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RAPID COMMUNICATION

Perinatal events and the risk of developing primary sclerosing cholangitis

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Abstract

AIM: To investigate whether perinatal events, intrauterine or postpartum, are associated with the development of primary sclerosing cholangitis (PSC) later in life.

METHODS: Birth records from 97 patients with adult PSC in Sweden were reviewed. Information on perinatal events including medications and complications during pregnancy, gestation length, birth weight and length were collected. Two control children of the same sex were selected for each subject. Conditional multiple logistic regression was used to assess associations of the perinatal measures with development of PSC.

RESULTS: No significant associations were found between gestational age, birth length, breastfeeding, and the majority of medical complications including infections or medication during pregnancy for the mothers or postpartum for the children. Vaginal bleeding and peripheral oedema showed associations with PSC, with matched odds ratios of 5.70 (95% CI, 1.13-28.83) and 2.28 (95% CI, 1.04-5.03), respectively.

CONCLUSION: The associations of vaginal bleeding and oedema with subsequent PSC cannot readily be explained, so our findings do not strongly support the hypothesis of a significant role of perinatal events as a risk for the development of PSC later in life.

Key words: Inflammatory bowel disease; Perinatal factors; Sclerosing cholangitis

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INTRODUCTION

Primary sclerosing cholangitis (PSC) is a complex disease likely to involve multiple susceptibility genes, environmental and immunological risk factors. PSC can present at any age and is characterised by a long subclinical asymptomatic period in many cases[1]. The aetiology of the disease is unknown. PSC is closely associated with inflammatory bowel disease (IBD) most commonly ulcerative colitis (UC)[1,2]. A role for perinatal events in the aetiology of IBD has been suggested. Non-specific exposures such as infections and more specific factors including measles virus infection and vaccination as well as appendectomy have been shown to be associated with later development of IBD[3-6]. There is evidence of genetic susceptibility in both IBD and PSC[7,8] and there is a possibility that some immune profiles inherited by the offspring may increase the risk for both these autoimmune diseases as well as for perinatal events and other complications during pregnancy. Since perinatal events represent an increased risk for IBD[6], some early life events may be a direct risk for PSC. The close association between IBD and PSC has been suggested to be part of the pathogenetic explanation for PSC through the existence of an entero-hepatic circulation of lymphocytes. Some lymphocytes generated in the gut during active IBD may subsequently persist as long-lived memory cells and be activated in the liver resulting in hepatic inflammation and the development of PSC. The molecular basis for this hypothesis is that liver and gut share the same lymphocyte homing receptors[9]. However,

this hypothesis does not explain why only 5% of patients with IBD eventually develop PSC[10] and why PSC can precede IBD. Whether perinatal factors play a role for the development of PSC later in life has not been previously evaluated.

The aim of this study was to assess whether perinatal events, intrauterine or postpartum, are associated with an increased risk of PSC.

MATERIALS AND METHODS

All patients with PSC treated at the five largest University Hospitals in Sweden between 1970 and 1998 were selected for this study (n = 311). Through the unique national registration number assigned to every Swedish citizen we were able to trace birth parish to identify the hospital where delivery occurred. To trace the medical records associated with delivery and pregnancy from these patients, we searched the respective hospital archives. The detailed medical records from 97 patients with PSC were collected. Individuals born abroad or delivered at home by midwives were excluded. As controls, we selected two children of the same sex as the subject, who were delivered at the same hospital immediately after the subjects. The controls had to be alive and living in Sweden at the date of PSC diagnosis for the case. Controls who had died or emigrated before the diagnosis of their matched case were excluded. One hundred and seventy five controls remained for analysis.

The diagnosis of PSC was based on biochemical, histological and cholangiographic features[11]. Onset of PSC was defined as first cholangiogram consistent with the diagnosis. Adult PSC was defined as onset of PSC at 16 years of age or later. A diagnosis of UC was based on a typical history and characteristic endoscopic and histological findings[12]. All 97 patients with PSC had undergone colonoscopy to look for IBD and no endoscopic or histological signs of IBD were found in the non-IBD PSC patients.

For both, subjects and controls, we retrieved information on the age of parents, delivery method, parity and maternal complications including proteinuria, peripheral oedema, hypertension or other diseases during the pregnancy. Other conditions and factors during pregnancy included surgeries, infections, nausea, anemia, varices, constipation, thrombosis or any other disease reported by the patients to the midwife and documented in the patient's record. Information concerning medication during pregnancy, gestational age, birth height and weight, weight of the placenta and medical problems experienced by the mother or child postpartum were also collected. Small and large for gestational age were defined as birth weights two standard deviations below and above normal for the gestational age. All data from the birth records were personally collected by one researcher (U.L). The study was approved by the Ethics committee at Karolinska Institute, Karolinska University Hospital, Huddinge, Sweden.

