Clinic Rev Allerg Immunol (2015) 48:236–242
DOI 10.1007/s12016-014-8433-z

Pregnancy and Primary Biliary Cirrhosis: A Case-Control Study

Annarosa Floreani · Chiara Infantolino · Irene Franceschet · Ivette Magne Tene · Nora Cazzagon · Alessandra Buja · Vincenzo Baldo · M. Eric Gershwin · Maria Teresa Gervasi

Published online: 3 July 2014

Abstract A very critical feature in women's health is the identification of risk factors for pregnancy and adverse fetal outcome. Primary biliary cirrhosis is an autoimmune disease of the liver that predominantly affects older women. However, the serologic onset of this disease appears to precede clinical manifestations by many years. The goal of this case controlled study was to analyze fertility in primary biliary cirrhosis (PBC) and investigate the outcome of pregnancy, and the influence of pregnancy on the course of the disease. The study included 233 consecutive female patients with PBC seen between 1987 and 2012. Among them, 186 had at least one conception and were matched for age with a 1:2 group of controls (367 healthy women with at least one conception in their life). PBC patients experienced 507 pregnancies as opposed to 700 pregnancies among controls (mean 1.91 vs 2.73, $p<0.05$). The two groups' life history was similar in terms of miscarriages, voluntary interruptions of pregnancy, and term and preterm deliveries. The rates for one or more cesarean deliveries were lower for PBC patients (5.7 vs 11.7 %, $p<0.05$). Pruritus during pregnancy was recorded in 15 pregnancies involving 13 PBC patients (3.0 %) and none of the controls. Perinatal and postnatal deaths and complications at childbirth were only recorded in the PBC patients, involving a total of 11 babies (2.7 %, $p<0.05$). Eight pregnancies occurred after PBC was diagnosed in six patients, all of which had a favorable course at term, with no complications at childbirth. Ursodeoxycholic acid was continued during pregnancy and no exacerbation of the disease was observed. In conclusion, successful completion of pregnancy is a realistic expectation for PBC patients, though pregnancy and delivery must be monitored for the potentially higher than normal risk of childbirth complications.

Keywords Primary biliary cirrhosis · Pregnancy · UDCA · Fertility

Abbreviations

PBC	Primary biliary cirrhosis
AMA	Antimitochondrial antibody
AST	Aminotransferase
SSc	Systemic sclerosis
UDCA	Ursodeoxycholic acid

Introduction

Pregnancy induces changes in maternal immunity, in particular leads to a shift of TH1 cellular response to a TH2 humoral response [1]. This process is necessary to maintain the fetus against the immunological processes of recognition and elimination of nonself molecules [2]. Moreover, the emerging role if interleukin 12 (IL-12), IL-15, IL-18, and other unidentified soluble factors dependent on natural killer (NK) cells have been reported [3]. In general, the relationship between pregnancy and autoimmunity can be represented by a bidirectional model: autoimmune diseases may be affected by pregnancy,

A. Floreani (✉) · I. Franceschet · I. M. Tene · N. Cazzagon
Department of Surgery, Oncology and Gastroenterology - DiSCOG, University of Padova, Via Giustiniani, 2, 35128 Padova, Italy
e-mail: annarosa.floreani@unipd.it

C. Infantolino
Department of Obstetrics and Gynecology, Azienda Ospedaliera, Padova, Italy

A. Buja · V. Baldo · M. T. Gervasi
Laboratory of Public Health and Population Studies, Department of Molecular Medicine, University of Padova, Padova, Italy

M. E. Gershwin
Division of Rheumatology, Allergy and Clinical Immunology, University of California at Davis School of Medicine, Davis, CA 95616, USA

and vice versa, pregnancy may be affected by autoimmunity. Nonetheless, pregnancies in most autoimmune diseases are still classified as high risk because of the potential for major complications, including disease exacerbation during pregnancy and increased fetal mortality. One of the major goals in improving women's health is identification of factors that adversely impact pregnancy and fetal outcome and this has been the focus of attention not only on systemic autoimmune diseases such as systemic lupus erythematosus (SLE), but also on organ-specific diseases, including autoimmune hepatitis [4–18].

