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The Association between Gravidity and Primary Biliary Cirrhosis

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Abstract

PURPOSE—Primary biliary cirrhosis is an autoimmune disease with female predominance that leads to liver failure. The goal of this study was to identify reproductive risk factors associated with this disease.

METHODS—We compared 182 cases of PBC with 225 age- and sex-matched friend controls to examine the role of reproductive factors. The survey instrument was developed using standardized questions obtained from the National Health and Nutrition Examination Survey (NHANES) III.

RESULTS—A total of 126/182 cases (69%) and 141/225 (62.6%) friend controls responded to the survey. More cases than controls reported ever having genitourinary infection [adjusted odds ratio (OR) = 2.12, 95% confidence interval (CI) 1.01, 4.42] among those without a personal or family history of autoimmune disease. The most notable finding was that cases reported significantly more pregnancies than controls ($p = 0.008$). The adjusted OR for each additional pregnancy among those without a personal or family history of autoimmune disease was 1.40 (95% CI 1.14, 1.7). More controls (24.4%) than cases (16.0%) were nulliparous. Cases reported having five or more children (16.0%) with double the frequency of controls (8.2%).

CONCLUSIONS—The association reported herein, between primary biliary cirrhosis and gravidity, is particularly significant because of the overwhelming female predominance.

Keywords

Pregnancy; Reproductive; Women’s Health

INTRODUCTION

Female reproductive history and outcomes have been studied to search for clues to the etiology of autoimmune diseases including the rare disease, primary biliary cirrhosis (PBC). Both reduced fertility and amenorrhea have been associated with PBC (1, 2). In addition, repeated pregnancy loss, endometriosis, and premature ovarian failure have been associated with other autoimmune diseases (3–9). Furthermore, autoantibodies were detected in 88% of women with unexplained infertility and in 70% of patients with pregnancy wastage (6). Another study suggested that women who showed no clinical signs of autoimmune disease might be at greater risk for adverse pregnancy outcomes if they have a family history of autoimmune diseases (10). In contrast, the role of gravidity in the occurrence and progression of many autoimmune diseases such as PBC has been debated and remains controversial.

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The relation of gravidity to PBC has not been studied in great detail and in other autoimmune diseases, the data have led to conflicting results; some studies have reported an increased risk with the number of pregnancies (11, 12), whereas others have found significant associations of nulliparity with disease occurrence (13–16). Still, other studies have failed to find any associations (17, 18). In the case of PBC, little epidemiologic research has been conducted and little emphasis has been placed on reproductive factors primarily because of the relative infrequency of the disease, most published research consists of case reports and laboratory studies. The present epidemiologic case-control study was undertaken to examine the association of PBC with a variety of proposed lifestyle and reproductive risk factors that may play a role in its occurrence. In this paper, we describe the results of the analysis of the association of PBC with reproductive history and outcomes.

MATERIALS AND METHODS

Study Population and Data Collection

The details of enrollment of the study population and disease verification as well as the description of the survey instrument for the present analyses have been previously described in detail (19). Briefly, the sample for the present analysis was comprised of female PBC cases identified from an Internet support group and their age- and gender-matched friend controls.

The questionnaire was developed using a series of standardized questions drawn from the NHANES (20). The survey instrument included questions about demographics (age, education, gender, race/ethnicity), general medical history (childhood illnesses, chronic diseases, infections, medications), reproductive history (gynecologic surgery and procedures, age at menarche and menopause, prior use of oral contraceptives, pregnancy history, history of infertility), and lifestyle factors (smoking, alcohol use). These questions have been tested for reliability and validity in a number of studies (21). The initial survey instrument was pilot tested in approximately 25 individuals without PBC, after which appropriate modifications were made.

Of a total of 199 cases that responded to the initial mailed survey, current address information was only available for 182 of these cases. The 182 cases were mailed a second, abbreviated focused questionnaire, in which they were to answer questions on reproductive history, smoking and alcohol use (to improve clarity of previous questions), and provide the names and addresses of three friends who were willing to participate in the survey. The friends had to be of the same sex as the case, and within 10 years of the age of the case. The friend controls were sent the same packet of information as the cases were originally sent (see below). A total of 225 friends were identified by the 126 cases that responded.

