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Review

# Pregnancy in women with primary biliary cirrhosis ☆,☆☆

Cumali Efe [a,*,1], Evrim Kahramanoğlu-Aksoy [a,1], Bülent Yılmaz [a,1], Burak Ozseker [a,1], Sahin Takcı [b,1], Emir Charles Roach [a,1], Tugrul Purnak [a,1], Taylan Kav [a,1], Ersan Ozaslan [c,1], Staffan Wahlin [d,1]

[a] Department of Gastroenterology, Hacettepe University, Ankara, Turkey
[b] Department of Neonatology, Gaziosmanpaşa University, Tokat, Turkey
[c] Department of Gastroenterology, Numune Research and Education Hospital, Ankara, Turkey
[d] Department of Gastroenterology and Hepatology, Karolinska Institutet, Karolinska University Hospital, Stockholm, Sweden

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ABSTRACT

*Background & Aims:* Primary biliary cirrhosis (PBC) may present in all decades of life, also in childbearing age. Data on maternal and fetal outcome is limited. We aimed to investigate the impact of pregnancy and childbirth on the disease course and possible effects of PBC on fetal outcome.
*Methods:* Retrospective study of local cases and a compact review of published reports between 1950 and 2014.
*Results:* Our cases along with literature review provided 98 pregnancies in 72 PBC patients. PBC was diagnosed during pregnancy in 26 (36%) patients and 46 (64%) had the diagnosis before conception. Twenty-four (30%) of the pregnancies were associated with biochemical flares and 55 (70%) with clinical improvement or stabilization. De novo onset or worsening of pruritus was seen in 49% (45/92). No maternal deaths were reported. Post-partum disease activation was observed in 60% (53/88). One patient was referred for liver transplantation after delivery. A miscarriage rate of 24% and three stillbirths were reported. Most patients were treated with ursodeoxycholic acid (UDCA) during breastfeeding and 12 patients also received UDCA during the first trimester without any identified side effects.
*Conclusion:* Most women with PBC maintain a stable disease during pregnancy, but post-partum biochemical flares are common. Symptomatic pruritus may be challenging in pregnant PBC patients. UDCA appears to be safe during pregnancy and breastfeeding. A successful pregnancy outcome is a realistic expectation for women with PBC.


**Contents**



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* Corresponding author at: Cumali Efe, Eceabat Sokak 21/12, Cebeci, Ankara, Turkey. Tel.: +90 5055025589; fax: +90 312315026.
*E-mail address:* drcumi21@hotmail.com (C. Efe).
[1] All authors contributed with their data and analyzed final manuscript.

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## 1. Introduction

Primary biliary cirrhosis (PBC) is an immune mediated disorder of the liver that predominantly affects women [1–4]. A significant proportion of the female patients are diagnosed in the post-menopausal period but PBC may also present in childbearing age [5,6]. The clinical outcome and management of pregnancy has been better described in other immune mediated liver diseases such as autoimmune hepatitis (AIH) and primary sclerosing cholangitis (PSC) [7–9]. However, there is a scarcity of reports on pregnancy in PBC and little is known about the clinical course of disease during pregnancy and the maternal and fetal outcomes. Most publications are limited by case reports and small cohort studies [10–30]. In studies published more than 15 years ago, pregnancy was found to be associated with high rates of maternal and fetal complications [10–19]. This information may have discouraged PBC patients from becoming pregnant. With the advent and success of ursodeoxycholic acid (UDCA) in improving liver biochemistry, delaying histological progression and improving control of the disease [31], this negative view has gradually changed. Recently, a large population based study was reported from Canada [28]. In this study, 50 pregnancies in 32 PBC patients were mainly uneventful. This information renders pregnancy a more realistic expectation for women with PBC.

We here report our experience of seven PBC patients who had nine pregnancies while on UDCA treatment. We also reviewed the existing English literature in order to give a comprehensive description of what is known about the management and outcomes of pregnancy in PBC.

## 2. Patients and methods

### 2.1. Local cases

The medical records of pregnant PBC patients at Hacettepe University and Ankara Numune Education and Research Hospital 2004–2013 were retrospectively evaluated.

