



Case Report

Caroli's disease: management of a rare condition during pregnancy

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Caroli's disease is a rare congenital condition characterized by dilation of the intrahepatic biliary tree. There are about 200 cases described in the international literature and only three in pregnant women. In this article we describe a fourth case dominated by the presence of severe cholestasis, with initial bile acids (BA) higher than 400 μ mol/L. We proposed a monitoring plan based on our knowledge about intrahepatic cholestasis of pregnancy (ICP), given its high prevalence in the obstetric population.

Keywords: Caroli's disease, Caroli's syndrome, cholestasis, bile acids, pregnancy

List of Abbreviations

AF, alkaline phosphatase; BA, bile acids; CPAP, continuous positive airway pressure; CT, computed tomography; CTG, cardiotocography; ERCP, endoscopic cholangiopancreatography; GGT, gamma-glutamyl transpeptidase; H, hours; ICP, intrahepatic cholestasis of pregnancy; IM, intramuscular; MRCP, resonance cholangiopancreatography; NICU, neonatal intensive care unit; RDS, respiratory distress syndrome; UDCA, ursodeoxycholic acid; W, weeks

INTRODUCTION

Caroli's disease is a rare congenital entity, characterized by segmental non obstructive cystic dilation of the large intrahepatic bile ducts. It has an estimated incidence of 1: 1 000 000/ inhabitants without any gender prevalence (Giovanardi, 2003). The diffuse form is more common; when bile ducts ectasia is present in a single lobe, mainly the left one, the disease is considered localized.

Two main variants have been described: type 1 or Caroli's disease, a more rare form often linked with autosomal recessive polycystic kidney disease, and type 2 or Caroli's syndrome associated with congenital hepatic

fibrosis (Tsunoda et al., 2008). Both terms have been described in the same family or even regarded as different stages of the same disease (Zhang et al., 2012). Most cases are transmitted in an autosomal recessive way, but the genetic basis is not yet fully defined. An abnormal remodeling of the ductal plate of the intrahepatic biliary tree is believed to be in the origin of its pathogenesis (Ananthakrishnan and Saeian, 2007).

The most used diagnosis methods are ultrasound, computed tomography (CT), magnetic resonance cholangiopancreatography (MRCP). Endoscopic cholangiopancreatography (ERCP) can be used both as diagnostic and or therapeutic tool; a liver biopsy is rarely needed (Suchy, 2013; Sato et al., 2012).

The differential diagnosis includes autosomal-dominant polycystic liver disease, type V choledochal cysts (cysts

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can extend into the intrahepatic bile ducts), primary sclerosing cholangitis, recurrent pyogenic cholangitis, biliary hamartomas, *etc* (Zhang et al., 2012).

The diagnosis is often established in the mid-twenties, however there are three prenatal cases described in the literature, based on sonographic findings (Hussman et al., 1991; Yuksel et al., 2002; Sgro et al., 2004). It is believed that early manifestation is associated with increased severity / aggressiveness of the disease and therefore poor prognosis. In some individuals there is mostly hepatic involvement, while other have mainly renal dysfunction.

Patients can complain of abdominal pain, pruritus, weight loss, anorexia, nausea and vomiting, but they can also be asymptomatic. The main complications are hepatolithiasis, affecting 1/3 of the patients (Ananthakrishnan and Saeian, 2007), recurrent cholangitis that usually dominates the clinical course and can lead to death within 5-10 years (Sato et al., 2012), portal hypertension and its systemic implications and secondary biliary cirrhosis. The feared cholangiocarcinoma has been reported in up to 7-14% of patients (Sato et al., 2012). Laboratory findings can include elevated transaminases, increased serum alkaline phosphatase and direct bilirubin, thrombocytopenia and leukopenia can also be found. When polycystic kidney disease is associated, renal dysfunction is often present. At physical examination, the kidneys could be palpable and high blood pressure, pyelonephritis and nephrolithiasis are frequent associated comorbidities.

