational diabetes and preeclampsia. In this study, we examined associations between ICP and cancer, and immune-mediated and cardiovascular diseases.

Methods: By linking the Swedish Medical Birth Register and the Swedish Patient Register, we identified 11,388 women with ICP and 113,893 matched women without ICP who gave birth between 1973 and 2009. Diagnoses of cancer and immune-mediated and cardiovascular diseases both before and after delivery were obtained from the Patient Register. The main outcome measures were hazard ratios (HRs), calculated through Cox regression, for the indicated diseases after delivery.

Results: ICP was not associated with later overall cancer (HR 1.07, 95% confidence interval [CI] 0.94–1.21), but it was associated with later liver and biliary tree cancer (HR 3.61, 95% CI 1.68–7.77, and 2.62, 95% CI 1.26–5.46, respectively). ICP was also associated with later immune-mediated diseases (HR 1.28, 95% CI 1.19–1.38), and specifically diabetes mellitus (HR 1.47, 95% CI 1.26–1.72), thyroid disease (HR 1.30, 95% CI 1.14–1.47), psoriasis (HR 1.27, 95% CI 1.07–1.51), inflammatory polyarthropathies (HR 1.32, 95% CI 1.11–1.58) and Crohn's disease (HR 1.55, 95% CI 1.14–2.10), but not ulcerative colitis (HR 1.21, 95% CI 0.93–1.58). Women with ICP also had a small increased risk of later cardiovascular disease (HR 1.12, 95% CI 1.06–1.19).

Conclusions: Women with ICP have increased risk of later hepatobiliary cancer and immune-mediated and cardiovascular diseases.

Introduction

Intrahepatic cholestasis of pregnancy (ICP) is the most common liver disease during pregnancy [1] with reported prevalence rates between 0.4% and 1.5% [2,3]. Genetic predisposition, gestational hormones and environmental factors have been implicated in its pathogenesis [2,3]. ICP is characterized by otherwise unexplained pruritus with elevated bile acids and/or transaminases in the late second and third trimester of pregnancy [2,3]. The fetuses of mothers with ICP are at increased risk of adverse outcomes, in particular preterm delivery [4,5] or even stillbirth in the case of severe ICP [6]. Women with ICP have a substantially increased risk of hepatobiliary diseases, such as hepatitis C, cirrhosis and gallstones, both before and after ICP diagnosis [7,8]. In addition, ICP is associated with a 3-fold increased risk of gestational diabetes and preeclampsia [3,5,9], both of which are considered to be cardiovascular risk conditions [10–13]. However, it is not known whether women with ICP are at increased risk of hepatobiliary cancer and immune-mediated and cardiovascular diseases after delivery.

Here, we perform a population-based study to investigate the association between ICP and later cancer, diabetes mellitus and other autoimmune-mediated diseases, and cardiovascular diseases.

Patients and methods

Data sources, statistical analyses and demographics of the current population have previously been described in detail [8]. In brief, we linked data from the Swedish Medical Birth Register on women with first and consecutive births between 1973 and 2009 with data from the Swedish Patient Register. We matched each woman with ICP to 10 women without ICP based on maternal age and calendar year of delivery, and ensured that each woman could only appear once in the ICP group and once in the control group. Table 1 lists the ICD 7-10 codes used to identify cancer and immune-mediated, cardiovascular (including stroke), and pregnancy-specific (ICP, gestational diabetes and preeclampsia) diseases in the Patient Register and Medical Birth Register between

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Abbreviations: ICP, intrahepatic cholestasis of pregnancy; HR, hazard ratio; CI, confidence interval; ICD, International Classification of Disease.

Table 1. International classification of diseases (ICD) codes used to identify malignant, immune-mediated, cardiovascular and pregnancy-associated diseases between 1964 and 2010.