The packets mailed to cases and controls contained a cover letter from the investigators, an informed consent, a questionnaire, and a prepaid return envelope for sending back completed questionnaires. A second request packet was sent approximately one month later to those people who did not respond to the first mailing. Upon return of questionnaires, attempts were made to verify the PBC diagnosis of the cases by contacting their physicians. In order to be considered a case, a patient had to exhibit AMA positivity and at least one of the following characteristics: 1) cholestatic liver function test; or 2) abnormal liver histology. Of the 100 cases whose physician information was available, only two were found not to be cases and were excluded from the study.

Variables and Statistical Analysis

All survey information was coded, double key entered, and read into a SAS database. Range and logic checks were performed on all of the data. SAS Version 8.0 was used for all

analyses. Given that this analysis was performed to examine the relation of reproductive factors to PBC, the analysis was limited to the female respondents in the sample. Only 15 (5.6%) of the original survey respondents were male, limiting the ability to examine differences by gender. A total of 119 female cases and their 134 controls with complete questionnaire data were included in the present analyses. The primary outcome variable was PBC occurrence, a dichotomous variable. Most of the independent variables were also dichotomous, including infertility, oral contraceptive use/female hormone use, various adverse pregnancy outcomes, complications of pregnancy and sexually transmitted diseases (STDs). Continuous variables included the age at which a medical condition occurred, age at menarche, age at menopause, age at first pregnancy and average menstrual cycle length.

For the purposes of this analysis, post-menopausal was defined as not having had a menstrual period in the past 12 months and included women who had experienced natural or surgical menopause. Women who indicated that their last period was between three and six months prior were classified as “peri-menopausal”, whereas women who reported having a period in the past three months were classified as “pre-menopausal”. Infertility was defined as having had unprotected intercourse for one year or more without the occurrence of pregnancy. A dichotomous variable, ‘Any STD’ was created by combining the information from five questions. If an individual indicated that she had had any of the five STDs we asked about, the new variable was coded 1 for yes, otherwise, it was coded 0. Gravidity was determined by adding up the number of live births, stillbirths, miscarriages and tubal pregnancies. A dichotomous genitourinary (GU) infection variable was also ‘yes’ (1) if a woman reported having had a urinary tract infection, vaginal infection, or any STDs; a ‘no’ (0) if she had none of these infections.

Descriptive statistics were generated for all variables. Frequencies and percents were generated for nominal variables, and means and standard deviations were generated for continuous variables. T-tests were used to assess differences in means. The distributions of continuous variables were examined to determine the best categories, if appropriate. For dichotomous variables, chi-square statistics were to assess the significance of differences in proportions among cases and controls for the conditions of interest.

Approximately half of the cases [$n = 64$ (50.8%)] provided either no controls or listed controls that did not respond to the survey. A total of 17 cases (13.5%) had one control respond to the survey. The remaining 45 cases had two or more controls. Based on the rationale that excluding cases without controls would cut the sample size in half (thus decreasing the statistical power to detect significant effects), the multivariate analysis was approached in three ways. First, an unmatched multiple logistic regression analysis was performed, including all of the cases and controls. Second, one control was selected at random for each case that had at least one associated control. A total of 58 such matched pairs were created. The remaining controls were paired to cases according to age and gender criteria. A total of 60 additional matched pairs were thus ‘created’.

Multiple conditional logistic regression using all 118 matched pairs was performed. Finally, another multiple conditional logistic regression analysis was performed, including only cases that originally had matched controls so as to examine whether the results were similar to the other logistic regression models. The results of the latter analysis are not presented here because the estimates were unstable due to the small sample size, although the point estimates were generally of the same magnitude and direction as in the other two analytic approaches.

The best subsets approach to modeling was used to select the final appropriate logistic regression model. In this approach, a statistical criterion of $p < 0.15$ or importance in past

research, was used to determine if a variable should included in the best subsets. F scores were assigned to each of the models that had different combinations of variables included. When one model was a subset of another, the amount of improvement in score with the addition of each new variable was examined to determine the best model. Goodness of fit of logistic models was assessed by the method of Hosmer and Lemeshow (22).

RESULTS

Demographic Characteristics

A total of 126 PBC cases out of the 182 contacted (69%) responded to the second survey. A total of 141 of the 225 friends named by the cases responded to the survey, for a response rate of 62.6%. As mentioned previously, the present analysis was restricted to the 119 female cases and 134 female controls for whom complete data were available. The mean age of the respondents was 53 years for cases and 54 years for controls (Table 1).