Treatment of Caroli's disease is mostly supportive and should be individualized and directed toward treating biliary infections and complications associated with portal hypertension. Ursodeoxycholic acid (UDCA) has shown to be useful in the treatment and prevention of hepatolithiasis and cholangitis; some studies advocate complete or partial clearance of the stones and normalization of the liver function tests (Ananthakrishnan and Saeian, 2007). ERCP can be used for drainage, stone extraction, stenting and sphincterotomy in selected cases. Segmental hepatic resection can be performed in localized Caroli's disease, but for patients with diffuse disease, liver transplant remains the only viable treatment.

Caroli's disease can affect young fertile women, however and due to its rarity, there are only three cases in pregnancy described in the literature (Tsunoda et al., 2008; Adair et al., 1995), two of them in the same women. In the first case, the authors described a pregnant woman with Caroli's disease complicated by chronic renal failure caused by polycystic kidney disease; the pregnancy was uneventful and her labor was induced at 37 weeks of gestation due to worsening renal function (Tsunoda et al., 2008). In the second case, the first pregnancy was uneventful but in the second one, she had acute ascending cholangitis, disseminated

intravascular coagulopathy and septic shock. Fetal distress determined an emergency cesarean section at 29 weeks and the mother required prolonged critical care (Adair et al., 1995). In both cases, mothers and neonates survived.

In this article, we report a fourth case of pregnancy in a woman with Caroli's disease.

Due to the overlap of concepts in the published literature, we decided to use the term Caroli's disease, since it's the most used term.

CASE REPORT

S.I.S.R., 37 year old, nulliparous, is referred to our unit at 13 weeks of pregnancy by her gastroenterology physician. At 22 years old, in consequence of repetitive episodes of cholestasis, she was submitted to right hepatic lobectomy and cholecystectomy. The histologic findings were compatible with the diagnosis of Caroli's disease accompanied with secondary cirrhosis. Since then, she only had one more episode of cholestasis and remained stable with a chronic cytocholestasis medicated with ursodeoxycholic acid (UDCA). In a recent endoscopy no evidence of esophageal varices was found. A suspected hepatic nodule found in a routine abdominal ultrasound, was not confirmed in a MRCP.

In the first appointment, the pregnant only complaint of a mild pruritus. She had interrupted the UDCA since the beginning of pregnancy afraid of its consequences to the fetus.

Her blood tests revealed a mild thrombocytopenia, with no signs of systemic infection; elevated hepatic transaminases (3 fold), alkaline phosphatase (AF), gamma glutamyl transferase (GGT) and bilirubin, and normal kidney function (figure 1), similarly to her values prior to pregnancy.

Due the rarity, complexity and lack of information regarding this disease and its management during pregnancy, a multidisciplinary team was established, including the obstetric and neonatology teams, an internist and her gastroenterology physician. The pregnant was informed of the major maternal and fetal risks involved, which she understood and accepted.

The UDCA was resumed and she was instructed to be alert to some warning signals and symptoms associated with cholestasis and cholangitis.

We decided to monitor the evolution of the disease based on the determination of BA, as it is a cholestatic disease. Initial evaluation showed a total bile acids of 449 μ mol/L and (serum normal value - 5 \pm 3 μ mol/L), with predominance of colic acid conjugated with taurine (as seen in intrahepatic cholestasis of pregnancy) (figure 2).

During the pregnancy, she had periodic appointments and performed serial blood tests. Her complaints of pruritus decreased and no signs of infection or cholangitis

Blood tests	January	UDCA			
		15-18s	19-23s	24-28s	29-30s
		February	March	April	May
Hemoglobin (g/L)	11.3	10.7	10.6	10.5	11.3
Leucocytes (x10 ⁹ /L)	5.300	6.900	6.200	8.300	7.400
Platelets (x10 ⁹ /L)	123	131	129	137	136
CRP	2,1	3,1	4,6	1,3	1,8
ALT/AST	109 / 159	59 / 64	65 / 78	73 / 87	84 / 90
AF	291	285	271	296	340
GGT	135	126	133	169	156
Bilirubin	3,4	2,7	3,1	3,4	5,0
Creatinine	0,7	0,5	0,6	0,6	0,6

