

Case Report

Assisted Reproductive Techniques in a Patient with History of Venous Thromboembolism: A Case Report and Review of Literature

Sumana Gurunath, Sriprada Vinekar¹, Reeta Biliangady

Departments of Reproductive Medicine and ¹Gynaecology, Cloudnine Hospitals, Bengaluru, Karnataka, India

ABSTRACT

We report a patient with a history of venous thrombosis following oral contraceptive pills who was planned for *in vitro* fertilization (IVF)-intracytoplasmic sperm injection for male factor infertility. This article discusses the mechanisms for predisposition to thrombosis during assisted reproduction in patients at high risk. Assessment of risk before commencement of treatment, use of mild stimulation, antagonist protocol, avoiding ovarian hyperstimulation, use of gonadotropin-releasing hormone agonist trigger and avoiding exposure to human chorionic gonadotropin, frozen embryo transfer in a natural cycle, single embryo transfer, avoiding multiple pregnancy, and use of prophylactic or therapeutic anticoagulation are the various risk-reduction strategies that must be adopted during IVF treatment to reduce the risk of thrombosis to that of natural conception.

KEYWORDS: Assisted reproduction, *in vitro* fertilization, thromboembolism

INTRODUCTION

The prevalence of venous thromboembolism (VTE) in patients undergoing assisted reproduction (0.1–0.2%)^[1] is ten times higher than the general population (2.2/10,000).^[2] This risk is increased to 100-fold in patients who develop ovarian hyperstimulation (1.7%).^[1] Although the absolute numbers of VTE events in assisted reproduction are low, it can be potentially fatal with serious morbidity or mortality. With increasing use of assisted reproductive techniques (ARTs), especially in women with advanced age, obesity, and smoking, it is important for clinicians to assess risk of VTE in patients and to adopt appropriate risk-reduction strategies to make treatment safer.

In this study, we report a case with a high risk of VTE and discuss the key areas in ART that can aggravate the risk of VTE and the various preventive measures that can be adopted to reduce the risk to that of natural conception.

CASE REPORT

A 26-year-old female patient presented to our fertility clinic with 3 years of primary infertility. Her menstrual cycles were irregular with cycles every 60–90 days. Her body mass index was 27 and she was a known hypothyroid

on 100 mcg levothyroxine. On investigations, her pelvic scan showed a normal uterus and bilateral polycystic ovaries. Her anti-Müllerian hormone was 5.6 ng/ml. Her husband was 36 years of age and a software professional. He was a nonsmoker and a teetotaler. He had no significant past medical or surgical history. His semen analysis revealed severe oligoasthenoteratospermia (volume 2 ml, 3 million/ml; 20% progressive motility; 1% normal forms). In view of severe male factor, relevant investigations were done and they were planned for *in vitro* fertilization-intracytoplasmic sperm injection (IVF-ICSI).

She gave a history of cortical venous thrombosis following oral contraceptive intake at the age of 22 years. After intake of five tablets, she had severe headache and vomiting. A magnetic resonance imaging then had revealed cerebral venous sinus thrombosis affecting the entire superior sagittal sinus. She had been treated with

Address for correspondence: Dr. Sumana Gurunath, Department of Reproductive Medicine, Cloudnine Hospitals, 47, 17th Cross, 11th Main, Malleshwaram, Bengaluru, Karnataka, India. E-mail: sumana.gurunath@gmail.com

This is an open access journal, and articles are distributed under the terms of the Creative Commons Attribution-NonCommercial-ShareAlike 4.0 License, which allows others to remix, tweak, and build upon the work non-commercially, as long as appropriate credit is given and the new creations are licensed under the identical terms.

For reprints contact: reprints@medknow.com

How to cite this article: Gurunath S, Vinekar S, Biliangady R. Assisted reproductive techniques in a patient with history of venous thromboembolism: A case report and review of literature. J Hum Reprod Sci 2018;11:193-7.

Access this article online	
Quick Response Code: 	Website: www.jhrsonline.org
	DOI: 10.4103/jhrs.JHRS_58_17

therapeutic anticoagulation and was on oral anticoagulant for 6 months. Her thrombophilia workup was as follows: anticardiolipin antibodies (IgG and IgM) negative, anti- β_2 glycoprotein 1 negative, lupus anticoagulant positive but repeat negative, protein C, protein S, antithrombin III, factor V Leiden mutation, and homocysteine normal.