### 2.2. Literature review

To identify eligible publications, we searched the PubMed in March 2014 using the terms 'primary biliary cirrhosis' or 'overlap syndrome' and 'pregnancy' or 'child birth' in the title or abstract or as keywords. We limited the search period to 1950–2014. The reference lists of the identified publications were further searched for additional publications. Data extraction included number of pregnancies and number of women. The primary outcome measures of interest were maternal and fetal outcomes. Other outcome measures of interest included UDCA or other treatments, pregnancy complications, symptomatic liver disease and biochemical course during pregnancy and in the post-partum period.

### 2.3. Definitions and measures

The diagnosis of PBC was made based on elevated alkaline phosphatase (ALP), seropositivity for AMA and compatible liver biopsy findings [6]. Biochemical response to UDCA was defined according to the Paris criteria [32], which requires ALP to be less than three times the upper limit of normal (ULN) together with aspartate transaminase (AST) $<2 \times$ ULN and a normal bilirubin level. A biochemical flare was defined as values beyond these levels. The main pregnancy and fetal/neonatal outcome measures were: pregnancy specific complications (hypertension, gestational diabetes mellitus and preeclampsia), caesarean section, still birth, miscarriage, preterm labor and congenital malformations.

## 3. Results

### 3.1. Local cases

We identified seven PBC patients who had nine pregnancies in our two centers. Among these, six had eight successful pregnancies. Four women had a single pregnancy and two had two pregnancies each. There was one miscarriage and one woman is currently pregnant in gestational week 20. The mean age at conception was 31 years (range 25–36). The clinical and biochemical features before and during pregnancy, as well as in the postpartum period are described in Table 1.

The PBC diagnosis was made in six patients before pregnancy while one was diagnosed during pregnancy. All patients showed seropositivity for AMA, two had concomitant seropositivity for ANA and one for SMA at the time of diagnosis. Liver biopsy was performed in six patients and none of them exhibited histological or clinical features of cirrhosis. UDCA therapy was maintained during all trimesters in three pregnancies; it was interrupted in four pregnancies during the first trimester but re-administered later during pregnancy. All patients received 13–15 mg/kg/day UDCA after delivery.

One 2750 g baby was prematurely born in gestational week 34. All other pregnancies ended with normal, term deliveries. Neither pregnancy specific nor serious hepatic complications were observed during pregnancy or in the post-partum period.

None of the women had pruritus before conception. De novo pruritus developed during the pregnancy of three patients. In two, pruritus resolved after re-administration of UDCA therapy while one was treated with anti-histamines. Pre-conception data was available for all patients and none of them had laboratory values consistent with disease activity. Biochemical flares were seen during the second trimester in both pregnancies of one woman, but all liver enzymes returned to normal after UDCA was initiated. AMA disappeared in the sera of two patients during their pregnancies but again turned positive in both after delivery.

Post-partum flares occurred in five pregnancies while three maintained biochemical stability in this period. The three patients who did not display post-partum disease activity were all treated with UDCA throughout all trimesters. Outcomes of the local cases are summarized together with cases from the literature in Table 2.

### 3.2. Published cases

We found 21 case reports and case series in the literature that describe pregnancy in PBC [10–30]. Two studies in Spanish and Italian were excluded because detailed information could not be obtained [29,30]. In the remaining studies, 72 PBC patients (three with overlapping AIH) who had 98 pregnancies were identified. Among them, 46 (64%) became pregnant after being diagnosed with PBC while 26 (36%) were diagnosed with PBC during pregnancy.

The clinical and biochemical course was assessable in 79 pregnancies. Flares were noted in 24 (30%) pregnancies and in five, biochemical remission was achieved by re-administration of UDCA. Clinical improvement or stabilization of disease activity was observed in the remaining 55 (70%) pregnancies. Information regarding outcome of pruritus could be obtained in 92 pregnancies. There was worsening or de novo onset of pruritus in the course of 49% (45/92) of pregnancies. Various management strategies for pruritus were reported. UDCA and antihistamines were able to control symptoms in some patients while cholestyramine, rifampicin, naloxone, dexamethasone, selective serotonin reuptake inhibitors or a combination of these agents were required for other patients. Ultraviolet light therapy or plasmapheresis was effective in patients who did not find relief with pharmacological therapies. Post-partum flares were reported in 60% (53/88) of assessable published pregnancies.

Among the 72 patients, there were 2 cases of preeclampsia and 14 cesarean sections. Premature labor occurred in 16% (16/98). Ectopic pregnancy and breech presentation were reported in one case each.

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