Pregnancy in primary sclerosing cholangitis

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Revised 17 January 2011
Accepted 19 January 2011
Published Online First 21 February 2011

ABSTRACT

Background There is a paucity of data on fertility or pregnancy in patients with primary sclerosing cholangitis (PSC).

Objective To assess fertility in PSC by comparing the number of children in a large cohort of PSC patients to healthy controls and to investigate the outcome of pregnancy, as well as the influence of pregnancy on the disease course.

Design Case series.

Setting Germany.

Participants 229 PSC patients and 569 healthy controls were evaluated for the number of children. 17 patients with PSC and at least one pregnancy, or who received a diagnosis of PSC within 6 months after delivery, were included in the more detailed analysis.

Main outcome measures Number of children per patient and control; disease activity during pregnancy and after delivery including maternal complications; long-term development of live births, fetal loss rate and the influence of medication on fetal and maternal outcome.

Results Fertility did not seem to be reduced in PSC since the number of children did not differ between PSC patients and healthy controls. 25 pregnancies in 17 female PSC patients (median age at conception 31 years) were investigated in detail. An increase in liver enzymes was documented during five pregnancies (20%) and eight times (32%) post-partum. There were no serious maternal complications. All 21 live births presented with a normal perinatal and postnatal development over a median observation time of 50 months. Two pregnancies were delivered pre-term and four fetal losses occurred early in pregnancy (<12 wk). Continuation of treatment with ursodeoxycholic acid (15/21) or azathioprine (2/21) had no negative effects on pregnancy outcome.

Conclusions Fertility does not seem to be reduced in patients with PSC, who are able to deliver healthy children without an apparent increase in risk for mother or child.

Significance of this study

What is already known about this subject?

- Potential effects of primary sclerosing cholangitis (PSC) on fertility are unknown.
- Few case reports have described pregnancy in PSC with variable maternal and fetal outcomes.

What are the new findings?

- Fertility does not seem to be reduced in patients with PSC as compared to healthy controls.
- Pregnancy in patients with PSC resulted in a normal fetal outcome.
- Despite a frequent rise in serum liver tests, no serious maternal complications were observed during pregnancy or after delivery.

How might it impact on clinical practice in the foreseeable future?

- PSC frequently presents in child-bearing age. The study reported provides new data required for the counselling and care of patients with PSC and pregnancy.

INTRODUCTION

Primary sclerosing cholangitis (PSC) is a chronic inflammatory and fibrosing disease of intra- and/or extrahepatic bile ducts leading to end-stage liver disease or cholangiocarcinoma in 10–20 years.[1 2] Since the onset of disease usually occurs before the age of 40, many female patients with PSC will be of child-bearing age. The desire to have a family frequently raises questions about the outcome of pregnancies including the associated risks for the mother and the best treatment and surveillance strategies.

Pregnancy may affect the course of autoimmune and immune-mediated diseases such as systemic lupus erythematosus and rheumatoid arthritis, as well as autoimmune hepatitis (AIH) and primary biliary cirrhosis.[3–9] Although the aetiology of PSC is still unknown, some characteristics such as the strong association with inflammatory bowel disease, HLA and other genetic associations, as well as histological and serological findings, point to an immune mediated, if not autoimmune pathogenesis.[10 11] Therefore, the course of PSC may be affected by pregnancy as well. To date, only a few cases of pregnancy and PSC have been published and there is no information about whether the disease affects fertility.[11–14] This renders the counselling of young patients with PSC and the care of patients with PSC and pregnancy difficult.

We here report the outcome of 25 pregnancies in patients with PSC and the effect of pregnancy on the disease course. In addition, the number of children from parents with PSC was compared to healthy controls in a large number of subjects in order to assess a potential reduction of patient's fertility. Pregnancy did not seem to have a negative impact on the short-term course of disease and, overall, pregnancy outcomes were favourable. Moreover, the number of children was not different between patients with PSC and healthy controls.

