Successful term pregnancy in a patient with acute portal vein thrombosis following in vitro fertilization

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ABSTRACT

Assisted reproductive technology (ART) procedures such as in vitro fertilization (IVF) can be complicated by both arterial and venous thromboembolic events. Acute portal vein thrombosis complicating IVF is particularly rare, with only one previously reported case in the literature. This thrombotic event is typically associated with various abdominal pathologies or observed in patients with thrombophilic conditions. However, IVF increases the global risk of a venous thromboembolic event by 10-fold. In this case report, we describe a 40-year-old woman who underwent IVF treatment and subsequently developed acute portal vein thrombosis with superimposed septicemia. Despite her severe illness, the patient was found to have a viable early pregnancy during her hospital admission. She was treated with intravenous antibiotics and therapeutic anticoagulation and discharged 18 days after initial presentation. Anticoagulation was continued throughout her pregnancy without complication and the patient went on to deliver a healthy term female. Successful pregnancy distinguishes this unique case from the other reported case of acute portal vein thrombosis secondary to IVF in the literature.

INTRODUCTION

Thromboembolic events are rare but serious complications in patients undergoing in vitro fertilization (IVF). Increased risk of venous or arterial thrombosis is secondary to the supra-physiological hormone levels resulting from controlled ovarian hyperstimulation (COH).¹ Thrombosis secondary to IVF occurs in the veins of the neck and upper extremities in 80% of cases.² Risk factors for the development of thrombosis secondary to IVF treatment include age over 39 years, being pregnant, ovarian hyperstimulation syndrome (OHSS), and inherited thrombophilias.¹⁻³ OHSS is a serious and potentially life-threatening clinical syndrome that results from excess stimulation of the ovaries by exogenous gonadotropins, which allows growth and retrieval of oocytes during assisted reproductive technology (ART) procedures.³ Symptoms of OHSS arise from ovarian enlargement and capillary leakage resulting in fluid accumulation in third spaces, such as abdominal, pleural, and pericardial cavities.²

Acute portal vein thrombosis (PVT) is a particularly rare thromboembolic event complicating IVF, with only 1 previous case reported in the literature.⁴ PVT is usually associated with cirrhosis or inflammatory processes of the abdomen such as appendicitis, cholecystitis, or various abdominal cancers.⁵ In patients with non-cirrhotic PVT, more than half are found to have one or more thrombophilic conditions.⁶

CASE REPORT

A 37-year-old female with no previous pregnancies presented in 2012 with a 3 year history of primary infertility. Her history was unremarkable other than mild asthma. She had no history of venous thromboembolism or abnormal bleeding. General physical examination was normal, though her BMI was elevated at 31 kg/m². She had regular menstrual cycles with 5 days of bleeding every 28-30 days. Her husband was a healthy 40-year-old with a normal semen analysis. All fertility investigations were normal, including diagnostic laparoscopy. On that basis, they had three cycles of ovarian stimulation using clomiphene citrate with intra-uterine insemination (IUI) without success. Subsequent IUI with FSH for ovarian stimulation (COH-IUI) resulted in pregnancy but early spontaneous abortion on two occasions. Routine testing for recurrent miscarriage, including a thrombophilia screen and karyotyping of both partners, was normal. The third COH-IUI cycle resulted in an uncomplicated pregnancy leading to spontaneous vaginal delivery of a healthy term female. She had no complications during or after treatment or delivery.

In March of 2015 the couple returned to attempt another pregnancy. COH-IUI was repeated and she had another early pregnancy loss. They then elected to proceed with IVF treatment in October of 2016. Routine stimulation yielded 8 mature oocytes. Four embryos developed to blastocyst stage, and 1 was transferred. At the time of embryo transfer she was asymptomatic. Four days following embryo transfer, the patient presented with epigastric and right upper quadrant pain, nausea, vomiting, anorexia, and malaise. She was admitted to hospital with a presumptive diagnosis of OHSS, although she did not present with symptoms of volume overload such as ascites or dyspnea. Following her admission, she was found to have significantly elevated liver enzymes (AST 3.79, ALT 4.85, ALP 2.98, GGT 4.70 μ kat/L), hyperbilirubinemia (total bilirubin 110, conjugated bilirubin 82 μ mol/L), and a white cell count of 17.5×10^9 /L. Hemoglobin was normal, and she was not hemoconcentrated. Amylase and lipase were normal. The patient denied a past history of abdominal pathology, including gallstones, jaundice, hepatitis, pancreatitis, or ulcers. Abdominal ultrasound revealed only a moderately distended gallbladder, and obscuring of the common bile duct. There was minimal dilatation of the intrahepatic biliary ducts.

The patient then had a blood culture drawn which grew *E. coli*. She developed symptoms of jaundice, leading to concern of possible abscess or infectious process. Antibiotic therapy was switched from cephazolin to piperacillin/tazobactam (Tazocin), though her white cell count and fever had resolved. Her transaminitis did begin to trend downward, but computerized tomography (CT) of the ab-

domen showed attenuation changes around the common bile duct and within both liver lobes, leading to speculation of cholangiocarcinoma. The patient developed profound jaundice about 1 week following admission. At this time, she had her first positive serum beta human chorionic gonadotropin (hCG).