Figure 1. Blood tests over pregnancy, before and after UDCA treatment

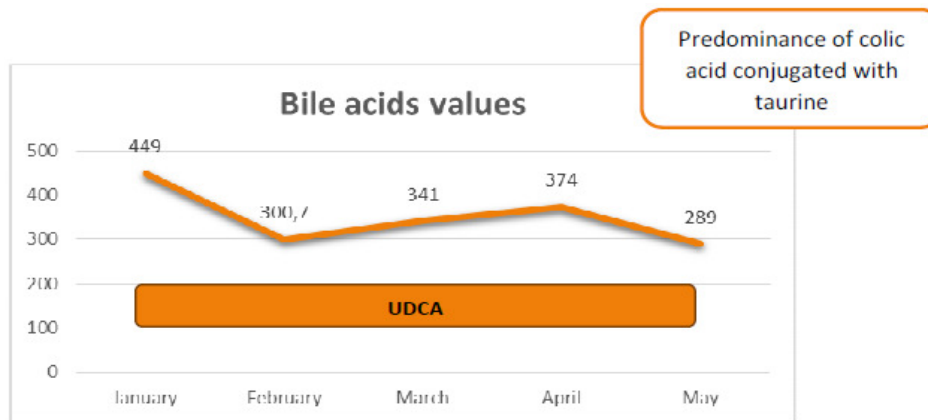


Figure 2. Bile acids values over pregnancy, before and after UDCA treatment.

was ever identified. Liver function tests improved at first, but quickly began to worsen (figure 1). UDCA was increased up to 1250mg (5 pills a day), with good response, demonstrated by the decrease of bile acids (figure 2).

No fetal anomalies were found and there was a consistent growth in the 50 percentile.

Antenatal corticosteroids for accelerating fetal lung maturation with dexamethasone 6mg IM 12/12h were administered at 26w given the high likelihood of preterm labor.

At 29w^{+5d}, her blood tests showed an increased total bilirubin and worsening of liver function tests and she complained of mild pruritus and sporadic contractions. The last bile acids known were 374µmol/L, higher than the previous determination (figure 2). She was then admitted to the obstetric service to maternal-fetal surveillance. At physical examination, a mild jaundice and telangiectasia in the upper limbs were noticed. No signs of infection or cholangitis were present. Fetal ultrasound

showed good vitality and CTG was reactive for gestational age.

It was decided to induce the labor at 30w^{+4d}, after neuroprotection with magnesium sulfate, however, even before beginning of induction, she went in spontaneous labor. After nine hours of labor, a live born female infant was delivery with Apgar scores of 8 and 9 at 1 and 5 minutes, respectively. Meconium stained amniotic fluid was observed intrapartum but the CTG was always reassuring.

The postpartum went uneventful and she was discharged after 3 days.

The newborn remained in the neonatal intensive care unit (NICU) 11 days, requiring ventilatory support with non-invasive ventilation (CPAP). An abdominal ultrasound was performed for screening of neonatal Caroli's disease that was negative. She was discharge at day 44 with 35w^{+5d}. To this day she remains well with no apparent sequelae and with adequate neuromotor development.

DISCUSSION

There are about 200 cases published on Caroli's disease and only three in the context of a pregnancy. The three cases published, two in the same woman, had different and serious maternal and fetal outcomes. Given the lack of information, it was near impossible to predict the evolution and the complications that could arise either for the pregnant or to the fetus. Therefore, the adequate pregnancy follow-up was unknown. A multidisciplinary team was then established, including an obstetrician and a pediatrician, an internist and a gastroenterologist.

Since Caroli's disease is a cholestatic disease and the total serum BA were greatly increased, we decided to take into account the knowledge we have about ICP and assumed that the follow-up should be done as if it were a severe form of ICP associated with a higher risk of hepatolithiasis, recurrent cholangitis and portal hypertension.

