Deep venous thrombosis in a patient undergoing *In-vitro* fertilization with oocyte donation

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ABSTRACT

Deep venous thrombosis (DVT) has been reported extensively following ovarian hyperstimulation syndrome during i*n-vitro* fertilization (IVF). Pregnancy *per se* increases the risk of DVT due to a hypercoagulable state. The long-term use of hormone replacement therapy (HRT) is another critical factor associated with DVT in women. However, an association between the short-term use of HRT in oocyte donation (OD) cycles and DVT has not yet been reported. We present a case of 43-year-old woman who developed DVT after IVF-OD. DVT was diagnosed at 7 weeks of pregnancy and was managed with low-molecular-weight heparin. We suggest that even a short-term use of HRT should be considered a risk factor for DVT especially in the presence of additional risk factors such as obesity. The patient had an uneventful recovery and delivered three healthy though preterm babies.

KEY WORDS: Frozen embryo transfer, hormone replacement therapy, i*n-vitro* fertilization-oocyte donation, venous thrombo-embolism

INTRODUCTION

Deep vein thrombosis (DVT) is the formation of a blood clot within a deep vein. It occurs more frequently in the lower limbs than upper limbs and is associated with an increased maternal morbidity and mortality.[1] Hypercoagulability, damage of the vessel wall, stasis, or low blood flow are the common causes of DVT in pregnancy. *In-vitro* fertilization (IVF) has been considered a risk factor for venous thrombosis (VT) with thrombosis known to occur after ovulation induction.[2,3] Ovarian stimulation during IVF induces supra-physiological endogenous levels of estradiol that might lead to hypercoagulability causing thrombosis.[4] Use of oral contraceptives and long-term use of hormone replacement therapy (HRT) have also been recognized to be crucial factors associated with DVT in women.[5] An increased level of fibrinogen and factor VIII coupled with a reduction in coagulation inhibitors and acquired resistance to activated protein C seem to be the most plausible mechanistic factors for VT in women undergoing HRT.[6] The risk of developing VT is reported to be high during the first year of use.[6] However, short-term use of HRT and association with VT has not yet been reported. Other predisposing factors for DVT are obesity, smoking, immobilization and a past or family history of thrombosis.[7]

We present a case of a 43-year-old woman who developed lower extremity DVT at around 7 weeks of pregnancy after IVF by oocyte donation (IVF-OD). The patient had undergone HRT on and off for IVF-OD over the last 1-year. The patient was managed with low-molecular-weight heparin (LMWH; enoxaparin, Bharat Serum and Vaccines Ltd., Hyderabad, India) and had an uneventful recovery.

CASE REPORT

A 43-year-old woman reported to our clinic with secondary infertility, a poor

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ovarian reserve and a bad obstetric history (BOH). Prior to visiting us, she had undergone four cycles of intrauterine insemination and four cycles of IVF (2 with self-eggs in Nigeria and 2 cycles of IVF with donor eggs in India) that had failed.

She was married for 16 years and had a normal menstrual cycle (4 days/26–27 days). Obstetric history revealed one full term birth and two early abortions with no living child. In 2002, the patient delivered a full term male baby after spontaneous conception. The baby expired at the age of one due to gastroenteritis. There was no history of pregnancy-induced hypertension, gestational diabetes or any other complication during that pregnancy.

In 2003 and 2013, she had missed abortions at 45 days after spontaneous conception. The last conception was after the first failed IVF-OD attempt. She had been investigated for BOH, and all investigations were normal. There was no evidence of congenital or acquired thrombophilia. The patient did not have any history of thrombosis, she was a nonsmoker. There was no family history of VT.

She had undergone laparotomy for an appendectomy in 1990 in Nigeria. In 1996, she had a diagnostic laparoscopy followed by diagnostic hysteroscopy done twice in 2009 and 2010 (all in Nigeria). The second hysteroscopy showed a false passage in the cervix at 11 O'clock position. No postoperative complications were reported in the patient.

In-vitro fertilization attempts

Two IVF procedures with self-eggs in Nigeria, the last one in 2010 using long agonist protocol had failed. In November 2013, the patient had an IVF with embryo transfer (ET) using donor oocytes (IVF-OD) in India. The patient then underwent operative hysteroscopy with adhesiolysis in December 2013 followed by HRT for 2 months. The cavity was normal, but bilateral (B/L) ostia were not visualized. In February 2014, she again underwent another cycle of IVF-OD with the transfer of four embryos but this too did not result in pregnancy.