Approximately 98% of the sample identified them as Caucasian. More than a third of cases (42.9%) and controls (36.3%) reported they had finished some college or vocational, school and an additional 36.1% of cases and 37.8% of controls had a bachelor's or graduate degree. All of the respondents reported having health insurance; the most common types in both groups were private insurance/HMO (94.1% of cases and 87.4% of controls) and Medicare/ Medicaid (16.8% of cases and 14.8% of controls). The health insurance categories were not mutually exclusive; respondents were allowed to indicate multiple sources of insurance.

Menstrual Cycle Characteristics

Menstrual cycle characteristics did not differ significantly between cases and controls (Table 2). The mean age at menarche for all respondents was about 13 years old ($p = 0.44$). The majority of women in both groups (66.4% of cases, 63.7% of controls, $p = 0.59$) indicated that they were post-menopausal. Of the women who were post-menopausal, 53.9% of cases vs. 41.3% of controls had had a surgical menopause.

The median age of the final menstrual period for post-menopausal women was about 45 years in cases and 47 years in controls. In addition, a similar proportion of cases (31.0) and controls (34.1) reported having had variable menstrual cycle lengths when they were in their twenties ($p = 0.60$). A question about usual menstrual cycle length was asked of the respondents, but the responses showed a large amount of variation, from three to 40 days. This led us to strongly suspect that the question had been misinterpreted by many of the respondents, with some respondents possibly interpreting menstrual cycle length to mean the length of their periods. As a result, these data are not presented here.

Reproductive Surgeries, Oral Contraceptive, and Estrogen Use

Hysterectomies and oophorectomies were reported with similar frequency by cases and controls (Table 3). Approximately 32% of cases reported hysterectomy, compared to 27% of controls (OR = 1.29, 95% CI = 0.74, 2.26, $p = 0.37$). Oophorectomies were reported in 26.5% and 21.1% of cases and controls, respectively (OR = 1.35, 95% CI = 0.75, 2.43; $p = 0.31$). These analyses were limited to cases whose surgeries occurred before they were diagnosed with PBC.

Cases reported ever having used oral contraceptives with greater frequency (81.5%) than controls (71.6%): OR = 1.75, 95% CI = 0.96, 3.17, $p = 0.07$. Approximately three times as many controls (6.4%) as cases (2.1%) reported current use ($p = 0.14$) of oral contraceptives, although the absolute numbers were small. Mean number of years of use did not differ significantly between the two groups ($p = 0.44$).

Controls also reported ever having used estrogen or female hormones with greater frequency (61.7%) than cases (53.4%), although this difference was not statistically significant (p = 0.22). No significant differences were observed between the two groups with respect to current use of estrogen/female hormones (p = 0.19), total years of estrogen use (p = 0.30), or having used an intrauterine device (0.61).

Unadjusted Pregnancy History and Reproductive Problems

Cases reported significantly more pregnancies than controls (Table 4). The mean number of pregnancies among cases was 2.6 while among controls it was 2.0 (p = 0.008).

More controls (24.4%) than cases (16.0%) had never been pregnant. In addition, cases reported having five or more children (16.0%) with double the frequency of controls (8.2%). Cases also had their first child at an earlier age than controls; the mean for cases was 21.4 years and for controls 22.5 years (p = 0.03).

No significant differences in adverse pregnancy outcomes were observed, including stillbirth, tubal pregnancy and birth defects of offspring among cases and controls (Table 4). A somewhat larger proportion of cases (26.1%) than controls (20%) reported having had a miscarriage (OR = 1.41 95% CI = 0.78, 2.54, p = 0.25). The absolute numbers of adverse pregnancy outcomes reported were small for both cases and controls. Respondents in both groups reported complications of pregnancy with similar frequency, including diabetes (p = 0.67), premature labor (p = 0.31), and toxemia (p = 0.45).

A larger proportion of cases than controls reported having had endometriosis: 15.9% vs. 9.1%, respectively (OR = 1.88, 95% CI = 0.86, 4.08, p = 0.11). Similarly, more cases than controls reported having had ovarian growths: 19% vs. 11.5%, respectively (OR = 1.81, 95% CI = 0.89, 3.68, p = 0.10). No significant differences were observed between cases and controls in reported rates of other reproductive problems, including inflamed/blocked fallopian tubes, uterine fibroids, or infertility.