ICP has consistently been associated with an increased incidence of adverse perinatal outcomes including meconium passage, spontaneous and iatrogenic preterm delivery, asphyxial events, late stillbirth and recently with respiratory distress syndrome (RDS).

Specific predictors for poor fetal outcome have not been clearly identified. In ICP the transplacental gradient for BA excretion from the fetus to the mother is reversed, leading to an accumulation of BA in the fetal serum and meconium (Brites, 2002; Shaw et al., 1982; Laatikainen, 1975). Increased maternal serum BA levels were associated with higher fetal complications rates, such that for every 1-2 $\mu\text{mol/L}$ increase in the BA level, there was a 1-2% increase in risk of adverse outcomes. However, the increase in risk seems to only become statistically significant in severe ICP (BA level $>40 \mu\text{mol/L}$) (Glantz et al., 2004). Zhou *et al* also showed that women presenting with early-onset of ICP ($<28\text{w}$) had a worse clinical course with a higher rate of preterm labor and fetal distress (Zhou et al., 2013).

How the BA exert an adverse effect on the fetus is not fully understood, but several theories have been proposed (figure 3).

Meconium passage

BA are known to have a vasoconstrictive effect on the placental chorionic veins, which can lead to fetal distress, explaining the increased meconium-stained amniotic fluid observed in ICP and possibly the occurrence of fetal distress, asphyxia and death (Sepulveda et al., 1991; Brouwers et al., 2015). However, some animal research suggests that BA stimulate gut motility and therefore meconium passage may not be a sign of fetal distress, but rather a

physiologic reaction (Campos et al., 1986).

Preterm birth

Spontaneous preterm birth is thought to be caused by the increased expression and reactivity of the oxytocin receptors in the myometrium in response to BA, specially cholic acid (Germain et al., 2003; Israel et al., 1986).

Stillbirth

Research in animals also linked the increased incidence of stillbirth in ICP to fetal cardiac event triggered by the effect of BA on the fetal cardiac conduction system, causing arrhythmias (Al Inizi et al., 2006; Williamson et al., 2001; Gorelik et al., 2002; Gorelik et al., 2004; Strhlow et al., 2010). However, given the low frequency of neonatal deaths, 3 to 10 per 1000 births in general population, the risk of stillbirth in cholestasis, reported to be 1.5-2.4% (but in some series as high as 7%) (Williamson et al., 2004; Rioseco et al., 1994; Geenes et al., 2014; Jin et al., 2015; Kawakita et al., 2015), seems to be clinically insignificant. Therefore, stillbirth could be mainly associated with higher BA levels of $>100 \mu\text{mol/L}$, as shown by Kawakita *et al* that reported a stillbirth rate of 15% in that specific group (Kawakita et al., 2015).

Respiratory distress syndrome

More recently, it has been hypothesized an association with RDS, explained by the enhancing activity of phospholipase A2 promoted by BA, leading to hampering of the synthesis of pulmonary surfactant (Zecca et al., 2004) and damage of the normal morphology of fetal lung tissue and alveolar-capillary membrane (Yu et al., 2014). A retrospective study found a 2 fold higher incidence of RDS in newborns from cholestatic pregnancies, independent of the risk of premature delivery (Zecca et al., 2006).

Maternal main complications include intractable pruritus, intrapartum and postpartum hemorrhage.

Given these assumptions, our biggest concerns from the beginning were:

1. Worsening of the underlying liver disease and progression of cirrhosis, with the emergence of portal hypertension and hepatic insufficiency.
2. Risk of cholangitis and serious systemic infection.
3. Presence of high BA ($>100 \mu\text{mol/L}$) since conception.
4. Increasing cholestasis with its unpredictable and potential harmful consequences to the mother and the fetus.