PATIENTS AND METHODS

The population-based recruitment of patients and controls for the analysis of complex genotype-phenotype relationships (PopGen) is a validated database that has been previously described.[15] For this study, the registry was queried for PSC patients and data on gender, age, presence of inflammatory bowel disease (IBD) and number of children. From the same database, information on the number of children was obtained from a healthy control group.

Patients diagnosed with PSC by generally accepted criteria[1 2 16] were included in the detailed analysis if they became pregnant after the diagnosis of PSC or if they had been diagnosed with PSC within 6 months from delivery or pregnancy loss. The records of female patients with PSC from the University Medical Center Hamburg-Eppendorf identified 11 patients who fulfilled the inclusion criteria. Three additional patients were included from the liver units of the Universities of Munich and Mainz. Three more patients could be identified by contacting the German patient support group (AK PSC of the Deutsche Crohn und Colitis Vereinigung, DCCV). Data was acquired retrospectively from patient records and prospectively by questionnaires addressing disease status at the time of pregnancy and pregnancy outcome.

Adverse pregnancy outcome was defined as a spontaneous pregnancy loss for which no obvious medical explanation was present (eg, chromosomal aberrations) or a pre-term delivery before the 36th week of gestation leading to perinatal death or severe disability. A flare in disease activity was defined as a rise in bilirubin, ALT or alkaline phosphatase to more than twofold of the latest pre-pregnancy value or reappearance of typical symptoms. Due to the natural rise in alkaline phosphatase levels during the third trimester caused by the placenta and increased maternal bone turnover,[17] an isolated rise in alkaline phosphatase levels was not rated as an acute flare during that period of pregnancy.

The study conformed to the guidelines of the 1975 Declaration of Helsinki and was approved by the local ethics committee. All patients gave written informed consent.

RESULTS

Number of children in PSC patients and healthy controls

We were first interested whether PSC results in reduced fertility leading to a lower number of children per person as compared to healthy controls. The number of children in 229 patients with PSC was compared to an age-matched healthy control group (n=569, table 1) from a prospectively acquired data base. Fifty nine per cent of PSC patients had concomitant inflammatory bowel disease. The number of children did not differ between patients and controls and the presence of PSC had no effect on the number of children per individual or the rate of nulliparity as compared to healthy controls. Also, there was no significant difference between men and women in the PSC or control group with regard to the number of children or the rate of nulliparity (tables 1 and 2). These data suggest that fertility may not be reduced in patients with PSC. In multivariate logistic regression analysis, the presence or absence of IBD had no influence on fertility of patients with PSC (data not shown).

Analysis of pregnancy in PSC—patient characteristics

Twenty-five pregnancies in 17 women with PSC could be investigated in more detail. Patient characteristics are given in table 3. The median age at diagnosis of PSC was 26 years (range 13–36) and the median age at conception was 31 years (range 22–37). One woman was diagnosed with PSC within 3 months after delivery. Two patients had histologically proven compensated liver cirrhosis at the time of pregnancy and concomitant IBD was present in 14 patients. In two patients, overlap syndrome with AIH had been diagnosed.

Table 1 Clinical characteristics and number of children from PSC patients and healthy controls obtained from the PopGen database

	PSC n=229		Healthy controls n=569	
	n	%	n	%
Female	86	38	233	41
With children	121	53	303	53
IBD	136	60	0	0
Ulcerative colitis	93	41	–	–
Crohn's disease	22	10	–	–
Indeterminate colitis	21	9	–	–
w/o IBD	89	39	–	–
Unknown	4	2	–	–
	Mean	SD	Mean	SD
Age (years)	44	13	42	13
Children/person	1.06	1.14	1.01	1.08
Children/sex				
Females	1.16	0.981	0.91	1.062
Males	0.92	1.209	1.07	1.086

PSC, primary sclerosing cholangitis; IBD, inflammatory bowel disease.

