Journal of the
Bahrain Medical Society

AlBuainain H, J Bahrain Med Soc. 2021;33(2):33-36

CASE REPORT

A Case Report: Infertility Treatment of a Female with Beta-thalassemia Major

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Received date: November 24, 2020; **Accepted date:** April 28, 2021; **Published date:** June 30, 2021

Abstract

Beta-thalassemia is caused by a genetically mediated deletion of beta-globin chain of hemoglobin. It is an autosomal recessive disease, which causes a severe medical condition that requires long-term blood transfusions. An impaired hypothalamic-pituitary-ovarian axis mainly causes infertility in such patients. This case report presents a 26-year-old female, a known case of beta-thalassemia major, that received monthly blood transfusions before conceiving. The patient sought consultation for the treatment of primary infertility at Bahrain Defence Force Royal Medical Services (BDF-RMS) Hospital. The patient underwent two trials of intrauterine insemination (IUI). The goal was to build up endometrial thickness by gonadotrophins administration for embryo implantation. To conclude, IUI combined with gonadotrophins for ovarian stimulation has shown success.

Keywords: Artificial Insemination, Beta-Thalassemia, Hypogonadism, Infertility, Pregnancy

Introduction

Thalassemia is a group of inherited anemias that are characterized by defects in the synthesis of one of the hemoglobin (Hgb) chains. Beta-thalassemia is an autosomal recessive disease caused by a genetically mediated deletion of beta-globin chains. It is heterogenous at the molecular level, and more than 200 disease-causing mutations are identified so far. Beta-thalassemia major (homozygous beta-thalassemia) is caused by a total absence of beta-globin chains or deficiency in their production. It predominantly occurs among patients of Mediterranean background and is considered one of the world's most common hemoglobin disorders.[1]

Infertility in thalassemia patients is caused by iron deposition in the pituitary gland, which disturbs the pituitary-gonadal axis in 40-90% of patients with regular transfusions. The anterior pituitary gland is responsible for the production of LH (Luteinizing hormone) and FSH (Follicular stimulating hormone)

and is highly sensitive to hemosiderosis. Therefore, the buildup of iron can lead to impairment in LH and FSH secretion, leading to a decrease in the synthesis of sex hormones. Patients with this condition present with pubertal failure symptoms, such as breast, uterus, and vaginal atrophy.[2]

Furthermore, the disturbance in hypothalamic-pituitary-ovarian axis secretion leads to gonadal dysfunction. This supports that steroidogenic function and ovulation can be restored by controlled ovarian stimulation with gonadotrophins. This case report introduces a modified stimulation to treat infertility in a beta-thalassemia patients.[1-4]

Case presentation

A 26-years-old female, a known case of beta-thalassemia major receiving monthly blood transfusions, came seeking help with conception at Bahrain Defence Force Royal Medical Services (BDF-RMS) Hospital. The patient was seen in a consultant clinic for treatment of primary infertility that was noticed for the past 14 months before her presentation. The onset of the patient's menarche was at the age of 12 years, with regular menstrual cycles followed by amenorrhea in the last two years. The baseline complete blood count (CBC) showed a low Hgb of 66 g/L and a high platelet count (PLT) of 777 x 10^9/L.

Speculum examination revealed a normal vulva, vagina, and cervix. Ultrasonography indicated a small uterus size that was 3cm in length. The thyroid function and hormonal profile were assessed on day two of the cycle, and the results were normal. Prolactin, thyroid-stimulating hormone (TSH), FSH, LH, and estradiol (E2) levels were 14.81 ng/ml, 0.59 uIU/ml, 3.63 mIU/ml, 2.56 mIU/ml, and 5 pg/ml, respectively. The husband's electrophoresis result was normal, and the semen analysis showed normozoospermia. Moreover, the patient was counseled regarding the high risk of pregnancy and was asked to obtain the Hematologist clearance for conception. The patient was started on hormonal replacement therapy (HRT) for 6 months to increase the uterine size.

Furthermore, the patient was seen in the Hematology consultant clinic and was informed that the pregnancy would be with high risks. Moreover, the patient was advised to undergo chelation therapy to reduce ferritin level, which was initially 233.9 ng/ml, and was referred to a Cardiologist for evaluation. In addition, the patient was advised that once pregnancy is achieved, blood transfusion should be continued as scheduled to maintain Hgb at 100g/L, while iron chelation therapy should be stopped, and aspirin should be taken along with prophylactic enoxaparin sodium (clexane) until six weeks after the delivery of the neonate.

The patient came to the clinic to start the infertility treatment after obtaining approval from both the Hematologist and Cardiologist. The cardiac echo result was normal, and the Hgb, PLT, and ferritin levels were 96 g/L, 959 x 10^9/L, and 220.8 ng/ml, respectively.

The patient was then counseled for intrauterine insemination (IUI) as the semen analysis showed normozoospermia. A repeated transvaginal scan (TVS) showed a normal uterine size with a length of approximately 6cm, endometrial thickness of 16mm, and antral follicular count (AFC) of 12. Furthermore, 75 IU of highly purified menotrophin human menopausal gonadotrophin (HMG) (Menopur; Ferring) was prescribed for nine days, followed by 150 IU for five days. TVS showed a thin endometrium of 6mm thickness and two dominant follicles with an average diameter greater than 18mm. Recombinant human chorionic gonadotropin hormone (hCG) (Ovitrelle Merck) at 250 mcg was given to trigger ovulation and estradiol valerate at 6mg daily was started to thicken the endometrium.