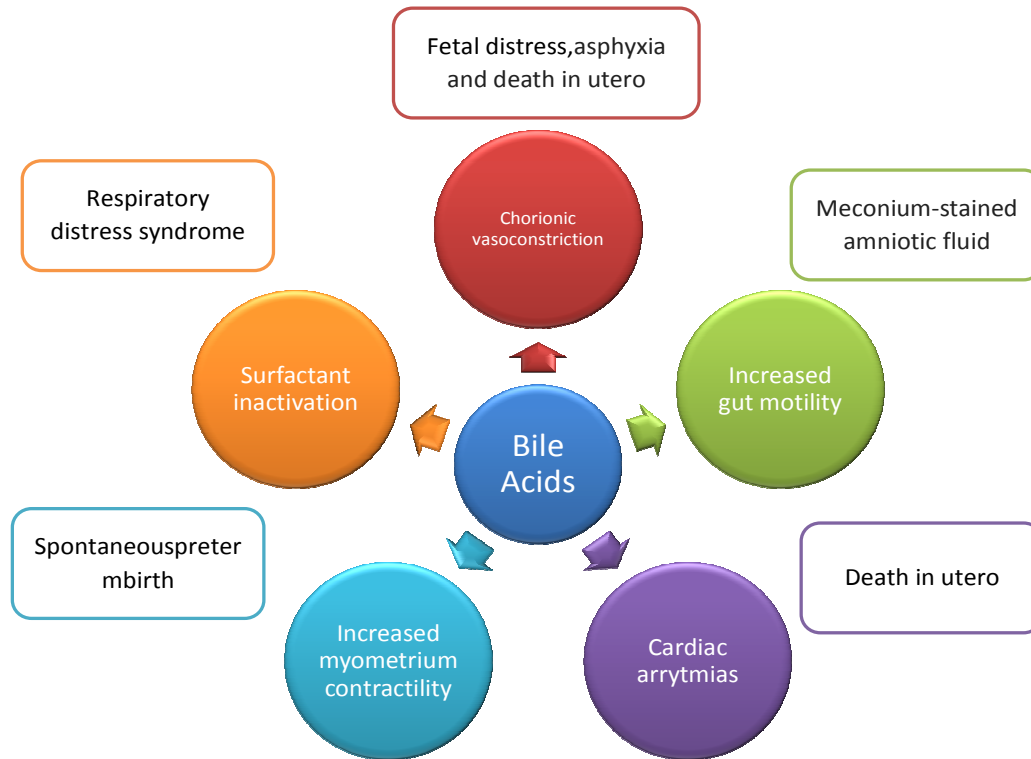


Figure 2. Adverse perinatal outcomes associated with high levels of maternal serum BA.

All the possible complications and adverse outcomes were discussed with the gravida that decided to continue with the pregnancy. A tight plan of surveillance was elaborated based on periodic appointments and serial blood tests including a complete blood count, CRP, liver and kidney function and total serum BA, besides the usual routines. Fetal wellbeing was assured through serial ultrasounds and regular CTG, although no method of fetal monitoring has shown unquestionable value predicting or reducing the risk. The pregnant was also instructed to be alert to any signs of fever, chills, choloria, acholia, edema, increased pruritus or jaundice.

AUDC has been the elected medical treatment in ICT since it has already been proved to be safe during pregnancy, improve pruritus and liver tests and decrease BA levels. Recent studies also suggest that AUDC improves fetal outcomes, decreasing the incidence of preterm birth, fetal distress, SDR and admission in the NICU (Bacq et al., 2012). The protect mechanism of AUDC is not fully known but it seems to be due to a global reduction in total serum BA in both maternal and fetal compartments, a qualitative change in the serum BA pool with a reduction in its hydrophobicity (reduction of taurine and glycine conjugates of cholic acid and chenodeoxycholic acid), an increase in the transport and secretion of BA by the liver and an improve of BA transport across the placenta by reversing the fetal-maternal BA gradient (Serrano et al., 1998; Beuers,

2010; Marschall et al., 2005; Brites et al., 1997; Brites et al., 1998).

Other therapies have been suggested, but lack strong evidence of its benefits.

