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In Vitro Fertilization(IVF) for Gilbert Syndrome Associated with ßeta-Thalassemia, A Case Report

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Abstract

The Gilbert syndrome is a familial tip of a benign condition characterized by a high level of unconjugated bilirubin without hemolysis or liver disease. In this syndrome, there is a mutation of the UGT1A1 gene on the long arm (q) of chromosome 2, which synthesize the enzyme uridine diphosphate-glucuronosyltransferase-1A1 (UGT1A1), that conjugate bilirubin. Hepatic glucuronidation activity is diminished by 30%. The association between Gilbert syndrome and in vitro fertilization (IVF) is not yet presented in the literature. A 34-year-old nulliparous woman presented to our clinic for primary infertility. Antimullerian hormone level was normal: 3.5 ng/ml. Her partner sperm analysis showed severe oligoasthenoteratozoospermia: 5milion/ml concentration, 25 % progressive motility, 3% standard form. She was known for Gilbert syndrome and ßeta thalassemia. She decided to go for in vitro fertilization (IVF) with ICSI (intracytoplasmic sperm injection). We used a short antagonist protocol with letrozole 2.5mg twice a day and 150 UI menotropins to avoid estradiol rising, which could determine, in her case, the level of serum bilirubin to increase. We collected fourteen oocytes; twelve of them were in metaphase II, nine fertilized by ICSI, and we obtained three good blastocyst 4aa, 4ab, and 4ba (according to Gardner-Schoolcraft criteria). We transferred one blastocyst, and ß HCG was negative on day eleven after embryo transfer. Next month, we transferred on a natural cycle one blastocyst: 4ab after thawing. Ultrasound confirmed a single pregnancy with a heartbeat. In this Gilbert syndrome, to avoid estradiol rising, we used aromatase inhibitors in conjunction with gonadotropins for IVF ovarian stimulation.

Keywords: in vitro fertilization; syndrome Gilbert; ß thalassemia; aromatase inhibitors.

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1. Introduction

Gilbert syndrome (GS) is a familial tip of a benign condition characterized by a high level of unconjugated bilirubin without hemolysis or liver disease. Gilbert syndrome is quite frequent, being seen in 5% of the patients [1]. It was described for the first time at the beginning of the twenty centuries by Augustine Gilbert and Pierre Lerebullet [2]. In this syndrome, there is a mutation of the UGT1A1 gene on the long arm (q) of chromosome 2, which produces the enzyme uridine diphosphate-glucuronosyltransferase-1A1 (UGT1A1), that conjugate bilirubin, then excreted it. In most cases, the hyperbilirubinemia is mild, less than 6mg/dl. Hepatic glucuronidation activity is diminished by 30% [3]. Females are less frequently affected than males [4]. During pregnancy, jaundice could appear at 10-16 weeks of gestation and remain increased until four weeks after cesarean section. In a significant number of pregnancies, Gilbert syndrome is uneventful. The patients' symptoms are generally mild: jaundice, nausea, fatigue, vomiting, abdominal pain, and itching. Thalassemia could accentuate hyperbilirubinemia in Gilbert syndrome [5]. The association of Gilbert syndrome and thalassemia is also discussed by other authors [4]. The association of Gilbert syndrome and IVF is not yet presented in the literature. The Gilbert syndrome is harmless in adults, but sometimes because of elevated hyperbilirubinemia could determine unnecessary investigations.

2. Case presentation

A 34 woman presented to our clinic for male infertility. She has 158 cm and 50kg, body mass index (BMI) 20 kg/m^2. Antimullerian hormone level was normal: 3.5 ng/ml. She was known for Gilbert syndrome and ßeta thalassemia. The level of indirect bilirubinemia was: 2.8 mg/dl, and the level of total bilirubinemia: 3.2 mg/dl. The diagnosis of ßeta thalassemia was based on the high level of fetal hemoglobin (HbA2>4%), reduced mean corpuscular volume (MCV<79fl) and mean corpuscular hemoglobin (MCH <27pg) [6]. She has undergone a short antagonist protocol with letrozole 2.5mg twice a day and 150 UI menotropins to avoid estradiol rising which could determine the level of serum bilirubin to increase. We used an antagonist sandwich protocol. The antagonist of GnRH(gonadotropin-releasing hormone), ganirelix acetate-(Cetrotide), was started on day two of the menstrual cycle in the morning and was kept for three days alone. On day five of the menstrual cycle, we added letrozole 5mg (2.5 mg every 12 hours) and menotropins (Menopur) 150UI in the evening. After five days of stimulation, we reintroduced the antagonist (ganirelix acetate in the morning). After ten days of stimulation, when we had two leading follicles of 20mm, we triggered ovulation with recombinant human chorionic gonadotropin (Ovitrelle). The bilirubin level was always mildly increased during ovarian stimulation, and the maximum oestradiol level was 243ng/ml. We collected fourteen oocytes; twelve of them were in metaphase II, nine fertilized by ICSI, and we obtained three good blastocyst 4aa, 4ab, and 4ba [7]. We transferred one blastocyst, and bHCG was negative on day eleven after embryo transfer. Next month, we transferred on a natural cycle one blastocyst: 4ab after thawing(fig.1).