IUI was done at 36 hours after the ovulation trigger by hCG, but two weeks later, the pregnancy test was negative. The patient was advised to start another cycle of IUI. TVS showed an endometrial thickness of 2mm and a total AFC of nine. HMG (Menogon; Ferring) was initiated at 75IU and 150IU on alternate days for four days. TVS showed a very thin endometrium and non-responding follicles, so the patient was given 150IU for three days. TVS showed three recruiting follicles, but the endometrium was thin, with 5.6mm in thickness. The patient continued with a dose of 150IU for six more days, and estradiol valerate at 6mg daily was added for endometrial support. TVS showed an

endometrial thickness of 8mm and three dominant follicles with an average diameter greater than 17 mm. Ovulation was triggered with a 250 mcg injection of hCG (Ovitrelle; Merck), and IUI was done after 36 hours.

Two weeks following IUI, the pregnancy test was positive. At six weeks of gestation, a repeated TVS showed an intrauterine gestational sac (IUGS) with a fetal pole at six weeks of gestation and positive cardiac pulsation. At 12 weeks of gestation, a nuchal translucency (NT) examination was normal (0.17 cm). Moreover, a detailed anomaly scan was performed at 21 weeks of gestation, which did not show gross anomalies. During the pregnancy, regular monthly blood transfusions, aspirin, and enoxaparin sodium (clexane) were given to the patient with close follow-ups.

The patient presented to the labor suite at 35 weeks of gestation with preterm labor. A multidisciplinary team was involved in the patient's management, including senior Nurses, Midwives, a senior Obstetrician, an Anesthetist, and a Hematologist. At 12 hours after admission, the cardiotocography (CTG) result was non-reassuring, with recurrent unprovoked decelerations; therefore, the patient was prepared for an emergency lower-segment cesarean section (EM-LSCS) under spinal anesthesia. The pregnancy outcome was a baby girl weighing 2.3 kg, with an APGAR score of 9 and 10, in 1 and 5 minutes, respectively.

Post-operatively, the patient was vitally stable, afebrile, and the Hgb level was 103 g/L. The Hematologist assessed the patient and advised her to resume prophylactic enoxaparin for six weeks postpartum. A repeated echocardiogram was done for reassurance, and the result was normal. Both the patient and the neonate were discharged from the hospital after 72hours.

Discussion

Patients with beta-thalassemia major are clinically challenging when it comes to infertility treatment. The survival rate of beta-thalassemia major patients is increasing, and with more reaching reproductive age, the will to have children among them is rising. These patients must fulfill multiple checklists to ensure their safety during pregnancy.[5]

Hemoglobinopathies in the male partner first have to be excluded to prevent their children from inheriting them. Then, pre-conception counseling should be offered for such patients seeking infertility treatment. Preimplantation genetic testing for monogenic disorders (PGT-M) offers couples the chance to reduce the risk of transmitting an inherited disorder caused by a single gene (monogenic) to their children through in vitro fertilization (IVF) techniques.[6]

According to the Royal College of Obstetrics and Gynecology (RCOG), thalassemia patients should be managed closely with pre-natal, intrapartum, and postpartum visits. Patients should be informed about the risks of pregnancy, as in the present case. The risks include cardiomyopathy, the development of new endocrinopathies, and fetal risks, such as intrauterine growth restriction.[5]

Furthermore, patients can be started on aggressive chelation to reduce body iron buildup to prevent further end-organ damage. If the thalassemic patient is diabetic, an Endocrinologist referral is needed to achieve good glycemic control and a euthyroid state, which is essential in pregnancy. In addition, all pregnant women should be assessed by a Cardiologist with echocardiograms and electro-cardiograms (ECG) to evaluate the presence and severity of iron-chelated cardiomyopathy.[5]

Infertility treatment in such patients is focused on hypogonadotropic hypogonadism treatment. Iron overload is the main factor behind the pathogenesis of hypogonadism in patients with beta-thalassemia major. Some studies have shown that the anterior pituitary has high susceptibility to iron accumulation; therefore iron chelation therapy before conception is highly recommended.[7]

IUI combined with gonadotrophins has shown success for ovarian stimulation. IUI involves the insertion of a high number of washed spermatozoa directly into the uterus at the time of ovulation with or without ovarian stimulation. This increases the chance of pregnancy in couples with infertility due to male factor, anovulation, endometriosis, or unexplained infertility. The above-mentioned patient was counseled to undergo IUI rather than IVF because the husband's semen analysis was

normal. IUI combined with gonadotrophins for ovarian stimulation can lead to a clinical pregnancy in 17.1% of patients with a live birth rate of 11.4% per cycle. Suboptimal endometrial thickness was noted in the first IUI trial. This was corrected in the second trial by administering a higher starting dosage of gonadotrophins for ovarian stimulation, in addition to estradiol valerate earlier to build up the endometrial thickness for embryo implantation.[8-11]

Conflict of Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Funding

No funding or grant support.

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