One of the most severe complications of pregnancy is pre-eclampsia, which affects 1–5 % of pregnancies worldwide in otherwise healthy women, the frequency being much higher in a variety of autoimmune diseases, e.g., anti-phospholipid syndrome (APS), type 1 diabetes, systemic lupus erythematosus (SLE), systemic sclerosis, rheumatoid arthritis (RA), and other connective tissue diseases. Pre-eclampsia is still an unexplained syndrome for which several mechanisms have been hypothesized. However, the possible association between maternal infection and pre-eclampsia has been the subject of two recent systematic reviews and meta-analyses [19, 20]. Recurrent miscarriages and fetal mortality are characteristic of the APS. The hallmarks of this syndrome are vascular thrombosis involving both the venous and arterial beds, as well as placental circulation; thrombosis in the placental vasculature may lead to infarctions and placental insufficiency [21]. The prognosis in APS-untreated patients is poor with only 10 % of less of all pregnancies resulting in live births [3]. Nonetheless, the live birth rate has now significantly improved raising to 47.7 % in the 590 women from the Euro-phospholipid project who had been pregnant [22].

There are in the literature two paradigms for the influence of pregnancy on established autoimmune disease. One is the RA in which a marked beneficial effect of pregnancy has been reported [23]. Other studies indicated that there is a disease flare in postpartum; moreover, an association between RA and preterm delivery and lower birthweight infants has been demonstrated [24].

In pregnancy, placental transfer of maternal IgG antibodies to the fetus is an important mechanism providing protection to the infant until the neonate's own immune system matures [25]. A growing body of recent literature is the use of tumor necrosis factors inhibitors (TNFI) or the biologic agents for the treatment of RA (and other autoimmune disease). Of note, there are observational studies showing that a substantial number of women will conceive while on these agents [26]. Cumulative evidence suggests that TNFI use during pregnancy carriers low risk for teratogenicity. The second paradigm is SLE which is characterized by a loss of tolerance both in the T and B cell compartment. One important factor that has emerged is the response of SLE to sex hormones. The high concentration of estrogens as achieved in pregnancy enhances antibody production, T-helper type 2 immune responses, and B-cell immunity [23]. Pregnancy in patients with SLE is often a critical moment that on one hand affects the course of the disease in the mother and on the other may have implications on the embryo/fetus [3]. Approximately 60 % of patients with SLE suffer from flares during pregnancy [3]; moreover, women with SLE have been shown to have up to 23 % of risk of pre-eclampsia, especially in the case of co-existence of APL syndrome [27]. Pregnancy loss remains one of the most concerning complications of pregnancy, although its frequency has dropped significantly over the past few decades from levels as high as 43 % in the 1960s to 17 % in the early 2000s [28].

Finally, within the autoimmune liver diseases, autoimmune hepatitis (AIH) represents an important problem for the management of pregnancy. In fact, AIH affects predominantly females of childbearing age. In general, there is a favorable outcome of pregnancy in these patients. However, a poor disease control in the years prior to pregnancy and the absence of drug therapy are associated with poor outcomes while pregnant [18].

Primary biliary cirrhosis (PBC) is a chronic cholestatic liver disease with a predilection for the female gender, characterized by destruction of intrahepatic bile ducts that ultimately progresses to cirrhosis [29]. The disease generally develops roughly around menopausal age, but with a broad range that includes both the fertile and the geriatric age groups. Pregnancies after PBC has been diagnosed are rather uncommon, and there are limited reports in the literature specifically focusing on the outcome of pregnancy in PBC patients, nor on the effect of pregnancy on the liver disease. A recent retrospective study identified 32 women (50 pregnancies) who either became pregnant after a diagnosis of PBC or in whom pregnancy led to diagnosis [30]. Liver chemistry remained stable in 70 % of patients throughout pregnancy in 70 % of cases, no adverse maternal events were observed during pregnancy or postpartum, and only 6 % developed progressive disease following delivery [30]. An intriguing case-control study was published in 2002 [31]. When a standardized questionnaire from the National Health and Nutrition in the USA was administered to 182 PBC patients and 225 age- and sex-matched friend controls, the results showed that there were significantly more pregnancies among the PBC cases than among the controls. This study suffered from several limitations; however, there was no confirmation of the self-reported data, no information on the timing of the pregnancies (before or after PBC was diagnosed), the bias in the selection of the control group.