Following consultation with gastroenterology, a colour Doppler ultrasound study demonstrated left portal vein thrombosis and associated inflammation of the liver, most likely due to infection. She was started on therapeutic anticoagulation: 10 000 units of low molecular weight Heparin (LMWH) every 12 hours. Liver profile and blood cultures were followed, and she was discharged with normalizing transaminitis and negative blood cultures 18 days after admission. She improved clinically, with no jaundice, nausea or vomiting, and only minimal abdominal pain. Hematology consultation was obtained, and screening for thrombophilia was again negative.

Surprisingly, despite this serious illness, her hCG rose normally. Early dating ultrasound and anatomic ultrasound at 20 weeks were normal. She declined the integrated prenatal screen. Other than bruising from the heparin injections, her pregnancy was uncomplicated and she went on to deliver a healthy female following induction of labor at 39 weeks gestation. Follow up Doppler ultrasound performed 6 months later showed persistence of the left portal vein thrombosis despite the resolution of symptoms. She continues to be followed by hematology.

DISCUSSION

The incidence of venous thromboembolic events in women undergoing IVF treatment is estimated at 0.08-0.11% of treatment cycles.^{7,8} This is a 10-fold increase compared to baseline risk in women of reproductive age.⁹ In the setting of OHSS, this relative risk increases further to 20 to 40-fold compared to baseline.¹⁰ A 2009 literature review examining instances of thromboembolic complications of ART reported that 90% of arterial events and 78% of venous events were complications of OHSS.³ Inherited thrombophilia is detected in 41% of women with venous thromboembolic events secondary to IVF.¹¹

The hyperestrogenic state achieved during IVF treatment very likely plays a role in the increased risk of venous thromboembolism, as a similar effect has been observed with oral contraceptives and hormone replacement.^{12,13} While there is limited information on the exact effect of exogenous estrogen on hemostatic parameters, a number of studies suggest that increased estradiol levels are associated with increased fibrinogen and D-dimer levels, as well as resistance to activated protein C.¹⁴⁻¹⁶ Furthermore, ovarian stimulation itself is associated with an increase in coagulation factors and markers such as factor V, fibrinogen, von Willebrand's factor (vWF), prothrombin fragments 1 and 2, and D-dimer. Ovarian stimulation also appears to impair the function of anti-coagulants such as antithrombin and protein S.¹⁷⁻²⁰ In the setting of OHSS, these coagulation changes are further pronounced.^{14,17,21} With IVF, administration of hCG for final oocyte maturation leads also to elevation of fibrinogen, as well as increased levels of factors II, V, VII, VIII and IX.¹⁹ Each of these compounds increase thrombotic activity.¹⁹ The

activation of the fibrinolytic system, which allows for clot turnover and remodeling, occurs within 2 days of hCG administration, and appears to peak at day 8.^{17,21}

It may be tempting to attribute the elevated risk of thromboembolic events to achieving pregnancy, as being pregnant results in a 10-fold increase in risk of venous thromboembolic events.^{22,23} However, the true pathophysiology is likely multi-factorial. The literature shows that a fair minority of women with thromboembolic events secondary to IVF did not achieve pregnancy.¹¹ Additionally, underlying thrombophilias were found in 41% of women who had venous thromboembolic events.²⁴ These points would argue against pregnancy as the sole factor in developing a thrombus.

Acute portal vein thrombosis has been reported 1 other time in the literature as a complication of IVF.⁴ Acute PVT presents as abdominal pain, nausea, and fever, although patients can also be asymptomatic or experience nonspecific symptoms.²⁵ The goals of PVT treatment are to allow for recanalization of the portal vein and to reduce the risk of thrombus progression into the mesenteric vessels. The most common regimen for anticoagulation is the use of low-molecular weight heparin (LMWH) with eventual transition to warfarin and a targeted international normalized ratio (INR) of between 2-3. Duration of treatment ranges from 6 months to lifelong, depending on systemic risk factors. Complete recanalization is achieved in 50% of cases of acute PVT, and partial recanalization in 40%, leaving 10% with failure to recanalize.²⁵ Results of anticoagulant therapy for acute PVT during pregnancy or secondary to IVF treatment have not been investigated. Furthermore, warfarin is contraindicated in pregnancy, so anticoagulation therapy must be modified for patients with thromboembolic events who have achieved pregnancy.

Prophylactic anticoagulation administration during ART is controversial. A publication from 2009 in Thrombosis Research suggests taking a proactive approach to preventing venous thromboembolic events secondary to ART by first stabilizing any modifiable risk factors which could contribute to a state of hypercoagulability, such as obesity or preexisting medical conditions.²⁶ Following this, they suggest an approach similar to one that has proven to significantly reduce venous thromboembolism risk during pregnancy.²⁷ It is important to educate women on the proven efficacy and safety of LMWH use during pregnancy, and reassure them of the drug's inability to cross the placenta and affect fetal development.²⁸ It would be advisable also to include other specialists in the treatment of these women to determine systemic risk factors that may benefit from lifelong anticoagulant prophylaxis.

CONCLUSION

We report the second case of acute portal vein thrombosis complicating IVF treatment, and the first case that resulted in a successful term pregnancy. The diagnosis was made relatively early in the patient's condition, and aggressive treatment with anticoagulation enabled her to follow through with successful pregnancy. She will require ongoing monitoring for the persistent thrombosis.

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