The mean number of sexual partners among cases (5.9) was higher than among controls (4.5, p = 0.07), and the reported age at first sexual activity was lower for cases than controls (18.5 years for cases vs. 19.3 years for controls, p = 0.05) (Table 5). Although the reported rates of individual STDs did not differ significantly between cases and controls, the proportion of cases (18.5%) who reported having had any STD was considerably higher than controls (10.4%): OR = 1.96, 95% CI = 0.95, 4.03, p = 0.06. Finally, the reported rates of urinary tract infection (OR = 2.37, 95% CI = 1.40, 3.98, p = 0.001) and vaginal infection (OR = 3.19, 95% CI = 1.87, 5.42, $p < 0.0001$) were significantly higher among cases (68.7% and 63.4%, respectively) than controls (48.1% and 35.2%, respectively).

Results of Multivariate Analyses

The best subsets approach was used to construct final multiple logistic regression models. Two separate models were run; one with all cases and controls, and another with only those individuals without history of any associated autoimmune diseases or family history of autoimmune disease. The rationale behind this exclusion was that these two variables strongly associated with PBC occurrence, which made more difficult observation of with less strong associations with other variables. However, regardless of whether the analysis was performed with or without people with personal or family history of autoimmune diseases, the results were similar.

Based on the results of the univariate analysis, the variables that were entered into the best subsets approach were: ever use of oral contraceptives, gravidity, mean age at first pregnancy, endometriosis, ovarian growths, mean number of sexual partners and age at first

sexual activity. In addition, from our previous analyses (20), in which we found that associated autoimmune diseases, ever having smoked, vaginal infection and urinary tract infection were associated with PBC (Table 1); thus, these variables were included in the best subsets evaluation. When both urinary tract and vaginal infection were entered separately, only vaginal infection stayed in the model, even though both individually were highly statistically significant. A new dichotomous genitourinary (GU) infection variable was created because STDs, urinary tract infection and vaginal infection were found to be highly correlated ($p < 0.001$). The new GU infection variable represented those individuals who reported a history of urinary tract infection, vaginal infection and/or STDs.

The results of the multiple logistic regression model with all cases and controls included indicated that none of the reproductive variables, with the exception of gravidity, remained significant when adjusted for the other variables (Table 6). This multivariate conditional logistic model indicated that PBC was associated with increasing number of pregnancies (OR = 1.29, 95% CI = 1.03, 1.61), other autoimmune diseases (OR = 11.96, 95% CI = 3.33, 42.93), smoking (OR = 2.61, 95% CI = 1.11, 3.37), and GU infection (OR = 1.71, 95% CI = 0.78, 3.75).

Excluding the cases and controls with associated autoimmune diseases or family history of autoimmune disease produced similar results (Table 6). None of the other reproductive variables maintained a significant relationship with PBC status in the multivariate analyses. PBC occurrence was more positively associated with gravidity (OR = 1.40, 95% CI = 1.14, 1.71), smoking, (OR = 4.67, 95% CI = 2.13, 10.22), and GU infection (OR = 2.12, 95% CI = 1.01, 4.42), when restricted to those without a personal or family history of autoimmune disease.

DISCUSSION

This study is amongst the largest studies of women's health in autoimmunity and is of particular interest to PBC, where such issues have not been studied in detail. Of particular interest in our data was the observation that PBC is associated with an increasing number of pregnancies. This finding was validated in our multivariate analysis. This has not been noted previously in PBC and is consistent with similar data on other autoimmune diseases (11, 12). Cases also had a significantly younger mean age at first pregnancy and first sexual activity in univariate analyses than did controls. These differences were not statistically significant in the multivariate analysis, however. The younger age at first pregnancy among cases is congruent with the increased gravidity in this group. We also emphasize that this study did not find a significant association of PBC with any other reproductive factors, including menstrual cycle characteristics, oral contraceptive use, or adverse reproductive outcomes, after adjusting for family history of autoimmune disease, associated autoimmune diseases, and other covariates, smoking and GU infection.

