Abstract

Jaundice related to embryo transfer or in early pregnancy after in vitro fertilization with or without ICSI is extremely rare. We report a case of severe jaundice in an IVF treated patient who is not successfully pregnant, with a clinical picture similar to hepatocellular hepatitis.

Keywords: in vitro fertilization; embryo transfer; jaundice; drug induced hepatitis

Case report

A 39-year old previously healthy lady developed severe jaundice noted 10 days after her fresh embryo transfer following IVF treatment. During her 11 years of primary subfertility, investigations revealed that she has stage 4 endometriosis and had evisceration of endometrioma 7 years ago. During the last 2 years since she was under our care, She had undergone bilateral tubal clippings and has had undergone three IVF cycles (including this episode) and one frozen embryo transfer. No jaundice was noted previously. She has practiced a healthy life style with no alcohol, no smoking, and never used illicit drugs. She never had any drug transfusion before.

In her previous IVF cycles ovarian stimulation were performed using Puregon (follitropin beta, FSH, Organon, Dublin, Ireland) however in her last IVF cycle, ovarian stimulation was performed using Gonal-F (follitropin alpha FSH, Merck Serono S.A. Succursale d’Aubone, Switzerland) 225 iu from day 2 until day 12 (11 days) with the addition of antagonist (Ganirelix, orgalutran, Schering-Plough, Schutzenstrasse, Ravensburg, Germany) on day 8 until trigger day on day 12. Human chorionic gonadotrophin (Ovidrel 6500 iu, Choriogonadotropin ?, Ovidrel, Merck Serono S.p.A, Modugno (BA), Italy) was given on trigger day 12. Oocyte retrieval (OR) was performed on day 14. Nine oocytes were retrieved of which only 5 were matured and had ICSI performed, and four were fertilized. Embryo transfer (ET) of three pre-embryos was performed after three days. Luteal phase support was given with oral dydrogesterone 10 mg tds (dydrogesterone, Duphaston, Abbot Biologicals B.V., the Netherlands), per vaginal Utrogestan 100 mg tds (Natural micronized progesterone, Utrogestan, Welchem, Besins Manufacturing Belgium, drogenbos, Belgium), and subcutaneous human chorionic gonadotropin 5000 iu (Pregnil, Schering-Plough, N.V. Organon, Oss, The Netherlands) biweekly. The luteal support drugs used were similar to the ones given previously.

Ten days after embryo transfer the patient complained of pruritus all over her body especially on the palms and soles, and increasing jaundice. However she had no pale stools or tea-coloured urine. She also has no fever, vomiting, lethargy, or myopathy. Blood test showed elevated liver enzymes, with alanine aminotransferase (ALT) 292 U/L (ref. <44) Aminotransferase of 130 U/L (ref <45), alkaline
phosphatase (ALP) 191 U/L (ref. 32-104), total bilirubin 0f 93 µmol/l (ref. <23). Oestradiol level was only 377 pmol/L. Serologic test for hepatitis A, B, and C and other viral screening were negative. Autoimmune hepatitis was ruled out by a negative Anti Nuclear Antibody (ANA), antimitochondrial antibody and anti Smooth Muscle Antibody. There is no evidence of hemolysis from the full blood picture and normal LDH level of 420 U/L (ref. 211-423). Coagulation test (INR and PT/APTT) was also normal. Abdominal ultrasound scan of the liver was essentially normal with no sonographic evidence of biliary obstruction.

The patient was cared for by the Gastroenterologist in view of her diagnosis of hepatitis and the provisional diagnosis was eventually made as drug induced hepatitis.

The jaundice lasted for almost 2 months and resolved after treatment with ursodeoxycholic acid 250 mg bd and syrup lactulose 15 mls tds for one week. The liver enzymes and bilirubin gradually normalized and medication ended. Unfortunately she was not pregnant following the embryo transfer.

Discussion
This case exhibited a clinical picture similar to hepatocellular jaundice which is extremely rare to occur after embryo transfer in IVF. In fact it is the first case of jaundice post embryo transfer that is experienced by this centre since ART is started in 1998. The provisional diagnosis of drug induced hepatitis is mainly a diagnosis of exclusion as it is a very rare to occur with the types of medications used.

Wånggren and colleague reported severe jaundice in an IVF patient with a clinical picture similar to intrahepatic cholestasis of pregnancy (ICP) which is extremely rare in early pregnancy. The cause of the ICP in the patient is believed to be because of the high oestrogen levels interacting with the liver of the susceptible individual, producing decreased bilirubin excretion and elevations of liver enzymes, bilirubin and bile acids 1,2. Zamah AM and colleague also reported two cases of intrahepatic cholestasis of pregnancy in the first trimester of pregnancies by IVF in association with ovarian hyperstimulation syndrome and markedly elevated maternal serum oestrogen levels 3. Our patient however did not have significant level of oestradiol.

A potential drug induced hepatitis in this case could be due to the progesterone.
Dydrogesterone-induced hepatitis was first described by Altintas et al in 2004. However the same patient could also had the provisional diagnosis of drug-induced autoimmunity, or classical autoimmune hepatitis based on her recurrent acute hepatitis attacks and other features reported in the case report. In contrast, our patient never had any hepatitis attack prior to this episode. To diagnose progesterone-induced hepatitis in this case is also arguable because the patient had used the same medications before and never developed jaundice. Gonal-f is the other potential drugs that may cause the hepatitis as it was the only drug that is different from the drugs used in the previous cycles. FDA reported three of 660 people (0.45%) who have have side effects when taking Gonal-f, have had cytolytic hepatitis. All three used the Gonal-f for the purpose of ovulation induction 6. The only way to confirm this is by exposing the patient to the same drug again in her next IVF cycle - which is a rather unethical action considering the financial, medicolegality, and emotional aspects related to it.

References