Rifampicin seems to enhance BA detoxification and excretion, acting synergically with AUDC and the combination of the two drugs could be a solution for severe forms of ICT. Cholestyramine, S-adenosyl-L-methionine and dexamethasone are no longer considered a first-line treatment over AUDC in ICT (Williamson and Geenes, 2014).

Taking into account the known benefits of AUDC in ICT and the presence of the same profile of serum BA usually seen in ICT (predominance of colic acid conjugates), we extrapolate the good results and decided to use it. We noticed a decrease in serum BA levels as well as an improvement in liver tests after restarting AUDC. There was also a significant reduction in pruritus. Later the BA levels started rising but decreased again when the dose of AUDC was increased, however never below $289\mu\text{mol/L}$, a value considered of high risk for adverse fetal outcomes. The liver tests continued to worsen throughout pregnancy, but never reached the initial values (figures 1 and 2).

In the late second trimester, there was a worsening of cholestasis. To ensure a constant maternal-fetal surveillance, she was admitted in our unit. During her stay, she was normotensive, apyretic and she only

complained of mild pruritus. CTG was performed twice a day and was always reassuring.

There is no robust evidence that elective induction of preterm labor in women with ICP improve fetal outcomes (Green-top Guideline No. 43). Nevertheless elective delivery at 37 weeks of gestation has become a current practice with the aim to reduce the risk of late stillbirth, with some authors supporting an even early delivery (Puljic et al., 2015).

Our protocol is to induce labor at 37w, especially in those with BA >40µmol/L. However given the worsening of liver tests and the high BA throughout pregnancy it was at first decided to induce labor at 30w, however she eventually went into spontaneous labor.

As described in the literature, we observed the occurrence of spontaneous premature contractions, preterm birth and the presence of stained amniotic fluid. The SDR could not be totally assumed to be related to the high levels of BA given the prematurity. It was never verified a non reassuring fetal status and both mother and daughter remain well until today.

CONCLUSION

Caroli's disease is a cholestatic entity that can affect fertile woman and although rare, could become a challenge to any obstetrician. There are only 3 cases described in the recent literature, 2 of them in the same woman and every pregnancy had different complications.

In this article we describe a fourth case of Caroli's disease in a pregnant woman. She was alerted for the possible maternal and fetal adverse outcomes, still she opted to continue the pregnancy. A multidisciplinary team was established and a tight surveillance plan was instituted.

Although impossible to predict the maternal-fetal outcomes, we were aware and alert to the possible complications that could arise in these pregnancies. On one hand, we had to face the risk of cholangitis and systemic infection, hepatolithiasis, portal hypertension, cirrhosis and even hepatic insufficiency. In cases associated with polycystic kidney disease, renal dysfunction is often present and pyelonephritis and nephrolithiasis are frequent comorbidities, which was not the case. On the other hand, we assumed Caroli's disease as a severe form of ICP and so, pregnancy follow-up included the determination of BA levels since there is sufficient evidence that higher levels are associated with increased fetal adverse outcomes, including stillbirth. However, could Caroli's disease really be compared to ICP?

BA levels >40µmol/L have been associated with adverse fetal outcomes, especially if >100µmol/L. Fortunately, although BA levels were extremely high since the beginning and always >200µmol/L and the liver tests

progressively worsened, it was possible to extend the pregnancy until 30w with no serious fetal and maternal complications. But could the AB levels in ICP and its influence in the maternal-fetal outcomes be extrapolated to Caroli's disease?

AUDC was a reasonable therapy to decrease pruritus and BA, improve liver tests and possibly fetal outcomes in this context. Rifampicin could have been an option, especially because we were never able to decrease BA to levels considered secure, but more studies are needed to understand its benefit.

The adequate fetal monitoring and the optimal gestational age for delivery are not known and given the diversity of complications that may be present, we believe that each case should be evaluated individually, considering the use of regular CTG and fetal ultrasound to reassure fetal wellbeing.

Many questions continue answered and future cases could help to better understand this disease, especially during pregnancy.

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