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Case report

Severe jaundice in early IVF pregnancy

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Abstract

Jaundice in early pregnancy after in vitro fertilization (IVF) is extremely rare. We report a case of severe jaundice in an IVF treated patient, with a clinical picture similar to intrahepatic cholestasis of pregnancy (ICP). We suggest strategies to prevent similar cases in the future.

Keywords: In vitro fertilization; Jaundice; Ovarian hyperstimulation syndrome; Pregnancy

1. Case report

A 33-year old previously healthy woman developed severe jaundice in early pregnancy following in vitro fertilization (IVF) treatment. After 7 years of primary infertility, investigation had only revealed mild endometriosis. The patient reported an earlier period of jaundice during intake of combined oral contraceptive pills. IVF treatment was performed with down-regulation using a gonadotrophin releasing hormone agonist (Suprefact; Svenska Hoechst AB, Stockholm, Sweden) 200 μg nasally, six times daily, followed by 11 days of stimulation with 150 IU of follicle stimulating hormone (FSH; Gonal-F, Serono Nordic AB, Sollentuna, Sweden) subcutaneously. Since the estradiol value rose to 9620 pmol/l on stimulation day 12, FSH injections were withheld 2 days, to reduce the risk of ovarian hyperstimulation syndrome (OHSS), after which 10,000 IU human chorion gonadotrophin (hCG; Profasi, Serono Nordic AB, Sollentuna, Sweden) was given on day 14. Ovum pick up (OPU) was performed on day 16. Sixteen oocytes were retrieved, of which eight were fertilized. Embryo transfer (ET) of two pre-embryos was performed after three days. Luteal phase support was given with Profasi 5000 IU at OPU and at ET, combined with suppositories of micronized progesterone 400 mg two times daily, replaced by Profasi 2500 IU on day 3, 6 and 9 after ET, and continued until 7 weeks of pregnancy in accordance with the protocol used at that time. Estradiol level 7 days after ET was 19,100 pmol/l, and the patient experienced discomfort with a swollen abdomen and shortness of breath. Vaginal ultrasound scan revealed enlargement of the ovaries and fluid in the pouch of douglas. Blood tests showed elevated liver enzymes, with aspartate aminotransferase (AST) 1.87 μkat/l (ref. <0.6) μkat/l, alanine aminotransferase (ALT) 2.98 μkat/l. (ref. <0.6) μkat/l, and alkaline phosphatase (ALP) 4.4 μkat/l (ref. 0.8–3.8 μkat/l). Serologic tests for hepatitis A, B, and C were negative. Abdominal ultrasound scan of the liver was normal. Eleven days after ET, the patient had increasing pruritus and abdominal distention and a slight jaundice, with bilirubin 41 μmol/l (ref. 4–22 μmol/l). Estradiol rose to a maximum value of 33,300 pmol/l, 15 days after ET (Fig. 1). Pregnancy test with S-hCG was positive, 17 days after ET. At 7 weeks of pregnancy ultrasound scan showed a viable singleton intrauterine pregnancy. The patient suffered from severe pruritus and increasing jaundice. As treatment with clemastin and hydroxizin was ineffective, the patient was given cholestyramine in increasing dosages. At the 8th week of pregnancy bilirubin reached a maximum value of 161 μmol/l. Estradiol values decreased (Fig. 1). Symptoms and bilirubin levels gradually normalized and medication was ended. At the 34th week of pregnancy, the patient again had pruritus and liver enzyme levels were raised (AST 2.56, ALT 4.98 μkat/l). At 39 weeks of pregnancy, she had a spontaneous vaginal uncomplicated delivery of a healthy daughter (birth weight 3220 g, height 48 cm). Maternal symptoms disappeared shortly after delivery and liver enzymes decreased to

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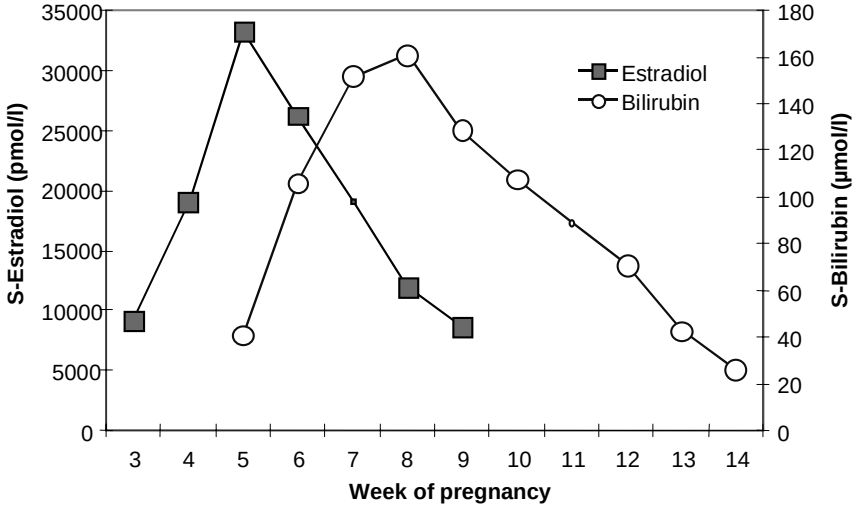

Fig. 1. Relationship between S-Estradiol and S-Bilirubin levels and week of pregnancy. The peak of S-Bilirubin is delayed 2–3 weeks after the peak of the S-Estradiol.

normal levels within 3 months. The baby girl has developed normally.

2. Discussion

The present case exhibited a clinical picture similar to ICP which is extremely rare in early pregnancy. It is, however, relatively common in Sweden in late pregnancy, with a prevalence of 2.4% [1]. The cause of ICP is unknown, but it is believed that high estrogen levels interact with the liver of the susceptible individual, producing decreased biliary excretion and elevations of liver enzymes, bilirubin and bile acids [2]. In this case, the serum concentration of estradiol was extremely high. This patient also had a history of contraceptive pill-induced cholestatic hepatitis, which is a risk factor for developing ICP during pregnancy [3].

ICP is a benign disorder for the pregnant women as no maternal mortality is reported. However, ICP is associated with high perinatal complications. The mechanism by which ICP leads to poor foetal outcome is poorly understood but may be related to toxic effects of bile acids [3]. Bilirubin has been shown to be neurotoxic in a variety of animal models. This was also of our concern in this case, since the patient had abnormally high bilirubin levels in her early pregnancy. There was, however, in this case no evidence of harm to the baby.

Since the therapeutic possibilities for ICP in early pregnancy is limited, prevention is recommended by avoiding high estradiol levels. This is achieved by using a mild or modest form of ovarian stimulation, using a low dose of FSH, only reinforcing the natural cycle or stimulating the growth of a limited number of follicles. In this case, it would probably have been beneficial if the dosage of hCG for ovulation induction had been decreased to 5000 IU and if luteal phase support had been provided by progesterone only rather than in combination with hCG injections [4]. Stimulation protocols including gonadotrophin antagonists could also be of value in similar cases because of lower serum peak estradiol concentration and reduced risk of OHSS.

In conclusion, we suggest that, until more knowledge is obtained concerning patients with risk factors for ICP, they should be mildly stimulated and carefully monitored when undergoing ovarian stimulation, thus avoiding high estradiol levels.

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