Journal of Obstetrics and Gynaecology

ISSN: 0144-3615 (Print) 1364-6893 (Online) Journal homepage: https://www.tandfonline.com/loi/ijog20

# Two cases of first onset intrahepatic cholestasis of pregnancy associated with moderate ovarian hyperstimulation syndrome after IVF treatment and review of the literature

Mehmet Firat Mutlu, Koray Aslan, Ismail Guler, Ilknur Mutlu, Mehmet Erdem, Nuray Bozkurt & Ahmet Erdem

**To cite this article:** Mehmet Firat Mutlu, Koray Aslan, Ismail Guler, Ilknur Mutlu, Mehmet Erdem, Nuray Bozkurt & Ahmet Erdem (2017) Two cases of first onset intrahepatic cholestasis of pregnancy associated with moderate ovarian hyperstimulation syndrome after IVF treatment and review of the literature, Journal of Obstetrics and Gynaecology, 37:5, 547-549, DOI: 10.1080/01443615.2017.1286302

**To link to this article:** https://doi.org/10.1080/01443615.2017.1286302

JOURNAL OF OBSTETRICS AND GYNAECOLOGY, 2017
VOL. 37, NO. 5, 547–549
http://dx.doi.org/10.1080/01443615.2017.1286302

Taylor & Francis
Taylor & Francis Group

REVIEW ARTICLE

# Two cases of first onset intrahepatic cholestasis of pregnancy associated with moderate ovarian hyperstimulation syndrome after IVF treatment and review of the literature

Mehmet Firat Mutlu[a], Koray Aslan[b], Ismail Guler[b], Ilknur Mutlu[c], Mehmet Erdem[b], Nuray Bozkurt[b] and Ahmet Erdem[b]

[a]Department of Obstetrics & Gynecology, Yuksek Ihtisas University Faculty of Medicine, Ankara, Turkey; [b]Department of Obstetrics & Gynecology, Gazi University Faculty of Medicine, Ankara, Turkey; [c]Novaart IVF Center, Ankara, Turkey

**ABSTRACT**

Intrahepatic cholestasis of pregnancy (ICP) is an uncommon disorder, which generally occurs in the second and third trimester of pregnancy with symptoms of pruritus. The cause of ICP is unknown but genetic, hormonal and environmental factors contribute to its pathogenesis. The aetiology of ICP is unclear but elevation in oestrogen levels thought to cause ICP is typically seen in the third trimester of pregnancy, and for this reason it is not usually considered in the differential diagnosis of pruritus and liver function disorders in the first trimester of the pregnancy. We present two cases of pregnancy after IVF treatment diagnosed with ICP following the development of OHSS, deteriorating liver function tests and severe pruritus.

**KEYWORDS**

Cholestasis; pregnancy; ovarian hyperstimulation; oestrogen

## Introduction

Intrahepatic cholestasis of pregnancy (ICP) typically presents during third trimester with an incidence of approximately 0.2–2% of all pregnancies (Williamson and Geenes 2014). Diagnosis of ICP is based on the presence of pruritus, which accompanies elevated total serum bile acids levels and aminotransferases, in the absence of other pathologies that may cause similar symptoms and laboratory findings (Pusl and Beuers 2007). ICP is a benign disorder, and symptoms of the disease and abnormal liver function tests resolve spontaneously a few days after delivery. However, it carries several risks for foetus including foetal prematurity, meconium-stained amniotic fluid, intrauterine demise and an increased risk of neonatal respiratory distress syndrome (Rioseco et al. 1994; Bacq et al. 1997; Zecca et al. 2008; Geenes et al. 2014; Brouwers et al. 2015).

The aetiology of ICP is unclear but elevation in oestrogen levels are thought to be the cause of ICP in both clinical and experimental conditions (Arrese et al. 2008). ICP is more common in conditions related to high oestrogen levels; as in the case of twin pregnancies and in the third trimester of pregnancy. For this reason ICP is not usually considered in the differential diagnosis of first trimester pruritus and liver function disorders. The mechanisms that play role in the pathogenesis of early onset ICP are unclear, however, the association of early onset ICP with ovarian hyperstimulation supports the role of elevated oestrogen levels in ICP pathogenesis. There are few case reports that describe first trimester ICP and all the cases are associated with ovarian hyperstimulation resulting in ovarian hyperstimulation syndrome (OHSS) (Midgley et al. 1999; Wanggren et al. 2004; Zamah et al. 2008). OHSS is a disorder associated with increased vascular permeability, ascites and renal and hepatic organ dysfunction with temporarily elevated liver enzymes especially after severe OHSS. We present two first trimester ICP patients with moderate OHSS after IVF.