Statistical analysis

Mean values of continuous measurements were compared in order to describe the characteristics of the case and control groups. To assess associations of the perinatal measures with PSC, conditional multiple logistic regression was used. All investigated parameters were modelled as a series of binary dummy variables. After investigation of univariate relationships, all measures associated with PSC ($P < 0.05$) that were statistically significant were included in multivariate analysis using conditional logistic regression. The final conditional logistic regression model excluded redundant measures co-linear with other significant risk factors.

Table 1 Description of perinatal factors in 97 PSC patients and 175 controls

	Patients with PSC (n = 97)	Controls (n = 175)	P
Age of the mother, yr (mean ± SD)	27.8 ± 5.1	27.4 ± 6.2	NS
Hospital stay days (mean ± SD)	7.9 ± 3.2	8.0 ± 4.7	NS
Birth weight in grams (mean ± SD)	3501 ± 537	3557 ± 480	NS
Birth length in cm (mean ± SD)	51.0 ± 2.2	51.0 ± 1.9	NS
Ponderal index (Weight/height^2)	2.6 ± 0.3	2.7 ± 0.3	NS
Vaginal delivery, n (%)	90 (93%)	166 (95%)	NS
Jaundice post partum, n (%)	7 (7%)	14 (8%)	NS
Breastfeeding at discharge from hospital, n (%)[1]	94 (97%)	170 (97%)	NS

[1]Missing data in 2 patients.

RESULTS

The mean age at PSC diagnosis in the 97 patients was 40 ± 12 years (± SD). 78% (76/97) were men, 80% (78/97) had a concomitant diagnosis of IBD. Sixty eight patients had UC, nine were diagnosed with Crohn's disease and one patient had indeterminate colitis.

A description of maternal and perinatal factors in the 97 PSC cases and the 175 controls is given in Table 1. Birth weight (BWT) was divided into five equally sized groups, where BWT 1 represented the lowest birth weight. Compared with the middle category, only the second lowest birth weight group was associated with PSC in a statistically significant manner. There were no statistically significant differences between the rates of maternal infections in subjects and controls. During pregnancy, maternal infections were reported in four cases (pneumonia (n = 1), tuberculosis (n = 1), urinary tract infection (n = 1), rubella in the first trimester (n = 1)). The child born to the rubella-infected mother was female and developed Crohn´s disease before PSC was diagnosed. In the control group, one mother suffered from tuberculosis. None of the mothers were diagnosed with IBD or chronic liver disease. 9.3% of the PSC cases and 8.0% of the controls had postpartum medical issues. The most common problems observed in the children were skin lesions and asphyxia-related problems, in both groups. The summated frequency of

Table 2 Matched odds ratios and 95% confidence intervals for the maternal perinatal risk factors studied in 97 patients with PSC and 175 controls

Risk factor	[1]*n* with PSC (%)	*n* without PSC(%)	OR (95% CI)	*P*
Vaginal bleeding	6 (6.2)	2 (1.1)	5.70 (1.13-28.83)	0.035
Oedema	15 (15.5)	13 (7.4)	2.28 (1.04-5.03)	0.040
Eclampsia	0	1 (0.6)	a	
Albuminuria during pregnancy	10 (11.4)	8 (5.2)	2.33 (0.88-6.15)	0.087
Albuminuria at arrival at the hospital	16 (17.2)	20 (13.1)	1.35 (0.66-2.76)	0.416
Albuminuria postpartum	13 (13.7)	22 (13.3)	1.02 (0.48-2.14)	0.963
Medical problems postpartum-mother	11 (11.3)	22 (12.6)	0.89 (0.41-1.93)	0.765
Medical problems postpartum-child	9 (9.3)	14 (8.0)	1.18 (0.49-2.83)	0.717
Breastfeeding	95 (97.9)	166 (97.1)	1.44 (0.27-7.67)	0.668
BWT 1	23 (23.7)	31 (17.7)	1.44 (0.57-3.65)	0.437
BWT 2	26 (26.8)	28 (16.0)	2.89 (1.17-7.18)	0.022
BWT 3	16 (16.5)	39 (22.3)	Reference	
BWT 4	14 (14.4)	42 (24.0)	0.76 (0.29-2.01)	0.576
BWT 5	18 (18.6)	35 (20.0)	1.44 (0.57-3.63)	0.437
Gestational weeks < 38	8 (8.4)	7 (4.1)	2.20 (0.77-6.29)	0.144
Gestational weeks 38-42	78 (82.1)	150 (87.2)	Reference	
Gestational weeks > 42	9 (9.5)	15 (8.7)	1.16 (0.48-2.76)	0.755
Small for gestational age			1.09 (0.25-4.71)	
Large for gestational age			2.33 (0.61-8.91)	

BWT 1-5, 5ths; 1, lowest ; BWT, body weight. [1]The cases are matched with controls for sex, age and hospital [a]No estimate due to an empty cell.

all postpartum medical problems for mothers of PSC patients was 11.3% and 12.6% for the controls, dominated by bleeding-anaemia in both groups. This difference is not statistically significant.