Maternal outcome

No serious adverse events were recorded in those patients with known PSC at the time of conception (table 4). It was noted that there were no complications in the two patients with known liver cirrhosis. Disease activity was assessed by changes in liver enzymes during pregnancy and after delivery. Data on liver enzymes before, during and after pregnancy were available in 20 of 21 live births. Details on the course of liver enzymes are given in figure 1. In 20% of pregnancies an elevation of liver enzymes above twice the pre-pregnancy value occurred during pregnancy and in 32% after delivery. This led to treatment modifications with an increased UDCA dose in two pregnancies. However, enzyme activity returned to pre-pregnancy levels in most patients within a few months after delivery.

Intrahepatic cholestasis of pregnancy (ICP) was suspected by the consulting hepatologist to cause the rise in liver enzymes within the third trimester in at least two pregnancies. In both of these patients severe pruritus developed during the last trimester as the primary clinical symptom. In one of the patients the onset of mild pruritus was after the 16th week of gestation but worsened severely in the last trimester. Of note, less severe symptoms were also present in the first pregnancy during the last trimester. There was no evidence of biliary obstruction or dominant stenoses by ultrasound examination; total bilirubin was in the upper normal range, the serum transaminases and γ glutamyl transpeptidase levels were up to threefold elevated. In

Table 2 Factors influencing the presence or the number of children in PSC patients or healthy controls

	Presence of children		Number of children	
	p	95% CI	p	95% CI
PSC/control group	0.83	0.66 to 1.40	0.88	−0.14 to 0.16
Gender	0.45	0.62 to 1.24	0.64	−0.11 to 0.17
Age	0.00	0.88 to 0.91	0.00	−0.04 to 0.05

Table 3 Characteristics of patients with PSC and pregnancy

Patients, n	17
Median age at conception, years (range)	31 (22–37)
Pregnancies, n	25
Patients with cirrhosis, n (%)	2 (12)
Inflammatory bowel disease, n (%)	14 (82)
Ulcerative colitis, n (%)	10 (59)
Crohn's disease, n (%)	3 (18)
Indeterminate colitis, n (%)	1 (6)
Autoimmune hepatitis overlap, n (%)	2 (12)

the second patient, elevated total fasting serum bile acid levels were documented with 53.0 μmol/l (reference 0–7.9 μmol/l).

One clinically relevant cholangitis episode requiring antibiotic treatment was recorded but no emergency endoscopic retrograde cholangiography was required in any of the patients during pregnancy. However, in one patient with cirrhosis who had been repeatedly treated with endoscopic balloon dilatation before pregnancy, dilatation of a dominant stenosis had to be performed within two months after delivery due to rising serum bilirubin levels. Liver enzymes improved in only 8% of cases during pregnancy.

Pruritus is common both in PSC and in pregnancy. Patients reported pruritus before pregnancy in five cases and in two of these, pruritus improved during pregnancy. Two patients developed pruritus de novo during pregnancy, of which one may have been related to the onset of ICP and another one appeared after discontinuation of UDCA treatment and improved after reintroduction of the drug. Patients complained of worsening pruritus post-partum in three cases and in one case this led to an increase in UDCA dosage as compared to the pre-conceptional dosage.

Only one flare of ulcerative colitis was recorded during pregnancy and none post-partum.

Pregnancy outcome

The 25 recorded pregnancies resulted in 21 live births with a median birth weight of 3200 g (range 1694–4075 g, table 5). Delivery was in the 39th week of gestation (range 31–41). All of the 21 live births had a normal perinatal development with a median APGAR score of 10 (range 7–10). The children developed normally over a median observation time of 50 months (range 3–132). Two pregnancies resulted in pre-term delivery before the 36th week of gestation due to ICP and pre-term ruptured membranes, respectively. Seven of the 21 children were delivered via caesarian section and one vacuum extraction had to be performed. No serious complications were reported for the other 13 vaginal deliveries.