Previous history of venous thrombosis made her high risk for thromboembolism during IVF in view of the changes in coagulation parameters due to ovarian stimulation. In an attempt to reduce chances of ovarian hyperstimulation, an antagonist cycle with mild stimulation was planned. She was started on 150 IU recombinant follicle-stimulating hormone (FSH, Gonal F, Merck Serono, Switzerland) from day 2 of cycle. Prophylactic anticoagulation with enoxaparin 40 IU daily was commenced along with the stimulation. Gonadotropin releasing hormone antagonist Cetorelix 0.25 mg daily was started on day 6 of stimulation. On day 10 of stimulation, her serum estradiol was 3100 pg/ml and >3 follicles were >17 mm in diameter. In an attempt to avoid exposure to human chorionic gonadotropin (hCG), which is known to cause a greater impact on coagulation parameters, GnRH agonist (injection triptorelin 0.2 mg s/c) was administered as final trigger and egg retrieval was done 35 h posttrigger. Sixteen oocytes were obtained, 15 were mature, ICSI was done and 14 oocytes were fertilized. Semen parameters were 2 million/ml with 20% progressive motility. The patient was planned for Single embryo transfer (SET) and hence embryos were grown to blastocyst stage and four good-quality blastocysts were frozen. The prophylactic anticoagulation was stopped on the day of egg retrieval and restarted the day after. The patient did not show any signs of ovarian hyperstimulation.

She was planned for an FET after 2 months. Since her cycles were irregular, a natural cycle FET was not possible and a hormone replacement cycle was planned. She was started on transdermal exogenous estrogen as they are known to have a lesser impact on coagulation parameters.^[3] Prophylactic anticoagulation was started with exogenous estrogen. When her endometrial thickness reached an optimal thickness of 8.5 mm, she was started on exogenous progesterone and an FET was planned. Single blastocyst transfer was performed and beta-hCG was positive after 14 days of embryo transfer. Her anticoagulation was continued during pregnancy and postpartum. She delivered a healthy baby girl weighing 2.6 kg at 37-week pregnancy.

DISCUSSION

This case highlights the key areas in the IVF treatment protocol which increase the risk of VTE and which may be modified to reduce the risk. The assessment

of risk before commencement of treatment, use of mild stimulation, antagonist protocol, avoiding ovarian hyperstimulation, use of GnRH agonist trigger and avoiding exposure to hCG, FET in a natural cycle, single embryo transfer, avoiding multiple pregnancy, and use of prophylactic or therapeutic anticoagulation are measures for risk reduction.^[4]

In vitro fertilization and increased risk of thromboembolism

A relationship between ovarian stimulation and thrombosis was first suggested in 1965,^[5] and following this, over 100 publications have reported the same complication.^[6-14] Large-cohort studies have reported increased risk of VTE throughout pregnancy and the postpartum period in IVF pregnancies, though the absolute numbers are low.^[15-17] A recent systematic review has confirmed that the antepartum risk of VTE after IVF is doubled (odds ratio, 2.18; 95% confidence interval, 1.63–2.92) in comparison with the background normal pregnant population.^[18] The incidence of VTE has been reported as 0.1%–0.5% of all IVF cycles started and the risk of arterial thrombosis is much lower. Nearly 70% of reported cases are venous thrombosis and 30% are arterial.^[19] VTE was invariably associated with occurrence of pregnancy, and on the other hand, arterial thrombosis was reported earlier and even when pregnancy was not achieved. Merely 40% of patients had coexisting thrombophilia.^[19] This increased risk of VTE in IVF pregnancies is due to a 5–10-fold increased risk in the first trimester. Ovarian hyperstimulation syndrome (OHSS) increases the risk of thrombosis dramatically to 100-fold or an absolute risk of 1.7%. Interestingly, the incidence of VTE was not found to be high in patients undergoing unsuccessful IVF treatment.^[20] The risk of VTE may be increased in women with obesity, multiple pregnancy, smoking, advanced age, hyperhomocysteinemia, and cesarean section. These known risk factors for thrombosis in spontaneous conceptions have not been studied in depth in IVF pregnancies. However, there has been no reported increased risk in FET cycles.^[1]

