PANCREAS, BILIARY TRACT, AND LIVER

A Population-based Cohort Study of Pregnancy Outcomes Among Women With Primary Sclerosing Cholangitis

Jonas F. Ludvigsson,[*,‡,§] Annika Bergquist,[‖] Gunilla Ajne,[¶] Sunanda Kane,[§] Anders Ekbom,[*] and Olof Stephansson[*,‖]

*Clinical Epidemiology Unit, Department of Medicine, ‖Department of Gastroenterology and Hepatology, ¶Department of Women's and Children's Health, Karolinska University Hospital and Karolinska Institutet, Stockholm, Sweden; ‡Department of Pediatrics, Örebro University Hospital, Örebro, Sweden; §Division of Gastroenterology and Hepatology, Department of Medicine, Mayo Clinic College of Medicine, Rochester, New York

BACKGROUND & AIMS: **Studies of primary sclerosing cholangitis (PSC) and pregnancy outcomes have been limited in size and have been inadequate to rule out excess risks. We examined pregnancy outcomes among women with PSC.**

METHODS: **Women with PSC were identified from inpatient and hospital-based outpatient data in the Swedish National Patient Register. Through linkage with the Medical Birth Register, we identified 229 singleton births, from 1987 through 2009, to women with PSC before delivery. These were compared with 2,304,863 births to women without a diagnosis of PSC. We used logistic regression, adjusted for maternal age, smoking, education, parity, and year of birth, to calculate adjusted prevalence odds ratios (aPORs) for adverse pregnancy outcomes.**

RESULTS: **Maternal PSC was associated with a 3.63-fold increase in preterm birth (95% confidence interval [CI] for aPOR, 2.35–5.61) as well as an increased risk of cesarean section (aPOR, 2.18; 95% CI, 1.50–3.17). We found no increased risk based on analyses of the 5-minute Apgar score, small for gestational age, stillbirths, or neonatal deaths. Maternal PSC was not a risk factor for congenital abnormalities (aPOR, 1.12; 95% CI, 0.56–2.22). Stratification by inflammatory bowel disease status did not affect the risk estimates more than marginally.**

CONCLUSIONS: **Maternal PSC is associated with both preterm birth and cesarean section but not with congenital malformation or other adverse outcomes of pregnancy. Pregnancy should not be discouraged in women with PSC.**

Keywords: Bile Duct Diseases; Child; Liver; Pregnancy; Primary Sclerosing Cholangitis.

Primary sclerosing cholangitis (PSC) is an immune-mediated cholestatic disorder with autoimmune traits.[1] It is characterized by inflammation and fibrosis in the intrahepatic and/or extrahepatic bile ducts.[1] Long-standing inflammation with obliterated ducts can lead to biliary cirrhosis as well as liver failure. Moreover, a recent study suggested that PSC patients are at a 4.2-fold increased risk of death.[2] The vast majority (60%–80%) of individuals with PSC also have inflammatory bowel disease (IBD), especially ulcerative colitis (UC).[1] We[3,4] and others[5–7] have shown previously that IBD may be associated with adverse pregnancy outcome.

The median age at PSC onset is about 35 to 40 years,[8] which means that many women with PSC are still in their fertile years. Data on pregnancy outcome in PSC are limited. In addition to a small number of case reports,[9] we are only aware of 2 case series examining PSC and pregnancy.[10,11] In 1996, Swedish researchers reported the outcome of 13 pregnancies in 10 women with PSC.[10] Seven of these patients had been diagnosed before pregnancy, with another 2 patients developing PSC during pregnancy, and 1 patient receiving the diagnosis just after delivery. Although that study had limited statistical power, it found no evidence that PSC would have a negative effect on pregnancy.

In a larger and more recent report from Germany, Wellge et al[11] examined 25 pregnancies in 17 women

Abbreviations used in this paper: aPOR, adjusted prevalence odds ratio; CD, Crohn's disease; CI, confidence interval; IBD, inflammatory bowel disease; ICD, International Classification of Diseases; LGA, large for gestational age; MBR, Swedish Medical Birth Registry; PH, portal hypertension; POR, prevalence odds ratio; PSC, primary sclerosing cholangitis; SGA, small for gestational age; UC, ulcerative colitis.