Another interesting point is the assumption of a reduced fertility in PBC. It has been reported that PBC patients have a history of miscarriages, limited fertility, and hysterectomies before the onset of the disease, suggesting an impaired hormone status [32]. There are several possible explanations for

this situation, however. Patients with PBC do not seem to have a specific sex hormone impairment [33]. When compared with healthy subjects, PBC patients had higher serum sex hormone binding protein levels and lower serum testosterone levels—a profile compatible more with their liver dysfunction than with any altered sex hormone metabolism peculiar to PBC.

The aim of the present study was to analyze fertility in PBC and investigate the outcome of pregnancy in women with PBC, and also the influence of pregnancy on the course of their disease.

Materials and Methods

This study concerned all consecutive female patients with a diagnosis of PBC collected between 1987 and 2012 with a follow-up of at least 1 year: the sample included 233 patients with a mean age at diagnosis of 52.9±12 years. PBC was diagnosed on the basis of antimitochondrial antibody (AMA) positivity higher than 1:40, abnormal alkaline phosphatase levels (at least 1.5 times the normal value), and/or a compatible liver histology. Ninety-five patients (40.7 %) were in histological stage I, 23 (9.8 %) in stage II, 57 (24.4 %) in stage III, and 24 (10.3 %) in stage IV according to Scheuer's classification [34]. Thirty-four patients (14.5 %) did not undergo liver biopsy. Information on their clinical data, recruitment, diagnostic criteria, and follow-up are available elsewhere [35]. All patients were treated with ursodeoxycholic acid (15 mg/kg/day) and underwent a physical and biochemical examination every 6 months after their initial diagnosis. At each visit, relevant clinical data were recorded as well as biochemical test findings. In the event of pregnancy during the follow-up, PBC patients were assigned to a team for the management of high-risk pregnancies (at the Department of Obstetrics and Gynecology, Padova General Hospital). Patients joined a specific program that included monthly physical examination, ultrasonography, and liver function tests. All patients were also monitored at and after delivery.

An adverse pregnancy outcome was defined as a spontaneous abortion for which there was no obvious medical explanation (e.g., chromosomal aberrations) or a preterm delivery before the 36th week of gestation leading to perinatal death or severe disability. Death between the 27th week of gestation and 7 days after birth was defined as perinatal, and death beyond 7 days after birth as postnatal.

The control group (1:2 selection) consisted of 367 healthy women consecutively selected among normal pregnant patients who were followed longitudinally in the Department of Obstetrics and Gynaecology, Azienda Ospedaliera, Padova. Patients of the control group were matched for age at the time of pregnancy with the 186 PBC patients who became pregnant. All of them had a normal pregnancy and had a regular follow-up.

In each pregnant woman who served as control, liver diseases were ruled out with the standard liver function tests, and liver diseases peculiar to pregnancy, in particular intrahepatic cholestasis of pregnancy, were also ruled out.

A detailed questionnaire was administered to each patient and control subject, containing information on their reproductive life, including the following: the number of previous pregnancies, live birth rate, miscarriages and terminations, symptoms profile during pregnancy, and maternal and infant complications. The presence of pruritus was evaluated according to a visual analogue scale scoring to 0–10 and was considered present when score reached at least 7.

The study which was approved by the local Ethical Committee and all patients and controls gave their informed consent to their participation.

Statistical Analysis

For the statistical analysis, to compare continuous variables, normality was verified using the Shapiro-Wilk test. Where normally distributed, mean differences among two groups were compared using Student's *t*-test. In cases where the assumption of normality was violated, data were analyzed using the nonparametric Mann-Whitney test. In the PBC group, a logistic regression analysis (with 95 % confidence intervals) was used as appropriate. In case of pregnancy preceding the diagnosis of PBC, the histological stage during pregnancy was arbitrarily estimated calculating the time interval between the pregnancy and the diagnosis, with the assumption that the histological progression to a more advanced stage requires a median time of 8 years. The statistical analysis was completed using SPSS software (Chicago, Il, USA).