The association between PBC and smoking and infection in this population has been previously reported (19), and agrees with the findings of other epidemiologic studies of PBC (23, 24). The autoantigens of PBC are highly conserved and there is significant homology between bacteria and the human mitochondrial E2 components of the 2-oxo-dehydrogenase pathway. One theory regarding PBC is that it begins with a breakdown of tolerance against E. Coli PDC-E2. This is an attractive hypothesis but has not been experimentally demonstrated (25). We should note that the prevalence of PBC in the U.S. is unclear. One recent study, which has attempted to address this issue, has suggested a prevalence of 65.4/100,000 persons (26). If this is generalized to the U.S. population, there may be as many as 185,000 women affected by PBC. Further studies are needed to address this point.

The only other large epidemiologic study to examine gravidity and PBC did not find a significant association (24). An early study by Engel found increased rates of rheumatoid arthritis (RA) among multiparous women compared with nulliparous women over the age of 45 (12). Indirect evidence for the possible association between multiparity and autoimmune disease is derived from a Mayo Clinic in which the incidence of RA in Olmstead County was examined. A significant decrease in the incidence over time was found in women but not in men (27). A possible explanation for this decline is the trend toward older age at first pregnancy and decrease in total number of pregnancies over the last 30 years among women in the U.S. (28). Jorgensen and coworkers (29) found no significant increase in parity among RA cases compared to controls but reported an increased risk of severe RA in cases who had two children (OR = 2.9, 95% CI = 1.0, 8.3) and those who had three or more children (OR = 4.8, 95% CI = 1.55, 5.6). These estimates were adjusted for age at first birth, oral contraceptive use, and breast-feeding (29).

In a hospital-based case-control study of 270 RA cases, Spector and coworkers reported a significant association between RA and nulliparity (OR = 2.9, 95% CI = 1.0, 8.3) (16). In a study of multiple sclerosis, Hernan and coworkers reported no significant association with parity (30). Similarly, no significant association between parity and Sjogren's syndrome was found in a study conducted by Skopouli and coworkers, although the sample size in this study was relatively small (31).

The hypothesis that pregnancy is a risk factor for autoimmune disease is intriguing and might serve as a partial explanation for the overwhelming female predominance in most autoimmune diseases such as PBC, scleroderma, multiple sclerosis, lupus, and Sjogren's syndrome. Furthermore, many of these diseases occur largely in middle-aged women, after their childbearing years (32, 33). Although the exact mechanism by which pregnancy leads to increased risk of autoimmune disease is not understood, it has been proposed that autoimmune diseases may be caused by fetal cells that remain in the maternal circulation long after the completion of pregnancy (34–37). The hypothesis is intriguing because of the similarity of PBC and scleroderma to chronic graft versus host disease (GVHD), a condition associated with chimerism (38). Nonetheless, although the possibility that fetal microchimerism is a factor in scleroderma (37) remains a viable hypothesis, it does not appear to be the case in PBC (39), although more studies with larger sample sizes need to be conducted in order to verify this. The relationship between gravidity and the immune response has not been studied in detail. We would suggest that the role of gravidity is not only to change hormone status, but also perhaps switch the immune response towards a Th1 bias; this would predispose an individual to a breakdown in tolerance (25).

The present study found no association between PBC and oral contraceptive (OC) use after adjustment for confounding variables. In light of the increased gravidity among cases, lower rates of OC use might have been expected. We found the opposite to be true, however; cases had a higher rate of OC use (81.5) than controls (71.6), although this difference was barely significant ($p = 0.07$). Other studies on the association between autoimmune diseases and OC use have yielded conflicting results. A prominent hypothesis is that exogenous female hormones such as OCs protect against autoimmune disease (40). Howel and coworkers found no significant association of PBC with OC use in their population-based case-control study (24). In the Nurses Health Study cohort, no clear association between multiple sclerosis and OC use was observed (OR = 1.2, 95% CI = 0.9, 1.5) (30). In a study of rheumatoid arthritis, Hazes and coworkers reported a protective effect of OCs (OR = 0.39, 95% CI = 0.24, 0.63) (41). Further complicating the issue, Spector and coworkers reported results that suggest a multiplicative protective effect of pregnancy and OC use on rheumatoid arthritis (16). A proposed mechanism by which OC may be protective for

autoimmune disease is by preventing pregnancy, although the direction of the effect of pregnancy on autoimmune disease is still being debated, as noted above.