## Case 1

Case 1 was a 24 years old nulligravid woman with a history of 4 years of anovulatory infertility who failed to conceive after ovulation induction (OI) cycles with clomiphene citrate and recombinant FSH. An IVF cycle was then commenced with a beginning gonadotropin dose of 225 IU rec FSH (Gonal F, MSD, Istanbul, Turkey) for 4 days after adequate long luteal suppression with leuprolide acetate. Oestradiol level was 1316 pg/ml on the fifth day of the stimulation and treatment was continued with 150 IU recFSH for 2 days and 75 IU for one day. Coasting was performed for 2 days before hCG injection to prevent OHSS. The E2 level at the day of hCG injection was 3800 pg/ml. Ovulation was triggered with rechCG and 27 oocytes (21 metaphase II) were retrieved after ovum pick up. 17 oocytes were fertilised normally yielding five blastocysts on day 5 after ovum pickup. One blastocyst embryo was transferred to the patient on day 5. Luteal phase was supported with vaginal progesterone gel (Crinone gel, Gonal F, MSD, Istanbul, Turkey). She was admitted to hospital two days after embryo transfer with complaints of pelvic

CONTACT Mehmet Firat Mutlu firatmutlu78@hotmail.com Department of Obstetrics & Gynecology, Yuksek Ihtisas University, Kızılırmak Mah. 1450. Sokak No: 13 Cukurambar Ankara/Turkey

pain, abdominal distension, nausea and mild dispnoea. She had moderate free fluid in the abdominal and pelvic cavity and hyperstimulated ovaries in abdominal ultrasound. Her blood count was completely normal without any haemoconcentration. She was diagnosed as moderate OHSS, and 6% HES (Hydroxyethyl starch) was given. Her symptoms resolved after conservative treatment and she was followed as outpatient. Her symptoms recurred 12 days after ET including mild dispnoea, abdominal distension and itching on her hands and feet. Initial serum βhCG 12 days after ET was 227 mIU/ml and ultrasound showed moderate ascites with enlarged ovaries up to10 cm. Her blood tests also revealed a normal haematocrit and elevated liver enzymes (Aspartate Aminotransferase (AST): 57U/L, Alanine Aminotransferase (ALT): 79 U/L) with normal bilirubin and renal function tests. The patient was hospitalised with the diagnosis of moderate OHSS and elevated liver enzymes. She was kept in fluid restriction, HES was also given daily for a few days. However, ongoing laboratory tests revealed significant elevation of liver enzymes which reached a peak value of AST: 400 U/L ALT: 903 U/L 2 weeks after positive B-hCG test. During this period, other diagnoses associated with elevated liver enzymes such as hepatitis and portal vein thrombosis were ruled out. Her complaints about respiratory distress and abdominal distension regressed. As the patient had pruritus, bile acid levels were measured to rule out cholestasis of pregnancy. The blood level of bile acids was high (166.8 μmol/L), which was compatible with early onset cholestasis of pregnancy. A blighted ovum was diagnosed at 7 weeks of pregnancy and the patient's symptoms resolved and her liver enzymes return to normal a few days after curettage.

## Case 2

The second patient was a 32 years old nulligravide woman who had a history of infertility for 6 years. After several failed intrauterine insemination attempts with clomiphene citrate and gonadotropins, IVF treatment was recommended to the patient. Her treatment commenced with 225 IU rec FSH (Puregon, MSD, Istanbul, Turkey). Oestradiol level was 1305 pg/ml on the fifth day of the stimulation and treatment was continued with 150 IU recFSH in remaining part of hyperstimulation. The oestradiol level at the day of hCG injection was 3930 pg/ml. Ovulation was triggered with rec hCG and 28 oocytes were retrieved after oocyte pick-up. Two blastocytes were transferred to the patient. Vaginal progesterone gel and aspirin was started on the day of embryo transfer.