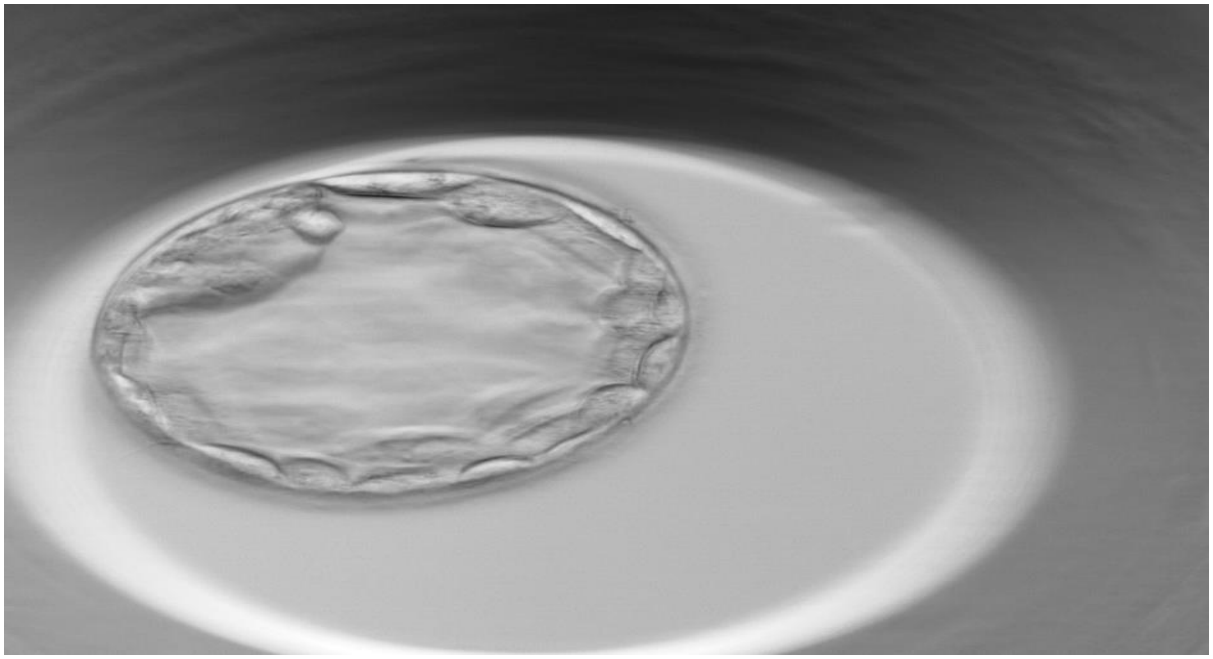

Figure 1: Time-lapse imaging of blastocyst transferred.

Ultrasound confirmed a single pregnancy with a heartbeat. The evolution of pregnancy was uneventful.

3. Discussion

The diagnosis of GS is based on four criteria [8]:

Elevated unconjugated serum bilirubin

Absence of hemolysis

Normal hepatic enzymes

Absence of other diseases associated with hyperbilirubinemia

Hemoglobin is metabolized in haem and globins in the mononuclear phagocytic system. Haem further is degraded in Fe++ and bilirubin. Bilirubin is transported to the liver, conjugated by uridine diphosphoglucose glucuronyltransferase (UGT1A1) to acid glucuronic [8]. The impairment of glucuronidation in Gilbert syndrome is determined by mutations in the TATA box upstream of the uridine diphosphoglucose glucuronyltransferase gene. Bilirubin-UGT is involve in estrogen metabolism through glucuronidation[9]. Standard IVF stimulation determines a high level of estradiol which in Gilbert syndrome could increase unconjugated and total bilirubin. The protocol of agents that suppress estradiol synthesis, such as aromatase inhibitors (letrozole), may be preferable to the conventional protocols. Thirty percent of Gilbert syndrome patients are asymptomatic. Some of the patients present jaundice, nausea, loss of appetite, vomiting, hypoglycemia, fatigue, itching, and abdominal pain. Itching and abdominal pain were not present in our patient [2].

Beta thalassemia could accompany GS. The factor that precipitates hyperbilirubinemia in these patients is the homozygote for the promoters (TA) [4]. It is essential to know what factors could aggravate hyperbilirubinemia in these cases to avoid clinical complications. That is why, in IVF patients, we have to adapt the stimulation protocol to avoid these unnecessary risks without compromising the outcome [10]**.** Periodically dosage of hyperbilirubinemia during controlled ovarian stimulation and further in pregnancy, is essential both for obtaining a viable pregnancy in IVF, but also for the health of the product of conception. This is the first situation we know in which it is discussed the potential particularities of these patients in IVF. GS could increase hyperbilirubinemia in newborns with the potential of complication of bilirubin encephalopathy[8]. It is reported in literature a case with GS where hyperbilirubinemia determines fetal distress and emergency cesarean section [8]. GS itself could not determine hyperbilirubinemia, only in association with a precipitating factor, in our case this was betatalasemia **[**11**].**

Differential diagnosis in GS is with Crigler-Najjar, Rotor, or Dubin-Johnson syndromes. Molecular genetics could help us in proper diagnosis, but also regarding other acquired hyperbilirubinemia conditions [4].

There is a limit here because this is only a case presentation, so we must confirm our hypothesis in further prospective and retrospective studies.

We should consider Gilbert syndrome in patients with unconjugated hyperbilirubinemia associated with stress, infection, and dehydration. PCR(polymorfism chain reduction) test could determine genetic polymorphism in the TATA box of the UDPGT1gene [2].

4. Conclusion

We presented this case because it is the first case regarding IVF and Gilbert syndrome in a patient with ßeta thalassemia, a situation which could increase hyperbilirubinemia . The particularitiy of ovarian stimulation in this situation is to avoid estradiol rising which could have a detrimental effect on serum bilirubin level. So that we used aromatase inhibitors in conjunction with gonadotropins, a similar protocol as in estrogen-positive cancers patients.

5. Recommendations

We suggest using the antagonist protocole with aromatase inhibitors and gonadotropins to avoid rising of estradiol in IVF patients with Gilbert syndrome.

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