Results

Among the 233 PBC patients, 186 had at least one conception (79.8 %) during their fertile life. There were 507 pregnancies in PBC patients (only eight of them after they had been diagnosed with PBC) and 700 pregnancies in controls; the difference was statistically significant: the mean number of pregnancies among PBC cases was 2.7±1.5 vs 1.9±1.4 in controls ($p<0.05$). The mean age of PBC patients when they became pregnant was 29.5±5.6 years and in controls was 28.9 ±4.8, p=n.s. The mean interval between the age at pregnancy and the age at diagnosis was 20.8±12.7 years. The estimated stage during pregnancy, according to the time interval between the age at pregnancy and at diagnosis, was I in 6.5 % of the pregnancies in PBC patients, II in 3.5 %, III in 1.6 %, IV in 0.6 %, not applicable in 37.3 %, while in 50.5 % of PBC

Table 1 Pregnancy in 186 patients with PBC and 367 controls

	PBC patients (no. 186)	Controls (no. 367)	*P*
Mean age when pregnant (years)	29.5±5.6	28.9±4.8	n.s.
No. of pregnancies	507	700	<0.05
Before onset of PBC	499		
After diagnosis of PBC	8		
Mean±SD of pregnancies	2.73±1.50	1.91±1.14	<0.05
Miscarriages	87 (17.2 %)	153 (21.8 %)	n.s.
Voluntary interruptions of pregnancy	11 (2.2 %)	16 (2.3 %)	n.s.
Pruritus during pregnancy	15 (3.0 %)	–	<0.05
Total deliveries	409 (80.7 %)	531 (75.9 %)	n.s.
Vaginal delivery	380 (74.9 %)	449 (64.1 %)	<0.05
Cesarean delivery	29 (5.7 %)	82 (11.7 %)	<0.05

pregnancies, there was no evidence of liver disease (estimated stage during pregnancy=0). The two groups' life history in terms of miscarriages, voluntary interruptions of pregnancy, and deliveries at term was much the same (Table 1). The risk of miscarriage in PBC patients, corrected for the age at pregnancy and the number of previous miscarriages, was inversely associated with the estimated early histological stage during pregnancy (stages I–II: odds ratio (OR) 0.32, 95 % confidence interval (CI) 0.10–0.97, $p<0.05$), but not with the advanced stage (stages III–IV: OR 0.53, 95 % CI 0.09–3.05, p=n.s.). The cesarean delivery rate was significantly higher in controls than in PBC patients (5.7 vs 11.7 %, OR 0.52, 95 % CI 0.29–0.94, $p<0.05$) (Table 1). Pruritus during pregnancy was recorded for 15 pregnancies in 13 patients with PBC (3 % of 507 pregnancies) and none of the controls ($p<0.05$).

The occurrence of pruritus was associated with the advanced estimated histologic stage during pregnancy, corrected for age at pregnancy (stages I–II: OR 13.8, 95 % CI 1.21–156.74, $p<0.05$; stages III–IV: OR 21.6, 95 % CI 2.18–214.25, $p<0.05$).

Table 2 shows the outcome of pregnancies for the PBC patients and controls. The proportion of preterm deliveries was similar in both PBC patients and controls (2.78 vs 2.8 %, p=n.s.). Perinatal and postnatal deaths were recorded only in the PBC group (and the difference between the groups was statistically significant for perinatal death, $p<0.05$). Childbirth complications were recorded in six newborn in the PBC group (1.21 %) vs none in the control group ($p<0.05$), and involved placenta previa in five cases and fetal distress in one.

