Deep Vein Thrombosis as a Complication of Severe Ovarian Hyperstimulation Syndrome

Thrombosis and thromboembolic phenomena are uncommon yet seem to present in a rapidly progressive clinical scenario following assisted reproduction. Deep vein thrombosis (DVT) is one of the rare consequences of ovarian hyperstimulation syndrome. It has been surmized that the underlying hypercoagulable state, probably due to the high serum levels of estrogen and hemoconcentration, contribute to the development of DVT.¹

**Case Report**

Mrs. SS, aged 24 years, married since 3.6 years, came to us for secondary infertility in February 2012. Her first conception through ovulation induction with clomiphene citrate resulted in an intrauterine fetal demise at 22 weeks of gestation in July 2011 due to oligohydramnios with severe placental dysfunction.

She then underwent diagnostic laparoscopy with hysteroscopy on 07/02/2012 which revealed normal uterus and appendages. Her husband’s semen analysis was also normal. After a few unsuccessful attempts at intrauterine insemination (IUI) the couple finally opted for in vitro fertilization (IVF) in July 2013. She underwent long protocol with down regulation using GnRh analogue 3.6mg SC (Zoladex, Astrazeneca, UK Limited) and controlled ovarian hyperstimulation using recombinant FSH, (Organon, USA) and Gonadotrophins (HP Gonadotrophins, LG, Korea). Injection HCG 10,000 IU (Unisankyo, Japan) was used for final follicular maturation on 3/08/2013. Fourteen oocytes were retrieved by transvaginal aspiration. On 06/08/13, Day 3 of culture, 2 embryos (8 cells, Grade I) were transferred using labotect embryotransfer catheter (Alpha & Omega, Germany).
During the next few days, she developed signs of moderate ovarian hyperstimulation syndrome (OHSS), which was managed and treated conservatively with IV fluids, IV Albumin, protein rich diet, micronized progesterone and careful monitoring of all vital parameters including abdomen girth, intake-output chart and weight chart. Ultrasound was performed every alternate day to monitor ovarian enlargement and to assess pelvic collection or ascites. All blood parameters including renal and hepatic were within normal limits. The one notable finding was the presence of hemoconcentration which is also common following OHSS.

On 13/08/13 she developed mild breathlessness and unilateral right limb edema. As per clinical, chest X-ray, and ultrasound findings she was diagnosed with ascites and left pleural effusion. Ascitic and pleural tapping were performed under aseptic precautions by the pulmonologist. On 15/08/2013 her serum β-HCG was positive for pregnancy and she developed moderate ascites and right pleural effusion for the second time on 22/08/2013. Once again the tapping was done. She was also on restricted mobility owing to severe lower back ache and hence on 25/08/2013, her right limb edema worsened and she now presented with a positive Homan’s sign.

An emergency doppler finding of both lower limbs revealed a thrombosis of right common femoral vein and right superficial femoral vein with diffuse subcutaneous edema of the calf and thigh. The long saphenous vein was also occluded at the junction. Suggestive of deep vein thrombosis of right limb.

The physician and vascular surgeon’s opinion was obtained and she was started on injection. Clexane 0.8 mL SC, twice daily. Antiembolic stockings, nil ambulation and foot end elevation were instructed. Due to financial constraints, the patient was discharged against medical advice. She was followed up at another hospital closer to her home and it was known that the pregnancy ended up in a blighted ovum and she was continued on oral anticoagulation and is currently on regular follow-up. This is one of the fortunate scenarios where an extensive thrombosis did not dislodge and lead to catastrophic events.

**Discussion**

Thromboembolic disease associated with ovarian stimulation is an uncommon yet potentially fatal complication of assisted reproductive technology (ART). Stewart et al performed a review of cases of thromboembolic disease associated with ovulation induction and reported 54 cases between 1964 and 1997. The authors found that 66% of these cases were associated with OHSS and 84% were associated with pregnancy. In addition, 75% of cases were venous in origin while 15% were arterial thrombosis (mostly intracerebral). Sixty percent of venous sites were located in the upper limbs, neck and head. While OHSS may be an important factor in the pathogenesis of thrombosis, it does not precede all cases. Severe OHSS is reported to account for 0.56-6.5% of all Ovarian hyperstimulation is responsible for the presence of hemoconcentration, elevated estrogen levels along with reduced venous return caused by enlarged ovaries that may in part explain the development of deep vein thrombosis (DVT). In review of literature, 74% of cases of thromboembolism following ovulation induction were associated with OHSS.