Both cases and controls in the present study reported high rates of infertility. The question that was asked was: “Has there ever been a time for a year or more when you were having sexual intercourse without using birth control, but you didn’t get pregnant during that time?” Approximately 42% of cases and 40% of controls responded “yes,” rates that are considerably higher than in the general population (42). Because the rates were similar among cases and controls, a possible explanation is that the term “birth control” was not noted or was misinterpreted by respondents. It is possible that many couples were using natural family planning or the rhythm method, which they may not have thought of as birth control. Similarly, the reported rates of miscarriage in both groups are higher than the general population rate; the reason for this is unclear. Prior studies of infertility and autoimmune disease have reported both significant association (43) and lack of association (44).

No significant differences in menstrual cycle characteristics or reproductive problems between cases and controls were found in the present study. As mentioned previously, the likely misinterpretation of the question on menstrual cycle length prevented us from analyzing this information. This is a bias in our study, as shorter cycles may lead to increased gravidity as well as increased rates of infertility independent of the incidence of PBC (45). While a slightly larger proportion of cases reported endometriosis and ovarian growths, these differences were not statistically significant. Other studies have reported significant associations, but we may have had insufficient sample size to detect a difference (5).

The present case-control study of the association of reproductive factors and PBC is one of the largest ever conducted in the U.S. Several limitations, however, must be taken into consideration when interpreting the data. Although our study had one of the largest sample sizes of PBC cases, we still lacked adequate statistical power to detect differences in rare exposures such as adverse reproductive outcomes and pregnancy complications. Our sample was a select group, drawn from an Internet support group, which probably accounts for the respondents’ demographic characteristics. The vast majority of participants were Caucasians, highly educated, and had health insurance. Thus, the generalizability of our results to the rest of the PBC population may be limited, as PBC has been reported throughout the world in many different ethnic groups. In addition, the data on which this analysis is based is largely self-reported; only the disease status of the cases was confirmed. Due to limited resources and limited availability of confirmatory sources for some of this information, we were not able to verify the exposure information by contacting physicians or through examination of medical records. The possibility of recall bias thus exists, although the association between gravidity and PBC is unlikely to be a product of this, since most other reproductive factors, particularly adverse ones, did not differ between cases and controls. In addition, many factors were examined in this study; thus some or all of the statistical associations may be due to chance. Furthermore, the use of friend controls may have biased the results. Friend controls are usually similar to cases in many ways, particularly with respect to their habits and exposures (46). This may have decreased the observed differences in the factors of interest. On the other hand, since friend controls are more similar to cases in many respects, any significant associations (such as gravidity), are more likely to be real. Finally, selection bias is also a possibility in the present study; many of the people who did not respond may have been healthier or sicker than the respondents.

Despite these limitations, the significant association between gravidity and PBC found in our study is an interesting, previously unreported finding which suggests the need for further

study. Larger epidemiologic studies of PBC utilizing population controls need to be conducted in order to evaluate these findings. One of the problems encountered in evaluating the results of the present study is the lack of comparable studies. While a number of epidemiologic studies of other, more common, autoimmune diseases have been conducted, information about risk factors for PBC is largely based on individual case reports or studies with extremely small sample sizes. The information from these types of epidemiologic studies needs to be combined with the results of laboratory studies in order to gain a comprehensive understanding of the pathogenesis of PBC.

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Selected Abbreviations and Acronyms

PBC	primary biliary cirrhosis
NHANES	National Health and Nutrition Examination Survey
STD	sexually transmitted diseases
HMO	health maintenance organization
RA	rheumatoid arthritis
OC	oral contraceptive
GVHD	chronic graft versus host disease