Indications for thromboprophylaxis in patients undergoing in vitro fertilization

Thromboprophylaxis is not indicated in all patients without any risk factors.^[21] All women should be assessed for risk of VTE as per the Royal College of Obstetricians and Gynaecologists^[22] or Swedish guidelines^[21] before commencement of treatment, and dose and duration of thromboprophylaxis must be decided in consultation with a hematologist. Wherever thromboprophylaxis is indicated during pregnancy, it should be commenced at the start of stimulation. Patients with history of prior VTE, Antiphospholipid syndrome (APAS) without VTE

or those with multiple risk factors are at high risk for thrombosis and require thromboprophylaxis during IVF stimulation and pregnancy. Patients who are very high risk for thrombosis include those with mechanical heart valves, VTE with APAS, recurrent VTE, or antithrombin deficiency.^[21,22]

Mechanism of thrombosis in patients undergoing *in vitro* fertilization

The hyperestrogenism that results from ovarian stimulation is a known thrombogenic agent. It causes increase in procoagulant factors (fibrinogen, von Willebrand factor, factors VIII and V, and increased activated protein C resistance^[23]), enhanced activation of coagulation (D-dimer), reduced fibrinolysis (reduced tissue plasminogen activator and plasminogen activator inhibitor type I), and reduced natural anticoagulants (antithrombin III and protein S).^[24] Changes in von Willebrand factor and von Willebrand factor-cleaving protease have also been reported. Tissue factor pathway inhibitor values progressively and significantly decreased throughout the ovarian stimulation and negatively correlated with estradiol.^[25] Although these changes suggest the possible development of a prothrombotic state, the clinical relevance of these changes is unclear and the levels of most of the parameters remain within normal limits.^[26] Having said that, it is rare to experience VTE before administration of hCG. Of over 100 reported cases of thrombosis in IVF, only 1 case was before the administration of hCG.^[19] Only 3% of both arterial and VTE have been known to occur before final oocyte maturation trigger.^[26] Post-hCG exposure, levels of fibrinogen, and factors II, V, VII, VIII, and IX are elevated in 2 days. Although hemostatic risk is accrued during stimulation phase, final event is often attributable to exogenous hCG.^[4]

Modifications in *In vitro* fertilization cycle to prevent venous thromboembolism

Risk factors for enhancing the probability of thrombosis in IVF include aggressive stimulation, elevated estradiol levels, hCG as a trigger, OHSS, occurrence of pregnancy, multiple pregnancy, and use of exogenous estrogen for FET.

- Ovarian hyperstimulation must be prevented by use of antagonist cycle, mild stimulation, and use of GnRH agonist trigger^[4]
- Cryopreservation of all embryos and natural cycle FET avoids the use of hCG completely. If natural cycle cannot be done and stimulation is necessary, prophylactic anticoagulation should be commenced along with it^[4]
- Single embryo transfer is preferable to avoid risk of multiple pregnancy

- Thromboprophylaxis with low-molecular-weight heparin is started along with the stimulation. On the day of oocyte retrieval, the dose can be omitted and the next dose either commenced the following day or in the evening after egg retrieval. Prophylactic or therapeutic dose is decided based on the risk factors and in association with hematologist advice^[4]
- If the patient develops OHSS and is pregnant, thromboprophylaxis should continue till 12 + 6 weeks. If not pregnant, it should be continued for 4 weeks after resolution of OHSS.^[21]

Special situations

Arterial thrombosis

Arterial thromboembolism (ATE) can result in stroke, myocardial infarction, and peripheral arterial embolism. Ischemic strokes, carotid or vertebral artery occlusion, aortic or peripheral vessel thrombosis, mesenteric artery occlusion, myocardial infarction, and intracardiac thrombosis have all been reported.^[27] ATE occurs earlier after a mean of 10–11 days postembryo transfer. It is less likely to occur concomitant to pregnancy unlike VTE. About 90% of ATE has been seen associated with ovarian hyperstimulation, and the likelihood of concurrent thrombophilia is low at 19–26%.^[26]

Deep vein thrombosis in a woman undergoing hormone replacement therapy for oocyte donation

Long-term hormone replacement therapy (HRT) is a known risk factor for VTE, but thrombosis in a woman receiving short course of HRT for oocyte donation has been reported.^[28] This must be kept in mind in women requiring short- and long-term HRT (premature ovarian failure)^[29] with advancing age and with comorbidities such as obesity.