Eight pregnancies occurred after PBC had been diagnosed in six patients (two of them with histological stage IV disease, without portal hypertension) (Table 3). Their age at delivery ranged between 26 and 40 years, they all delivered at term, and their pregnancies all had a favorable course: five had vaginal and three cesarean deliveries. In two pregnancies, pruritus developed at the third trimester. Ursodeoxycholic acid (UDCA) was continued during pregnancy and no exacerbation of PBC symptoms was observed. Three mothers had a significant increase in serum liver enzymes levels after delivery (nos. 4, 5, and 6), which returned to normal within 6 months. The newborn's male to female rate was 1:1; the birth weight ranged between 2.12 and 3.78 kg (mean 3.15± 0.48 kg), and none of the babies suffered from complications (Table 4).

Discussion

The results of our study indicate that pregnancy is quite rare after the onset of PBC—hardly surprisingly, since the disease tends to develop mainly around menopause. Pregnancy is nonetheless a realistic expectation for PBC patients of fertile age. The disease has a very long natural history, particularly in the asymptomatic phase—the duration of which, in the absence of altered liver function test findings, is unknown, but may last roughly 15–20 years [36]. The life history of patients is consequently very important when it comes to exploring any fertility anomalies. It is worth emphasizing that PBC patients' mean age of both menarche and menopause was within normal range, and only 5.6 % of them had menstrual irregularities—a rate well within the limits of the general population (reportedly up

Table 2 Outcome of pregnancy in PBC patients and controls

	Pregnancies in PBC patients, n=507 (%)	Pregnancies in controls, n=700 (%)	*P*
Total deliveries	409 (80.7)	531 (75.9)	n.s
Preterm delivery	14 (2.7)	20 (2.8)	n.s.
Perinatal death	3 (0.6)	0	<0.05
Postnatal death	2 (0.4)	0	n.s.
Childbirth complications	6 (1.21)	0	<0.05
Placenta previa	5 (1)		
Fetal distress	1 (0.2)		

Table 3 Maternal outcome in eight conceptions in PBC patients after the diagnosis of their disease

N	Age at diagnosis	Histological stage	AMA	Age at delivery	Maternal complications	Type of delivery	Maternal outcome	Peak GGT/ALP after delivery (IU/L)	Peak AST/ALT after delivery (IU/L)
1[a]	24	IV	+	26	–	Vaginal	Alive/stable	250/360	40/45
2[a]	24	IV	+	28	Pruritus	Vaginal	Alive/stable	350/324	70/116
3	35	I	+	38	–	Cesarean	Alive/stable	12/68	24/39
4	38	I		40	–	Vaginal	Alive/stable	377/502	450/1,025
5	32	IV	+	33	Pruritus	Vaginal	OLTx after 20 years, died after 3 years	276/524	151/284
6	32	III	+	33	–	Vaginal	Alive/stable	277/493	76/122
7[a]	29	I	+	35	–	Cesarean	Alive/stable	209/1,419	46/68
8[a]	29	I	+	40	–	Cesarean	Alive/stable	300/506	50/65

[a] Two pregnancies in the same woman

to 25 % in adolescent girls and up to 53 % in adult females) [37, 38]. These results also confirm our previous findings of a normal sex hormone profile in women with PBC [33]. We found a significantly higher overall number of pregnancies among PBC patients than in controls, confirming a previous report by Parikh-Patel et al. [31]. There is no full explanation for this finding as yet, but the hypothesis that pregnancy is a risk factor for triggering autoimmune diseases may partially explain it. Interestingly, a study by Cockrill et al. [39] showed that having at least one pregnancy (leading to delivery or fetal loss) before developing systemic sclerosis (SSc) was associated with the onset of the disease. SSc patients with pulmonary fibrosis have also been shown to have more children than patients without pulmonary fibrosis [40]. Another theory relating to fetal microchimerism has been advanced, based on the observation that most autoimmune liver diseases have a peak incidence following the fertile period, and that maternal and fetal cells are exchanged during pregnancy, leading to fetal cell persistence in the mother. Be that as it may, cumulative data on the role of microchimerism in PBC are weak or inconclusive, bearing in mind that microchimerism is not uncommon in healthy women [41].