Table 4 Maternal outcome in 17 PSC patients with 25 pregnancies

	n	%
Maternal death or liver transplantation	0	0
Biochemical activity		
Increase in liver enzymes during pregnancy	5	20
Increase in liver enzymes post-partum	8	32
IBD activity (n=14 with IBD)		
Flare during pregnancy	1	7
Flare post-partum	0	0
Pruritus		
Before pregnancy	5	20
During pregnancy	7	28
Post-partum	4	16

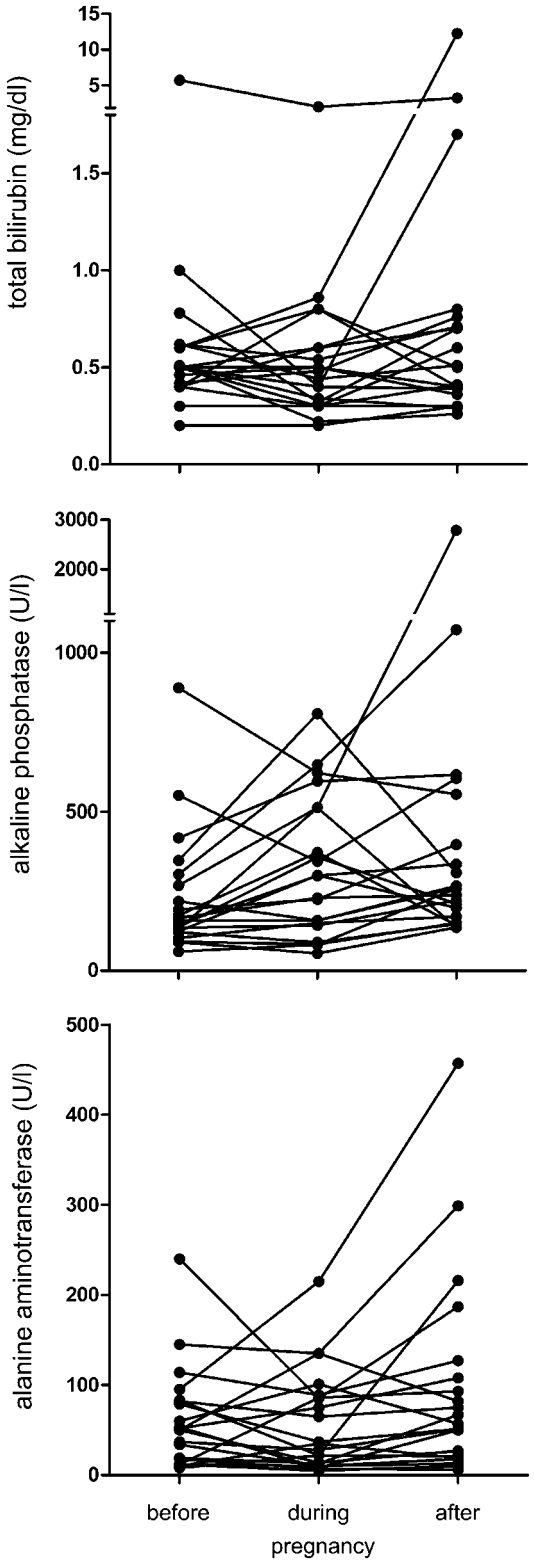

Figure 1 Serum liver tests before, during and after pregnancy in patients with PSC.

Adverse pregnancy outcomes

Four of the 25 pregnancies ended with a spontaneous pregnancy loss, giving a fetal loss rate of 16% (table 5). The median gestational week at the time of pregnancy loss was the 8th week (range 6th–11th week): fetal loss was not associated with an advanced stage of maternal disease. Two pregnancy losses

Table 5 Fetal outcome of 25 pregnancies in 17 patients with PSC

	Median	Range
Week of gestation (wk)	39	31–41
Size at birth (cm)	50	46–56
Weight at birth (g)	3200	1694–4075
Perinatal developmental status (APGAR)	10	7–10
Follow-up period (months)	50	3–132
	n	**%**
Live births	21	84
Normal long-term development of children	21	100
Fetal losses	4	16
Pre-term deliveries	2	10

occurred after stopping UDCA/azathioprine treatment. For the other two, no associated event could be elucidated.