She presented to the emergency service complaining of abdominal distention and mild dyspnoea 7 days after ET. Both ovaries were moderately hyperstimulated and moderate pelvic free fluid was detected during abdominal USS examination. Blood tests revealed normal liver enzymes and haemaconcentration (haematocrit 45%). She was hospitalised with a diagnosis of moderate OHSS; HES 6% and albumin solution 5% was given and her symptoms improved until a positive hCG test conducted 10 days after ET. The symptoms related to OHSS worsened after the diagnosis of pregnancy, 360 cc and 1500 cc free fluid was drained with USS guidance from the pelvis 12 and 14 days after ET, respectively. However, she had some improvement in OHSS-related symptoms, she started to complain of severe itching especially on her palms and soles during the fifth week of pregnancy which was typical for ICP. Her liver function tests were elevated to the levels of AST: 108 U/L, ALT: 137 U/L. A gastroenterology opinion was obtained to rule out liver pathologies such primary biliary cirrhosis, portal vein thrombosis and hepatitis, which were considered in differential diagnosis. Liver enzymes peaked during the sixth week of gestation (AST: 195 U/L, ALT: 369 U/L) during hospitalisation, and serum bile acid level was also high with the level of 122 μmol/L. She was diagnosed as early onset ICP in the setting of OHSS. Ursodeoxycolic acid (UDCA) three times a day started to relieve her symptoms. USS examination at sixth week of gestation showed twin intrauterine pregnancy and normal ovaries. Her pruritus and liver enzymes resolved gradually after treatment and in the third week after onset of UDCA liver enzymes decreased to normal levels (AST 23 U/L, ALT: 36 U/L). The rest of the pregnancy progressed without any significant problem. The foetus and mother were reviewed every 4 weeks, with the last liver enzymes at 35 weeks of gestation being completely normal (AST: 14 U/L, ALT: 7 U/L). She delivered a 2560 g male and a 2470 g female healthy infant by caesarean section at 36 + 2 weeks of gestation due to spontaneous membrane rupture.

## Discussion

The ICP is an uncommon disorder, which generally occurs in the second and third trimester of pregnancy with the symptoms of pruritus. The cause of ICP is unknown but genetic, hormonal and environmental factors contribute to pathogenesis. Specific risk factors include multiple gestation, history of pruritus, oral contraceptive pills and gallstone disease. Diagnosis is based on exclusion of other medical conditions that cause pruritus during pregnancy. Elevation in the serum bile acid level is the gold standard for diagnosis, also there may be a mild elevation in serum aminotransferase levels.

Hormonal factors play a key role in the pathogenesis of ICP. Oestrogen was found to be cholestastic in animal studies (Forker 1969). Oestrogens diminish the uptake of bile acids to hepatocytes and decrease fluidity of bile acid. Many of the risk factors, which are related to ICP are associated with high oestrogen levels. Progesterone is also thought to play an important role in the pathogenesis of ICP (Reyes and Sjovall 2000). 3β-Sulphated progesterone metabolites have been shown to be elevated in patients with ICP and downstream the genes that control bile acid secretion (Abu-Hayyeh et al. 2013). In clinical trials, it was shown that progesterone administration during the third trimester to prevent preterm delivery significantly increases the risk for ICP (Bacq et al. 1997). Beside hormonal factors, there is a familial and ethnic clustering which point to a genetic predisposition to the disease (Zamah et al. 2008). Mutations in the hepatocellular phospholipid transporter, ABCB4 (MDR3), which helps secretion of phosphatidylcholine into bile, have been found to be present in 15% of all ICP cases (Pauli-Magnus et al. 2004). Also homozygous mutations in the ATP8B1 gene cause cholestasis with a normal serum gamma-glutamyl trans peptidase (Mullenbach et al. 2005).

ICP during the first trimester of pregnancy is a rare condition. There have been few case reports, which describe first trimester ICP. In a previous case report, a patient with a twin pregnancy achieved by IVF treatment showed recurrent ICP following OHSS. Genetic predisposition has been suggested as the reason for developing ICP in two different trimester of the same pregnancy (Midgley et al. 1999). A majority of the patients were infertile and underwent controlled ovarian hyperstimulation which would cause hyper-oestrogenic condition. We suggest that a high oestrogenic environment and suspicious effect of progesterone administration may cause early onset ICP in these patients. This finding is supported by the resolution of ICP after termination of pregnancy. UDCA can be helpful in relieving pruritus and diminishing liver enzymes in ongoing pregnancies, which is safe to for mothers and babies (Meng et al. 1997; Grand'maison et al. 2014; Parizek et al. 2016). ICP is typically seen in the last trimester of pregnancy and for that reason it might be appropriate to name the ICP seen in first trimester as ICP like disease rather than ICP.

A rise in oestradiol begins in weeks 6–8 when placental function becomes apparent. These levels generally reach up to 2000 pg/mL. It is a well-known fact that individual oestradiol values increase to 6000 and 40,000 pg/mL at 36 weeks of gestation and then undergo an accelerated rate of increase (Salat-Baroux et al. 1992). For that reason ICP occurs predominantly in late pregnancy. The higher oestradiol levels both in luteal phase after IVF treatment and early pregnancy might predispose to early ICP.

It is important to consider ICP in the differential diagnosis of pruritus and elevated liver enzymes during the first trimester of pregnancy especially in pregnancies conceived through assisted reproductive technology with OHSS. Mild elevation in the liver enzymes can be seen in OHSS. If there is a prolonged and discordant elevation in the liver enzymes; serum bile acid levels will be useful in differential diagnosis.

## Disclosure statement

The authors report no conflicts of interest. The authors alone are responsible for the content and writing of the paper.