However, it is interesting to note that the thrombosis often presents weeks after resolution of clinical syndrome. Venous thromboembolism in pregnancy is most commonly located in lower extremity with 70% occurring in the ileo femoral region. The majority of thrombosis following ovarian stimulation occurs in the upper extremity.

Not all cases of DVT following ovarian stimulation are associated with OHSS and not all patients with OHSS develop thromboembolism. Therefore investigators have proposed that other predisposing factors must exist that precipitate thrombus formation. All patients who do develop a thrombus in the above scenarios deserve a workup for the presence of thrombophilias. Hyperestrogenic states like polycystic ovarian syndrome are also prone. A history of previous episodes and adequate precautions like down regulating in a natural cycle or avoiding excessive use of hormones can be preventive.

Obesity and sedentary lifestyle during treatment...
cycles can also be addressed before initiation of therapy. Although low dose preventive treatment with heparin is of some theoretical value, rapid alleviation of hemoconcentration is far more important. In our case, we promptly treated this patient by measured hydration and paracentesis in an effort to combat a rapidly depleting intravascular while compartment at the same time preventing collection in the third space. This case demonstrated the need for early diagnosis and treatment, being crucial for both maternal and fetal well-being. Patient with severe OHSS with lower limb pain and swelling should undergo a thorough and complete evaluation for DVT. Further clinical studies are required to elucidate the role of prophylactic anticoagulation in patients with OHSS following ovulation induction although consideration must be given to screening patients at risk for OHSS for thrombophilias as well as administering prophylactic heparin for well indicated situations.

Given the increased likelihood of thromboembolism, should patients with severe OHSS receive prophylactic anticoagulation regardless of thrombophilia testing? To our knowledge, there have been no randomized controlled studies to address these issues.

Fabregues et al. suggested that thrombophilia screening in general IVF population is not cost effective and also reported that the prevalence of thrombophilia is not increased in women with severe OHSS. However, since the co-existence of thrombophilia and OHSS could have catastrophic sequence, consideration should be given to screening patients with severe OHSS.

All of our IVF patients however start on tablet Aspirin 75 mg at the onset of ovarian stimulation. Although it is possible that anticoagulation with low-molecular-weight heparin (LMWH) may be beneficial in cases of severe OHSS, it is not uniformly established practice to give it to all women with OHSS. Most authors reserve treatment by heparin for special circumstances in which thromboembolic events have already occurred, or there is abnormal clotting, often owing to congenital coagulopathy.

To surmise it is important to
- Identify high risk factors:
- Presence of blood dyscrasias
- Obesity
- Polycystic ovarian syndrome
- Previous episodes with use of oral contraceptive (OC) pills
- Use of antiepileptics
- Varicose veins
- Antiphospholipid antibody syndrome
- Do a coagulation work-up when needed.
- Opine with a hematologist as well as a vascular surgeon.
- Institute therapy either as prophylaxis or be on high alert to identify a case for timely intervention.

References

Successful Management of a Post-salpingectomy Right Cornual Heterotopic Pregnancy

Introduction

A heterotopic pregnancy is a rare complication which has recently found a rising incidence in ART. It is one in which both extrauterine (ectopic pregnancy) and intrauterine pregnancy occurs simultaneously. It may also be referred to as a combined ectopic pregnancy, multiple-sited pregnancy, or coincident pregnancy. The prevalence of heterotopic pregnancy is estimated at 0.6-2.5: 10,000 pregnancies. Cornual heterotopic pregnancy is a very rare condition. Its occurrence rate ranges from 1/2500 to 1/5000 live births and represents 1% of ectopic pregnancies.
Case Report

A 34-year-old lady, married for 9 years presented to us for primary infertility. Menstrual history and general physical and pelvic examinations were normal. She had a previous history of treatment for antinuclear antibodies (ANA) positive connective tissue disorder and had subsequently undergone aspiration of bilateral endometriotic cysts in 2004 followed by an adenomyotic nodule excision in 2009 by laparoscopic intervention. She underwent first cycle of IVF at our centre on 29/07/13 which ended in a left tubal ectopic for which a salpingectomy was performed on 18/02/13.