1542-3565/$36.00
http://dx.doi.org/10.1016/j.cgh.2013.07.011

with PSC. Of these, 4 resulted in fetal loss.[11] In the remaining 21 pregnancies, there were 2 preterm births. Despite the low number of preterm births (n = 2 of 21; 10%), it could not be ruled out that PSC was associated with a significant risk increase for preterm birth in that the 95% confidence intervals (CIs) (recalculated by us) were 1% to 30%.[11] Given that 7 of 21 pregnancies with a live born infant were delivered by cesarean section (33%; 95% CI, 15%–57%), it may be that the incidence of cesarean section may be increased in patients with PSC.[11] This is presumably because many PSC patients suffer from UC or Crohn's disease (CD),[3,4,7] which is known to be linked to an adverse pregnancy outcome. The main objective of this study was to examine the risk of adverse pregnancy outcomes in a nationwide population-based sample of women with PSC.

Methods

Definitions of Primary Sclerosing Cholangitis and Other Comorbidities

From the Swedish Medical Birth Register (MBR), we identified 2,305,092 women with singleton pregnancies giving birth between 1987 and 2009. The MBR, started in 1973, was used to identify pregnancy outcomes and potential confounders. By using the unique personal identity number[12] assigned to each citizen at birth or upon arrival in Sweden, we linked data from the MBR with the Swedish national patient and education registers. We identified women with PSC in Sweden through the National Patient Register.[13] The Patient Register was initiated in 1964, covered approximately 75% of the Swedish population in the early 1980s, and became nationwide in 1987.[13] It includes data on hospital admissions and, since 2001, the register also contains hospital-based outpatient care.

PSC was defined as having a relevant International Classification of Disease, 9th revision (ICD-9) code (ICD-9 code, 576B; ICD, 10th revision [ICD-10] code, K830). The Patient Register also was used to identify UC (ICD-9 code, 556; ICD-10 code, K51), CD (ICD-9 code, 555; ICD-10 code, K50), and portal hypertension (PH) as defined by either esophageal varices (ICD-9 code, 456A-C; ICD-10 code, I85) or PH (ICD-9 code, 572D; ICD-10 code, K76.6).

We identified 229 singleton births to women with PSC diagnosed before delivery. These were compared with 2,304,863 births to women without a diagnosis of PSC. We restricted our data to 1987 and onward because the ICD-9 was introduced in Sweden that year (followed by the ICD-10 in 1997).

Pregnancy-related Variables

In the MBR, maternal and pregnancy data, including smoking, are recorded on structured forms by midwives during the first antenatal visits. Body mass index can be calculated from antenatal data on height and weight at the first maternity visit (since 1992). Through the MBR, we also obtained information on the pregnancy outcomes listed in the paragraph below.

We defined small for gestational age (SGA) as having a birth weight more than 2 standard deviations below the mean for gestational age. Preterm birth was defined as 36 or fewer completed weeks of gestation (very preterm was defined as <32 gestational weeks and moderate preterm was defined as 32–36 completed weeks). The MBR allows the distinction between spontaneous and induced preterm birth. The MBR also contains data on cesarean section. Finally, we obtained data on low Apgar score at 5 minutes (<7) and stillbirth (defined as having a dead fetus ≥28 completed gestational weeks). Preeclampsia was defined according to the following ICD-9 codes: 642E, 642F, 642G, and 642H, or ICD-10 codes: O14 and O15. Parity was categorized into primipara or multipara.

Data on congenital abnormalities were retrieved from the MBR according to the following ICD codes (ICD-9 codes, 740–759; ICD-10 codes, Q00–Q99).

Statistics

By using logistic regression, we calculated crude and adjusted prevalence odds ratios (PORs) with 95% CIs. In separate analyses we adjusted for maternal age at delivery (<19, 20–24, 25–29, 30–34, and ≥35 y), calendar year of birth, smoking (yes vs no), parity (primiparas or multipara), IBD before pregnancy (yes/no), and maternal education (≤11 or ≥12 y). Calendar year was considered as well, given the changes in management and therapy (including the use of biological treatment in patients with concomitant IBD). Similarly, we examined the risk of these 4 outcomes in women with and without PH. Because of the small number of women with both PSC and PH (Table 1), PORs were calculated only in women with PSC but without PH.

Statistical analyses were conducted using SAS software version 9.2 (SAS Institute, Cary, NC). PORs with 95% CIs that did not include 1.0 were regarded as statistically significant. Because observations are not independent in women who delivered more than once during the study period, we calculated estimates using clustered data in the generalized estimation equation method (PROC GENMOD).

Ethics

The study was approved (2008/182-31/4) by the ethics review board in Stockholm (Sweden).

Results

There were 229 deliveries in mothers with a diagnosis of PSC, with the median interval between first diagnosis and delivery of 3.8 years. A total of 13 women were diagnosed with PSC during pregnancy. Maternal characteristics are presented in Table 1. The median age at