Medical treatment during pregnancy and its effect on maternal and fetal outcome

The influence of medication on maternal and fetal outcome was investigated. Details on medication and on the effect of UDCA on fetal outcome are given in tables 6 and 7. UDCA was not applied during eight pregnancies. In two of these cases UDCA had not been introduced before pregnancy, in one case it was stopped after recognition of pregnancy at week 4, and in five cases UDCA was stopped due to planned conception. During nine pregnancies, UDCA treatment was continued throughout all three trimesters, and in eight pregnancies it was re-administered after the first trimester. The median dose of UDCA during pregnancy was 1000 mg per day (range 500–1500 mg) at a weight-based dosage of 16 mg/kg/d (8–21 mg/kg/d).

Treatment with UDCA during pregnancy did not seem to affect fetal outcome. However, in patients on UDCA treatment, liver enzymes remained stable more often compared to patients not receiving UDCA during pregnancy (increase to more than twice the pre-conceptional value: (13% vs 67%, p=0.049)).

In four cases, azathioprine had been stopped before conception due to planned pregnancy. During two pregnancies azathioprine at a dose of 75 mg per day was continued permanently and in another one it was re-administered after the first trimester. All three had a beneficial pregnancy outcome.

DISCUSSION

In autoimmune and immune-mediated diseases such as autoimmune hepatitis or systemic lupus erythematosus, pregnancy may significantly affect the course of disease.[3–7] Several lines of evidence including recent genome-wide association studies support the notion that PSC has properties of both, an autoimmune and immune-mediated disease of the liver and bile ducts.[8–10] Our assessment of the rate and outcome of pregnancies in a cohort of pregnant PSC patients revealed no differences to normal controls. Pregnancy in patients with PSC frequently caused a rise in serum liver tests but did not cause serious maternal complications.

Table 6 Therapeutic regimen during pregnancy

	Azathioprine n (%)	UDCA n (%)	Prednisolone n (%)
Before pregnancy	6 (24)	21 (84)	6 (24)
During complete pregnancy	2 (8)	9 (36)	4 (16)
After first trimester	3 (12)	17 (68)	4 (16)
Post-partum	3 (12)	23 (92)	5 (20)

Table 7 Influence of UDCA treatment during pregnancy on fetal outcome

	No UDCA (n=8) n (%)	UDCA (n=17) n (%)
Pregnancies	8 (32)	17 (68)
Fetal outcome		
Live births	6 (75)	15 (88)
Fetal losses	2 (25)	2 (12)
Pre-term delivery	1 (13)	1 (6)

Female sex hormones are known to modulate cellular and humoural immune functions including the cytokine profile and a state of tolerance may predominate during pregnancy.[7 18] Consistently, in autoimmune hepatitis remissions occur during pregnancy and flares can be observed in up to 50% after delivery,[3–7] whereas in IBD the influence of pregnancy and delivery on the activity of disease is less pronounced.[19]

Assessing disease activity in patients with PSC is difficult. We here report the rate of serum liver tests increasing to more than twice the pre-pregnancy values. Clearly, this is a rather crude method that may not reflect histological activity or indicate disease progression. Differentiation from episodes of bacterial cholangitis may also be difficult. Serum liver tests increased markedly in 20% during pregnancy and in 32% within the first 3 months post-partum. One patient presented with de novo PSC after delivery. These numbers are within the reported range for patients with autoimmune hepatitis and may support the notion that PSC is at least an immune-mediated disease of the liver.

Despite the frequent rise in serum liver tests, no serious maternal complications were recorded during pregnancy or after delivery and, notably, no emergency endoscopic treatment had to be performed during pregnancy. This stands in contrast to patients with autoimmune hepatitis, in whom—probably due to a higher rate of liver cirrhosis and immunosuppression—maternal complications are of concern and may even result in maternal death.[3 4 6] Of note, in this series only two patients had known liver cirrhosis, which may contribute to the low complication rate reported. In the Swedish series reported before, 4 of 10 patients had liver cirrhosis and the course of disease did not seem to be affected by pregnancy.[11] From the limited data available one could therefore conclude that pregnancy in PSC seems to be safe for the mother, at least unless advanced liver cirrhosis is present.