	ICD-7	ICD-8	ICD-9	ICD-10
Malignant diseases				
Liver cancer	155	155	155	C22
Biliary tree cancer		156	156	C23-C24
Lung cancer	162	162-I63	162-I63	C34
	163.9			
Colon cancer	153	153	153	C18
Rectum cancer	154	154	154	C19-C21
Breast cancer	170.9	174	174	C50
Uterus cancer	171-172	180-182	179-180 182	C54-C55
Ovary cancer	175	183	183-184	C56
Immune-mediated diseases				
Sarcoidosis	138.00-10	135	135	D86
Thyroid	252.00 252.01 252.02	242.00 242.09 244	242A 242X 244X	E03.5 E03.9 E05.0
	253.10 253.19 253.20	245.03	245C 245W	E05.5 E05.9 E06.3
	253.29 254.00			E06.5
Diabetes mellitus	260	250	250	E10 E11
Crohn's	572.00 572.09	563.00 563.98 563.99	555	K50
Ulcerative colitis	572.20 572.21	563.10 569.02	556	K51
	572.30 578.03			
Celiac disease	286	269	579A	K90.0
Psoriasis	706 724.03	696.00-19	696A-B	L40
Inflammatory polyarthropathies	722	712	714 720	M05-09
Systemic connective tissue disorders	456.2	734.1	710.A	M32
Cardiovascular diseases				
Arterial hypertension	440-447	400-404	401-405	I10-115
Coronary heart disease	420	410-414	410-414	I21-I25
Pulmonary heart disease	434	426	415	I26
Cerebrovascular disease	330	430	416-417 430	I27-I28 G45
	331-334	431-438	431-438	I60-I68
Artery diseases	450-456	440-448	440-448	I70-I79
Pregnancy-associated diseases				
Intrahepatic cholestasis of pregnancy		639.00 639.01 639.09	6467A 6467X	O26.6
Preeclampsia	642.20-642.30	637.03-637.04	624.4-642.7	O14.0-O14.2
Gestational diabetes			648.8	O24.4
Thrombosis in pregnancy	682.1	671.01	671D	O22.3 O22.5
		673.02	671E	O87.1 O87.3 O87.8
Lung embolism in pregnancy	684.99	673.98	673C	O88.2

1964 and 2010 (i.e. before and at least one year after delivery). The diagnosis of ICP in Sweden is based on otherwise unexplained pruritus, increased bile acid and/or liver enzymes. Six to twelve weeks after delivery, all mothers are seen by a midwife and specifically asked if any complaints experienced during pregnancy remain. Mothers with persisting pruritus will undergo liver function tests; if liver enzymes are elevated, the mother will be referred to a hepatologist for further evaluation. The local ethics review board at Karolinska Institutet approved this study (Dnr 2008/1182-31/4 and 2011/1860-32).

Statistical analysis

The primary objective of the study was to estimate the relative risk (hazard ratio, HR) of developing cancer, diabetes mellitus and other immune-mediated conditions and cardiovascular disease after ICP. Time to first respective disease diagnosis was analyzed using a stratified Cox proportional hazards model where each woman with ICP was compared separately with her matched controls before a summary estimate was calculated. The observation time was censored at the date of migration, date of death, or end of study (December 31, 2010), unless a positive event had occurred. In the separate analyses of the three endpoints; cancer, immune-mediated disease and cardiovascular disease, women with the specific condition before the pregnancy with ICP (and their individual controls) were excluded. Thus, the numbers of subjects included in the analyses differ to some extent. The proportionality assumption was tested using scaled Schoenfeld residuals with time since ICP diagnosis (or corresponding birth in matched controls) as the principal time scale. In this article, we report HRs with 95% confidence intervals (CI) adjusted for the mother's country of birth, body mass index (BMI) and smoking. In addition, sensitivity analyses regarding the confounding effect of a time-updated diagnosis of hepatitis C on liver cancer as well as the effect of a time-updated diagnosis of gallstone disease or cholangitis on biliary tree cancer were performed using stratified Cox proportional hazards models.

Results

The study cohort consisted of 125,281 women of whom 11,388 were diagnosed with ICP. Women with ICP and their matched