The mean age at pregnancy was similar in the PBC group compared to controls (29.5±5.6 vs 28.9±4.8 years); however, most of PBC patients had pregnancy before the diagnosis of the liver disease (approximately 20 years before), indicating that these patients were presumably in the asymptomatic phase of the disease during pregnancy, and the histological stage at that time was obviously unknown. Interestingly, the mean age at the diagnosis of PBC was similar in patients who became pregnant as in nulliparous (53.1±12.4 vs 52.2±12.5, p=n.s.). These data suggest that parity does not seem to influence the age of onset of PBC, unlike for other autoimmune disease, as scleroderma (SSc) [42]. We also found that 3 % of our PBC patients experienced pruritus during pregnancy, suggesting that cholestatic abnormalities were probably already presents and exacerbated by pregnancy, even in the absence of an evident liver disease.

Our findings also go to show that there is no higher risk of miscarriage or preterm delivery in PBC patients than in age-matched controls, nor does the type of delivery differ between the two groups. We observed a higher risk of perinatal death and childbirth complications in our PBC group, but no fetal malformations; the main problem was placenta previa, observed in 1 % of cases. The risk of placenta previa in the general population is reportedly low, at around 5 per 1,000 pregnancies, with some regional variations; the prevalence in Europe is 3.6 per 1,000 [43]. We found a higher rate of cesarean deliveries in controls than in PBC patients, but this type of delivery is often related to the woman's personal choice rather than for medical reasons. More interestingly, the eight conceptions occurring after PBC was diagnosed were monitored accurately by a specialized team. Notably, three of these pregnancies occurred in two women with cirrhotic livers (one of them underwent liver transplantation 20 years after delivery and died 3 years later, but the long time elapsing between delivery and liver transplantation means that the unfavorable course of her PBC was not pregnancy-related). The outcome of pregnancy was favorable in all cases and with no apparent exacerbation of the liver

Table 4 Fetal outcome in eight conceptions in PBC patients after the diagnosis of their disease

N.	Gestational week	Birth weight (kg)	Apgar 0/5 min	Gender	Childbirth complications
1[a]	39	3,100	9/10	M	NO
2[a]	38	3,250	9/10	F	NO
3	38	2,210	9/10	F	NO
4	39	3,780	9/10	F	NO
5	37	3,125	9/10	M	NO
6	38	3,135	9/10	F	NO
7[a]	39	3,105	9/10	M	NO
8[a]	38	3,554	9/10	M	NO

[a] Two pregnancies in the same woman

disease. The main limitation of our study the lack of defining the timing of pregnancy within the natural course of the disease. In the attempt to approximately estimate this timing, we arbitrarily calculated the time interval between the pregnancy and the diagnosis, with the assumption that the histological progression to a more advanced stage requires a median time of 8 years. As expected, either the risk of miscarriage and the risk of pruritus in pregnancy is much more frequent in advanced estimated histological stage during pregnancy.

Finally, we showed that UDCA during pregnancy is safe and well tolerated. Although the safety and efficacy of UDCA treatment for intrahepatic cholestasis of pregnancy was demonstrated in a meta-analysis [44], few reports have been published on the use of UDCA during pregnancy in PBC patients. In a clinical case report involving a 41-year-old patient with stage III PBC [45], UDCA was withdrawn when she became pregnant, and she developed severe pruritus together with a rise in cholestatic enzymes. UDCA treatment was restored and prompted a rapid improvement in pruritus and liver function tests, and no drug-related side-effects were detected during pregnancy and lactation. A report from a French group [46] described six patients with PBC having nine pregnancies: their UDCA treatment was withdrawn in the first trimester and restored during the second and third. All the women remained asymptomatic and their liver function tests fell within normal range for a normal pregnancy; and there were no delivery issues or childbirth complications. There was a flare in liver function test findings after delivery, which returned to normal within 12 months in all but two patients. Our data confirm the safety of UDCA throughout pregnancy—and the absence of any significant enzyme flares in our patients could well be because the treatment was not suspended.

In conclusion, successful completion of pregnancy and a favorable outcome is a realistic expectation for PBC patients. UDCA treatment must be continued throughout pregnancy to prevent the liver disease from progressing. It is nonetheless essential to monitor pregnancy and delivery carefully in PBC patients due to a potentially higher risk of childbirth complications.

Financial Support The work was partially supported by a grant from Padova University.

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