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TABLE 1

Demographic and lifestyle characteristics of female PBC cases and controls

	Cases (%) (*n* = 119)	**Controls (%) (*n* = 134)**
Mean Age (yrs.)	52.9 yrs. (S.D. = 8.1)	54.3 yrs (S.D. = 9.4)
Age Group (yrs)		
20–29	0 (0.0)	1 (0.8)
30–39	4 (3.5)	6 (4.5)
40–49	32 (27.8)	35 (26.1)
50–59	58 (50.4)	52 (38.8)
60–69	17 (14.8)	33 (24.6)
70–79	4 (3.5)	7 (5.2)
Race		
White	115 (98.3)	131 (97.8)
Other	2 (1.7)	3 (2.2)
Education (highest level completed)		
Less than high school	6 (5.0)	2 (1.5)
High school graduate	19 (16.0)	33 (24.4)
Some college/vocational school	51 (42.9)	49 (36.3)
College graduate	26 (21.9)	32 (23.7)
Graduate degree	17 (14.2)	19 (14.1)
Health Insurance (all that apply)		
Private/HMO	112 (94.1)	118 (87.4)
Medicare/Medicaid	20 (16.8)	20 (14.8)
Veteran’s Administration	1 (0.9)	0 (0.0)
Other insurance	3 (2.6)	12 (8.9)
Smoking and History of Autoimmune Disease		
Ever smoked ($p = 0.009$)	77 (64.7)	65 (48.5)
Associated autoimmune diseases ($p < 0.001$)	40 (33.6)	9 (6.7)
Family history of autoimmune disease ($p = 0.001$)	36 (30.2)	18 (13.4)

TABLE 2

Menstrual cycle characteristics of female cases and controls

	Cases (%) (*n* = 119)	Controls (%) (*n* = 134)	*p*-value*
Mean age at menarche (SD)	12.5 (1.7)	13.1 (7.6)	0.44
Menstrual Status			
Pre-menopausal	35 (29.4)	46 (34.1)	
Peri-menopausal	5 (4.2)	3 (2.2)	
Post-menopausal	79 (66.4)	86 (63.7)	0.59
Surgical menopause	42 (53.9)	33 (41.3)	
Natural menopause	37 (46.1)	53 (58.7)	
Reason for no period in past 12 months			
Menopausal	37 (45.7)	47 (56.6)	
Surgery	43 (53.1)	34 (41.0)	0.25
Breastfeeding	0 (0.0)	1 (1.2)	
Other	1 (1.2)	0 (0.0)	
Median age in years at last period (for post-menopausal women)	45.0	47.0	0.46
Women who stated that their menstrual cycle lengths varied by more than 5 days at age 20–29 years	36 (31.0)	44 (34.1)	0.60

* Differences in means were assessed by using t-tests while χ^2 tests were done to assess differences in proportions.

TABLE 3

Reproductive surgeries and use of hormones among female PBC cases and controls

	Cases (%)	Controls (%)	OR	95% CI	*p*-value
Surgeries					
Hysterectomy	35 (31.8)	35 (26.5)	1.29	0.74, 2.26	0.37
Oophorectomy	31 (26.5)	28 (21.1)	1.35	0.75, 2.43	0.31
Oral Contraceptive Use					
Ever used	97 (81.5)	96 (71.6)	1.75	0.96, 3.17	0.07
Currently use	2 (2.1)	6 (6.4)	0.31	0.06, 1.57	0.14
Mean # of years of use (S.D.)	6.8 (5.6)	7.6 (6.1)	—	—	0.44
Estrogen/Female Hormones					
Ever used	63 (53.4)	82 (61.7)	0.74	0.45, 1.21	0.22
Currently use	46 (39.5)	65 (47.8)	0.71	0.43, 1.17	0.19
Mean # of years of use (S.D.)	7.0 (5.1)	8.2 (8.0)	—	—	0.30
Ever had IUD inserted	32 (26.9)	32 (24.1)	1.16	0.66, 2.05	0.61