The patient presented at our facility in March 2014. At the time of presentation, the patient had a high body mass index (35.6 kg/m^2; weight - 91.2 kg, height - 160 cm). Her blood pressure (130/80 mmHg), chest and cardiovascular examinations were normal. Pap's smear, breast ultrasound sonography (USG) and routine electrocardiography were normal. She had a deep vagina, the cervix was flush with the vagina. A false passage was identified at 11 O' clock position, and the external ostium of the uterus was visualized with difficulty at 6 O' clock position lying posteriorly. Her per vaginal examination showed that uterus was ante-verted, bulky, and mobility was restricted.

After reviewing the patient's history and examination, and in view of multiple IVF failures and BOH, she was advised to go for IVF-OD after determining the exact window of endometrial receptivity. The patient had an endometrial receptivity array test done in March 2014. The dose of estradiol valerate (Zydus Cadila Healthcare Ltd.; German Remedies) had to be stepped up to 12 mg daily orally and 4 mg vaginally to build up the endometrial lining as her endometrial lining was consistent below 7 mm. She received a total of 2 cycles of HRT before the next IVF-OD attempt.

In April 2014, IVF-OD was done and 2 grade A blastocysts were transferred. ET procedure was traumatic as there was considerable difficulty in accessing the cervix. It was extremely difficult to identify the external cervical os due to the presence of a cystocoele, made worse because of the full bladder, depth of the vagina and the flush torn cervix. The bladder was half emptied by catheterization and ET catheter was negotiated after holding the cervix with an allis forceps. This attempt failed as expected.

The next frozen ET (FET) was planned in May–June 2014 cycle, and on patient's request three embryos were transferred. During this FET cycle, the patient again received estradiol valerate (OD, 12 mg) and progesterone (BD, 400 mg). Fourteen days after ET, her urine pregnancy test was positive and beta-human chorionic gonadotropin was reported to be 5013 mIU/ml.

Low-dose asprin-loprin (OD, 75 mg; Unichem Laboratories) was given along with all cycles of HRT. A subcutaneous injection of lonopin (20 mg, Bharat Serums and Vaccines Ltd., Hyderabad, India) was administered on alternate days to improve implantation. In view of spotting during early pregnancy, both loprin and lonopin were stopped.

A transvaginal ultrasound done on 5 July 2014 showed three I/U gestational sacs of 5 weeks and 3 days. Estradiol valerate dose was dropped from 12 mg to 6 mg after identification of gestation sacs on transvaginal sonography. Progesterone pessaries were continued. Ultrasound at 6 weeks revealed cardiac activity present in all the three embryos.

The patient reported with pain and swelling in left leg at around 7 weeks of the pregnancy. There was no antecedent history of trauma, fever, and varicose veins. On examination, the entire left leg showed edema, there was no discoloration or change in skin temperature. DVT was diagnosed clinically and was confirmed on Doppler test done on 14 July 2014. On Doppler, left common iliac, left external iliac and left common femoral in its upper one-third showed distension with soft tissue echogenicity of a thrombus, occupying the entire lumen of the vein. The diameter of

the veins was approximately doubled. Right leg veins appeared normal. Other investigations done were normal including liver function test, serum blood urea (38 mg/dl), serum creatinine (1.35 mg), serum uric acid (3.5 mg), platelets (1.4×10^5/cc), prothrombin time (PT - 17.3 s at 1 min and 1.43 s at 2 min) and activated partial thromboplastin time (36 s). The patient was hospitalized and managed with enoxaparin (BD, 0.8 ml) subcutaneously in association with a hematologist. The thrombus started resolving within 3 weeks with the Doppler showing improved blood flow and was completely resolved on the scan done after 7 weeks of treatment. The patient was maintained on a daily dose of LMWH until 34 weeks of pregnancy and then in the postmartum phase. Thromboembolic deterrent stocking was given after the first 2 weeks of LMWH.

At 34 weeks, she had a premature rupture of membranes, and an emergency lower (uterine) segment cesarean section was done. She delivered one female 1.4 kg and two male babies 2.1 kg and 1.8 kg birth weight. The female baby died of necrotizing enterocolitis 1-week after the birth; the other two were discharged from the hospital after 2 weeks of delivery.

DISCUSSION

DVT is manifested by the presence of blood clot in the deep vein of the limbs occurring predominantly in the lower limb. The clot limits the flow of the blood through the affected vein causing pain and swelling in the leg.[8] Venous thromboembolism (VTE: includes DVT and pulmonary embolism) though rare remains a major cause of maternal mortality and morbidity.