With regard to symptoms, pruritus was the most prominent complaint which occurred during seven pregnancies. Of three cases with worsening pruritus during the last trimester of pregnancy, two were suspected as suffering from ICP by the consulting hepatologists. ICP generally occurs in late pregnancy with an estimated prevalence of 1/1000.[20] In 2 of the 10 Swedish PSC patients with pregnancy, pruritus was so intense as to bring on premature delivery, a typical complication of ICP.[11] Therefore it may be tempting to speculate on overlapping features of pruritus in PSC and ICP and a potentially increased prevalence of ICP in pregnant patients with PSC. ICP and PSC may share common genetic traits such as polymorphisms within the ABCB4 gene.[21 22] UDCA has been established as the treatment of choice for ICP.[23] In the Swedish series,[11] none of the patients had been treated with UDCA. In many European countries, patients with PSC are treated with UDCA and the patients described within this paper were treated before the data on potentially harmful effects of UDCA in patients with advanced disease emerged.[16] Although beneficial effects of UDCA on the progression of PSC

have not been shown to date and high-dose UDCA should not be applied,[2 16] moderate doses of UDCA may be tried in the treatment of pregnant PSC patients with pruritus.

The number of children was not different between the PSC patients and healthy controls analysed. As doctors may be reluctant to prescribe hormonal contraception to their patients with PSC, this potential bias may lead to an overestimation of the number of children in the PSC group as compared to the healthy control group. Unfortunately, information on the potential use and type of contraception was not available from the PopGen database. Therefore, the conclusion that fertility is not reduced in patients with PSC must be interpreted with caution.

UDCA treatment is presumed to be safe during the second and third trimester and may be safe earlier in pregnancy although formal approval is lacking in most countries. In the series reported here, UDCA was administered continuously during eight pregnancies, and was re-administered in another eight pregnancies after the first trimester. A negative impact on fetal outcome was not detected.

The number of pregnancies exposed to azathioprine reported here is too low to draw any conclusions. Of note however is that two of the four fetal losses occurred after having stopped azathioprine and UDCA treatment after the detection of pregnancy. Experience from solid organ transplantation and IBD patients suggests that the teratogenic potential of azathioprine is outweighed by the beneficial effects of controlling disease.[19 24] Therefore it seems justified to continue low-dose treatment with azathioprine in pregnant patients with PSC and associated IBD.

Fetal loss rates of up to 30% have been reported in patients with autoimmune hepatitis[3 4 6] and comparable rates can be found in other autoimmune diseases, such as type I diabetes mellitus.[25] We here report a fetal loss rate of 16%, which overall seems to be similar to the rates reported for autoimmune hepatitis and for the general US population.[26] Fetal loss in our series did not seem to be related to the severity of liver disease. However, all patients with fetal loss had concomitant IBD. Active IBD has been associated with miscarriage, stillbirth, prematurity and low birth weight.[19] Correspondingly, in one of our patients two fetal losses occurred in the presence of active ulcerative colitis. Together with the positive fetal outcome reported before, these numbers may indicate that PSC does not bear an increased risk of fetal loss by itself.

In conclusion, fertility does not seem to be reduced in PSC. We here report from the largest series of patients with PSC and pregnancy available to date, that successful pregnancies can be achieved by patients with PSC. No impairment of fetal outcome and no serious maternal complications were recorded. Pruritus is common in late pregnancy and the potential clinical and genetic overlap with ICP may warrant further study.

Acknowledgements We acknowledge the Deutsche Morbus Crohn/Colitis ulcerosa Vereinigung (DCCV e.V.) for supporting patient recruitment.

Competing interests None.

Ethics approval This study was conducted with the approval of the Ethics Committee of Hamburg.

Provenance and peer review Not commissioned; externally peer reviewed.

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Gut 2011 60: 1117-1121 originally published online February 21, 2011
doi: 10.1136/gut.2010.228924