TABLE 4

Pregnancy history and infertility problems among female PBC cases and controls

	Cases (*n* = 119)	Controls (*n* = 134)	OR	95% CI	*p*
Mean gravidity (S.D.)	2.6 (1.9)	2.0 (1.7)	—	—	0.008
Number of Pregnancies					
0	19 (16.0)	33 (24.4)			
1–2	46 (38.7)	61 (45.2)			
3–4	35 (29.3)	30 (22.2)			
5+	19 (16.0)	11 (8.2)			
Mean age at 1st pregnancy (S.D.)	21.4 (3.7)	22.5 (4.0)	—	—	0.03
Adverse Pregnancy Outcomes (%)					
Ever had stillbirth	1 (0.9)	2 (1.5)	0.56	0.05, 6.29	0.63
Ever had miscarriage	31 (26.1)	27 (20.0)	1.41	0.78, 2.54	0.25
Ever had tubal pregnancy	8 (6.7)	9 (6.7)	1.00	0.38, 2.70	0.98
Birth defect in baby	4 (4.4)	6 (5.9)	0.74	0.20, 2.69	0.75
Complications of Pregnancy (%)					
Diabetes	3 (3.2)	2 (1.9)	1.72	0.28, 10.5	0.67
Premature labor	11 (12.0)	8 (7.7)	1.63	0.63, 4.25	0.31
Toxemia/preeclampsia/eclampsia	14 (14.9)	12 (11.3)	1.37	0.59, 3.13	0.45
Bleeding other than spotting	15 (16.3)	12 (11.4)	1.51	0.67, 3.42	0.32
Other complications	19 (27.1)	12 (23.1)	1.24	0.54, 2.86	0.61
Reproductive Problems (%)					
Endometriosis	18 (15.8)	12 (9.1)	1.88	0.86, 4.08	0.11
Inflamed or blocked fallopian tubes	8 (6.8)	5 (3.7)	1.89	0.60, 5.96	0.27
Incompetent cervix	3 (2.7)	1 (0.8)	3.52	0.36, 34.3	0.25
Fibroids or other growths of the uterus	46 (39.3)	41 (31.8)	1.39	0.82, 2.35	0.22
Growths on ovaries or tubes	22 (19.0)	15 (11.5)	1.81	0.89, 3.68	0.10
Infertility (unprotected sexual intercourse for >1 year without getting pregnant)	47 (42.0)	48 (40.3)	1.06	0.63, 1.81	0.80
Clinical or hormonal tests for problems with reproduction	12 (10.3)	13 (9.8)	1.05	0.46, 2.41	0.90

TABLE 5

Sexually transmitted diseases (STDs) and related infections among female PBC cases and controls

	Cases (*n* = 119) (%)	Controls (*n* = 134) (%)	OR	95% CI	*P*-value
Mean number of sexual partners (S.D.)	5.9 (6.3)	4.5 (5.6)	—	—	0.07
Age at First Sexual Activity (S.D.)	18.5 (2.8)	19.3 (3.3)	—	—	0.05
Any STD	22.5 (18.5)	14 (10.4)	1.96	0.95, 4.03	0.06
Chlamydia	1 (0.90)	2 (1.5)	0.57	0.05, 6.31	1.000
Gonorrhea	3 (2.7)	1 (0.8)	3.50	0.36, 34.1	0.25
Herpes	6 (5.1)	5 (3.7)	1.38	0.41, 4.65	0.60
Syphilis	1 (0.9)	0 (0.0)	—	—	0.46
Trichomonas	9 (7.6)	5 (3.8)	2.11	0.69, 6.50	0.18
Other STD	8 (6.9)	6 (4.6)	1.56	0.52, 4.62	0.42
Pelvic inflammatory disease	4 (3.6)	4 (3.0)	1.19	0.29, 4.85	1.00
Urinary tract infection	79 (68.7)	64 (48.1)	2.37	1.40, 3.98	0.001
Vaginal infection	71 (63.4)	44 (35.2)	3.19	1.87, 5.42	<0.0001

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TABLE 6

Results of four models for multiple logistic regression analyses

All cases and controls (*n* = 253)								
	Matched				**Unmatched**			
Variable	**β**	**Odds ratio**	**95% CI**	***P*-value**	**β**	**Odds ratio**	**95% CI**	***P*-value**
Associated autoimmune diseases	2.481	11.96	3.33, 42.93	0.0001	1.795	6.02	2.65, 13.6	<0.0001
Gravidity[a]	0.253	1.29	1.03, 1.61	0.026	0.199	1.22	1.04, 1.43	0.013
Ever smoked	0.960	2.61	1.27, 5.36	0.009	0.657	1.93	1.11, 3.37	0.021
GU Infection	0.536	1.71	0.78, 3.75	0.182	0.821	2.27	1.23, 4.21	0.009
Cases & controls without other autoimmune diseases or family history of autoimmune disease (*n* = 170)								
Gravidity[a]	0.334	1.40	1.14, 1.71	0.001	0.171	1.19	0.98, 1.43	0.073
Ever smoked	1.540	4.67	2.13, 10.22	0.010	0.870	2.39	1.21, 4.71	0.012
GU Infection	0.750	2.12	1.01, 4.42	0.0001	0.858	2.36	1.17, 4.76	0.017

[a]Continuous variable, odds ratio is for each additional pregnancy.