The major risk factors for VT are endogenous patient characteristics such as obesity and genetic factors, and triggering factors such as surgery, immobility or pregnancy. The additive effects of endogenous, genetic and environmental risk factors present simultaneously can cause VT[9] [Figure 1]. Hypothesis prevails that all risk factors for VT share in common an elevated risk of cell death due to oxidative stress and/or an imbalance in cell energy supply and demand. Cell death in turn triggers coagulation activation.[5]

There is an increased risk of VTE, especially during the third trimester of pregnancy and the first 6 weeks after delivery.[10,11] An increase in circulating blood volume, expansion of the uterus, weight gain and hormonal changes are the factors that make pregnancy a risk factor for VTE. Pregnancy changes induce a pro-coagulant state. Hypercoagulability and hypofibrinolysis is a result of increased plasma levels of fibrinogen, von-Willebrand factor and factors VII, VIII, IX, and X, and a decreased

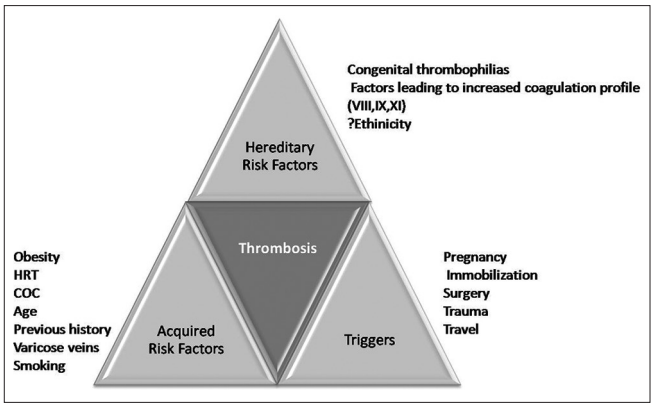

Figure 1: Factors causing thrombosis

plasma level of protein S and platelets. A review by Richter and Rath demonstrated that pregnant women are at a six times higher risk of developing thromboembolic complications. The chance of developing venous insufficiency is reported to be increased with multiple pregnancies and obesity.[12]

Previous studies have provided important evidence for considering IVF as a risk factor for VTE. Jacobsen *et al*. found that the VTE risk during pregnancy and the postpartum period was significantly increased in IVF pregnancies compared with other pregnancies, and Henriksson *et al.* and Rova *et al.* showed a significantly increased VTE risk among IVF-pregnancies during the first trimester.[7,13,14] Hansen *et al*. reported no evidence of increased VTE risk after IVF treatment in unsuccessful cycles suggesting thereby that pregnancy was the precipitating factor.[15]

HRT use among postmenopausal women is known to be associated with VTE in more than 2 of 5 women.[8] A prospective case-control study demonstrated that the risk of developing DVT increases in patients taking combined estrogen-progestin HRT than in patients on estrogen-only HRT.[16] However, all these studies refer to long-term use of HRT.

Obesity is another risk factor that can increase the chance of developing DVT by creating a prothrombotic milieu.[17] Recently, a case-control study by Waldman *et al*. aimed to assess the risk factors for VTE during pregnancy and later in life. The study concluded that maternal age, obesity, pregnancy-related hypertension, grand multiparity, cesarean delivery, stillbirth and peripartum hysterectomy are independent risk factors responsible for the development of VTE.[18] A study by Kloviate *et al*., compared obese people with normal weighted people to assess the risk of DVT. The study observed that 10-year risk of DVT was high in 35% of the obese people and was only 18% in normal-weight individuals.[19]

There are several reports of DVT in patients with ovarian stimulation and IVF owing to high estrogen levels, however; we report a unique case of a patient with DVT after undergoing IVF-OD.

The precipitating factors-in our case could be obesity (BMI: 35.6 kg/m^2), age (there is an increased risk in older patients, though she was just 43-year-old), multiple pregnancy (she was carrying triplets) and multiple cycles of HRT with high doses of estradiol valerate. The patient was on combined HRT off and on since last 1-year for IVF-OD. She had undergone four cycles of HRT before she came to our center. At our center, she again underwent three cycles of HRT with a high dose of estradiol valerate before she had a successful pregnancy. Ethnicity could also be a factor, an increased risk in patients of African ethnicity has been reported.[20]

Patients who have undergone IVF tend to take bed rest as they feel it increases their chances of implantation and reduces chances of abortion. A period of immobility of even 4 days has been reported to increase risk of DVT. Immobility increases the risk of thrombosis, presumably due to stasis of blood flow in the venous system. Minor forms of immobility, such as after minor surgery or injury, have also been linked to thrombosis risk.[21] Though, we could not establish that our patient had been on complete bed rest, we feel that some degree of immobility must have added to the problem.

We suggest that even short-term HRT should be considered a risk factor for DVT especially if there are any additional existing risk/triggering factors in this case multiple pregnancy and obesity. Complete bed rest/immobility should be discouraged more so in the high-risk group.

The patient received LMWH therapeutic doses till the clot resolved and was continued on prophylactic therapy until delivery. She had an uneventful recovery and delivered three healthy babies.

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Conflicts of interest

There are no conflicts of interest.

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