## References


Abu-Hayyeh S, Papacleovoulou G, Lovgren-Sandblom A, Tahir M, Oduwole O, Jamaludin NA, et al. 2013. Intrahepatic cholestasis of pregnancy levels of sulfated progesterone metabolites inhibit farnesoid X receptor resulting in a cholestatic phenotype. Hepatology 57:716–726.

Arrese M, Macias RI, Briz O, Perez MJ, Marin JJ. 2008. Molecular pathogenesis of intrahepatic cholestasis of pregnancy. Expert Reviews in Molecular Medicine 10:e9

Bacq Y, Sapey T, Brechot MC, Pierre F, Fignon A, Dubois F. 1997. Intrahepatic cholestasis of pregnancy: a French prospective study. Hepatology 26:358–364.

Brouwers L, Koster MP, Page-Christiaens GC, Kemperman H, Boon J, Evers IM, et al. 2015. Intrahepatic cholestasis of pregnancy: maternal and fetal outcomes associated with elevated bile acid levels. American Journal of Obstetrics and Gynecology 212:100 e1–107.

Forker EL. 1969. The effect of estrogen on bile formation in the rat. Journal of Clinical Investment 48:654–663.

Geenes V, Chappell LC, Seed PT, Steer PJ, Knight M, Williamson C. 2014. Association of severe intrahepatic cholestasis of pregnancy with adverse pregnancy outcomes: a prospective population-based case-control study. Hepatology 59:1482–1491.

Grand'maison S, Durand M, Mahone M. 2014. The effects of ursodeoxycholic acid treatment for intrahepatic cholestasis of pregnancy on maternal and fetal outcomes: a meta-analysis including non-randomized studies. Journal of Obstetric and Gynaecology Canada 36:632–641.

Meng LJ, Reyes H, Axelson M, Palma J, Hernandez I, Ribalta J, et al. 1997. Progesterone metabolites and bile acids in serum of patients with intrahepatic cholestasis of pregnancy: effect of ursodeoxycholic acid therapy. Hepatology 26:1573–1579.

Midgley DY, Khalaf Y, Braude PR, Nelson-Piercy C. 1999. Recurrent cholestasis following ovarian hyperstimulation syndrome: case report. Human Reproduction 14:2249–2251.

Mullenbach R, Bennett A, Tetlow N, Patel N, Hamilton G, Cheng F, et al. 2005. ATP8B1 mutations in British cases with intrahepatic cholestasis of pregnancy. Gut 54:829–834.

Parizek A, Simjak P, Cerny A, Sestinova A, Zdenkova A, Hill M, et al. 2016. Efficacy and safety of ursodeoxycholic acid in patients with intrahepatic cholestasis of pregnancy. Ann Hepatol 15:757–761.

Pauli-Magnus C, Lang T, Meier Y, Zodan-Marin T, Jung D, Breymann C, et al. 2004. Sequence analysis of bile salt export pump (ABCB11) and multidrug resistance p-glycoprotein 3 (ABCB4, MDR3) in patients with intrahepatic cholestasis of pregnancy. Pharmacogenetics 14:91–102.

Pusl T, Beuers U. 2007. Intrahepatic cholestasis of pregnancy. Orphanet Journal of Rare Diseases 2:26

Reyes H, Sjovall J. 2000. Bile acids and progesterone metabolites in intrahepatic cholestasis of pregnancy. Annals of Medicine 32:94–106.

Rioseco AJ, Ivankovic MB, Manzur A, Hamed F, Kato SR, Parer JT, et al. 1994. Intrahepatic cholestasis of pregnancy: a retrospective case-control study of perinatal outcome. American Journal of Obstetrics and Gynecology 170:890–895.

Salat-Baroux J, Cornet D, Alvarez S, Antoine JM, Mandelbaum J, Plachot M. 1992. Hormonal secretions in singleton pregnancies arising from the implantation of fresh or frozen embryos after oocyte donation in women with ovarian failure. Fertility and Sterility 57:150–155.

Wanggren K, Sparre LS, Wramsby H. 2004. Severe jaundice in early IVF pregnancy. European Journal of Obstetrics and Gynecology Reproduction and Biology 112:228–229.

Williamson C, Geenes V. 2014. Intrahepatic cholestasis of pregnancy. Obstetrics and Gynecology 124:120–133.

Zamah AM, El-Sayed YY, Milki AA. 2008. Two cases of cholestasis in the first trimester of pregnancy after ovarian hyperstimulation. Fertility and Sterility 90:1202 e7–1210.

Zecca E, De Luca D, Baroni S, Vento G, Tiberi E, Romagnoli C. 2008. Bile acid-induced lung injury in newborn infants: a bronchoalveolar lavage fluid study. Pediatrics 121:e146–e149.