Intraoperatively, as is the norm, the right tube was also examined and it was found to be deformed with severe hydrosalphinx for which a right salpingectomy was also performed after obtaining informed consent from her husband. After 6 months, she underwent a second cycle of ICSI-ET on 01/08/2013 and she tested positive for pregnancy.

An intrauterine gestational sac was confirmed by the transvaginal ultrasound on the 37th day of pregnancy on 21/08/2013. She was subsequently admitted for threatened miscarriage on the 39th day with a hemorrhagic area of 1.1 × 0.6 cm seen near the cervix by ultrasound. She was managed conservatively with bed rest, styptics and hormonal support. The
pregnancy was progressing well until she returned on the 47th day with complaints of brown discharge and an ultrasound performed at that time revealed the viable intrauterine pregnancy complete with a yolk sac, fetal pole and fetal heart pulsation along with another sac seen near the right adnexa/cornua.

Following the diagnosis of a heterotopic pregnancy an emergency laparoscopy was performed and its presence was confirmed in the right cornua, at the site of the previous salpingectomy. Cauterization of the base of the ectopic sac was performed using bipolar coagulation and sac contents were evacuated. The resultant defect was repaired using 1-0 vicryl suture. Patient was stable postprocedure. Ultrasonographic (USG) was done on 49th day, which showed viable intrauterine pregnancy. Patient is now 16-18 weeks into her pregnancy and is doing well on follow-up.

Discussion

In the general population, the major risk factors for heterotopic pregnancy are the same as those for ectopic pregnancy. For women in an ART program, there are additional factors: A higher incidence of ovarian hyperstimulation, a higher incidence of tubal malformation and/or tubal damage and technical factors in embryo transfer which may increase the risk for ectopic and heterotopic pregnancy.

Diagnosis of this condition is difficult due to the existence of the intrauterine gestational sac. The most frequent danger lies in the nonrecognition of the condition and subsequent uterine rupture at a more advanced gestation. Cornual rupture in the context of cornual heterotopic pregnancy occurs in approximately 48.6% of cases, and usually results in brisk hemorrhage due to the fact that the gestational sac lies next to an extensive vascular area and the uterine artery.

Maternal mortality is estimated to occur in 2% to 2.5% of cases. The treatment option for a heterotopic pregnancy with a viable intrauterine pregnancy is almost always surgical intervention with adequate precautions such as need for emergency transfusion and also an informed high risk consent from the patient and guardian about risk of losing the viable pregnancy itself. There have been case reports of expectant management only in the advent of an empty nonviable extrauterine sac.

There is no place for methotrexate administration. However in an inoperable scenario where a surgical intervention is impossible due to dense adhesions and in the presence of a viable intrauterine pregnancy, one could administer, with the help of an interventional sonologist, Potassium chloride (KCL) under ultrasound guidance into the viable extrauterine
Heterotopic pregnancies are not a rarity at our centre since we perform numerous ART procedures. But the co-existing cornual ectopic gestation especially one which is viable still remains a challenging situation. It's always dealt with great caution and the management is carefully planned so as to not lose the intrauterine pregnancy as well.

The ultimate intervention that has made management a lot more simple and safe is the use of high resolution transvaginal ultrasound and operative laparoscopy. If not for these two tools, one could miss an early lifesaving diagnosis and also result in a prolonged open surgery. In this particular case, both assisted in early diagnosis as well as minimal invasive surgical technique that allowed the pregnancy to proceed uneventfully till date.

References