The matched odds ratios for perinatal factors are shown in Table 2. Both vaginal bleeding and peripheral oedema are statistically significantly associated with PSC. There was also an association of albuminuria during pregnancy with PSC that is not statistically significant. There was no association between jaundice and the risk of PSC. The non-matched odds ratios did not differ notably from the matched odds ratios shown in Table 2 (data not shown).

A multivariate analysis was conducted for the factors associated with a statistically significant increased risk of PSC: vaginal bleeding, peripheral oedema and birth weight. For vaginal bleeding, the adjusted OR (95% CI) is 6.7 (1.3-34.8), 2.4 (1.1-5.3) for peripheral oedema and 2.24 (1.00-5.02) for the second lowest birth weight category. An additional adjustment for gestational age was conducted separately (data not shown) and did not significantly alter the odds ratios for birth weight, vaginal bleeding or peripheral oedema.

DISCUSSION

To our knowledge, this is the first study investigating the associations of perinatal factors with PSC. The rationale for conducting such a study is that the foetal environment may be a contributing factor in the aetiology of some adult conditions such as diabetes, insulin resistance and rheumatoid arthritis[13,14]. In addition, IBD (both CD and UC) is closely associated with PSC and "non-infectious health events" during pregnancy[4,6]. In celiac disease, which is also associated with PSC[15], it has been shown that a low birth weight for gestational age and neonatal infections are associated with later development of celiac disease[16].

We found no associations between PSC and birth length, gestational age, or medical problems for the mother or child, during pregnancy or postpartum. Mothers who had specific infections were identified. Neither individually nor combined were the specific infections associated with PSC risk. However, the number of events is low so detailed analysis was not possible. The association of PSC with birth weight was limited to one part of the birth weight distribution and there was no evidence of a trend. This suggests a chance association that should not be over-interpreted.

Some specific factors, vaginal bleeding during pregnancy and peripheral oedema, proved to be statistically significant in association with higher PSC risk. Interpretation of these data should be cautious. The number of women with vaginal bleeding was small and a clear mechanism to link this event with PSC is not readily apparent. As more women displayed peripheral oedema, its association with PSC is of greater relevance, yet it is a somewhat non-specific symptom, and again, a biologically plausible mechanism linking it with PSC is not obvious. It may be worthwhile to note that peripheral oedema is a symptom of pre-eclampsia; the other important symptoms are hypertension and proteinuria. Only one mother in this study was diagnosed with pre-eclampsia and we could not fully evaluate possible sub-clinical diseases as data were missing for proteinuria in both groups. However, the weak association of proteinuria with the risk for PSC provides further, but limited, evidence that some symptoms of pre-

eclampsia are associated with PSC. If the link between PSC and these maternal symptoms is not due to chance, then they could indicate some inherited characteristics that represent susceptibility to PSC. Alternatively, they might represent foetal exposure, possibly to pro-inflammatory factors, which increase the risk of PSC among susceptible individuals, perhaps through the initiation of an autoimmune process.

Although the detailed aetiology of PSC is unknown, its close association with IBD indicates that these two diseases share important risk factors relevant to exposure or susceptibility.

It is possible that risk factors identified by this study could be intermediates in a causal pathway between IBD and PSC: this could not be investigated here due to the small number of IBD-free subjects. However, it is also possible that the associations are specific to PSC or identify a subset of people with both diagnoses. IBD may indicate greater susceptibility to PSC, but exposure to other risk factors may be required to initiate the pathogenesis of this disease. Given the close association of PSC and IBD, known risks for IBD should be considered.

Bacterial colonisation of the gut is implicated in the aetiology of IBD; this occurs first in early life and the critical stages of early gut colonisation include exposure to bacteria in the birth canal, maternal faecal bacteria and during weaning[17]. Breastfeeding is important for colonic bacterial colonisation[17]. Previous studies investigating the association between breast feeding and development of IBD have shown inconsistent results[18,19]. In the present study, there was a similarly high frequency of breastfeeding among patients and controls (97% in both groups). However, the observation period was short (approximately one week) since breastfeeding was only registered at the time when the mothers were discharged from the hospital and no follow-up was available.

Although the number of subjects included in this study was not large, it includes a high proportion of Swedish PSC patients between the years 1970 and 1998. Differential selection bias is not a concern as subjects and controls were closely matched and the analysis was conditional, such that patients were compared with their matched controls. The controls were selected from the same birth unit (next two consecutive births with the same gender as the subject) and the data was retrieved by the same person. Furthermore, differential information bias is not a determining factor either, as the selection of cases or controls was not influenced by whether perinatal adverse events occurred or not. The general characteristics of the PSC patients in the present study, such as age at onset of PSC, association with IBD and sex distribution, are similar to other studies, suggesting that selection bias among cases is unlikely[1,2].

In summary, no significant associations with PSC were found for gestational age, birth length, breastfeeding, or most medical complications, including infections, during pregnancy for the mothers or postpartum for the children. The associations with vaginal bleeding and some symptoms of pre-eclampsia could be due to chance, but should be considered as putative risk factors by further studies. Overall, our findings do not support the hypothesis of a substantial role for perinatal events in the aetiology of PSC later in life.

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