Thrombosis reported in a case of ectopic pregnancy following *In vitro* fertilization

Thrombosis may occur irrespective of the site of pregnancy. A case of cerebral thrombosis was reported following a diagnosis of ectopic pregnancy.^[30]

Risk of thrombosis in women with cancer for fertility preservation

Cancer is one of the acquired risk factors for thrombosis, and the risk of VTE in cancer patients is 10-fold higher than the general population. Pathogenesis of thrombosis in cancer depends on direct activation of procoagulant factors by cancer cells, some thrombogenic chemotherapeutic agents (fluorouracil, cisplatin, paclitaxel, and tamoxifen), age, and type of cancer and surgery. Women with cancer referred for fertility preservation may not be a high risk for thrombosis in view of their young age, early stage of cancer, most common cancer being breast cancer

(low risk for thrombosis), unlikely to experience OHSS (GnRH agonist trigger recommended for all), no embryo transfer, and no ensuing pregnancy. Hence, based on the available evidence, women undergoing fertility preservation for cancer must be informed about the risk of thrombosis but can be reassured that the magnitude of the risk is small. Systematic antithromboprophylaxis is not indicated in all patients and can be considered in those developing early OHSS (low-dose aspirin is preferred after egg retrieval to reduce the risk of early arterial thrombosis) or those who may benefit irrespective of ovarian stimulation (thrombogenic malignancies, high-dose thrombogenic chemotherapy, surgery, risk factors for thrombosis, and personal or family history of thrombosis).^[26]

To conclude,

- The absolute numbers of thrombosis after ovarian stimulation is usually very low^[18]
- Thrombosis is more likely to occur in women who achieve pregnancy^[19]
- Thromboprophylaxis is not indicated in patients without known risk factors undergoing IVF treatment^[21]
- Administration of hCG plays a pivotal role in the occurrence of thrombosis^[19]
- Patients diagnosed with OHSS and who need hospitalization or intervention should be started on thromboprophylaxis immediately. Thromboprophylaxis should be continued until resolution of OHSS or at least until week 12 + 6 in pregnancy.^[21]
- Thromboprophylaxis can be discontinued 4 weeks after resolution of OHSS in patients that are not pregnant^[19]
- In patients where thromboprophylaxis is indicated during pregnancy, this should be initiated at the start of FSH/human menopausal gonadotropin stimulation^[21]
- Frozen embryo replacement in women with known risk factors for thrombosis should preferably be done in a natural cycle. If stimulation is considered necessary, thromboprophylaxis should be commenced at the start of stimulation^[19]
- To decrease the risk of hemorrhage at follicular aspiration, thromboprophylaxis should be withheld in the morning before a follicular aspiration and restarted in the evening.

Declaration of patient consent

The authors certify that they have obtained all appropriate patient consent forms. In the form the patient(s) has/have given his/her/their consent for his/her/their images and other clinical information to be reported in the journal.

The patients understand that their names and initials will not be published and due efforts will be made to conceal their identity, but anonymity cannot be guaranteed.

Financial support and sponsorship

Nil.

Conflicts of interest

There are no conflicts of interest.

REFERENCES

1. Rova K, Passmark H, Lindqvist PG. Venous thromboembolism in relation to *in vitro* fertilization: An approach to determining the incidence and increase in risk in successful cycles. *Fertil Steril* 2012;97:95-100.
2. Bates SM, Middeldorp S, Rodger M, James AH, Greer I. Guidance for the treatment and prevention of obstetric-associated venous thromboembolism. *J Thromb Thrombolysis* 2016;41:92-128.
3. Mohammed K, Abu Dabrh AM, Benkhadra K, Al Nofal A, Carranza Leon BG, Prokop LJ, et al. Oral vs transdermal estrogen therapy and vascular events: A Systematic review and meta-analysis. *J Clin Endocrinol Metab* 2015;100:4012-20.
4. Nelson SM. Venous thrombosis during assisted reproduction: Novel risk reduction strategies. *Thromb Res* 2013;131 Suppl 1:S1-3.
5. Mozes M, Bogokowsky H, Antebi E, Lunenfeld B, Rabau E, Serr DM, et al. Thromboembolic phenomena after ovarian stimulation with human gonadotrophins. *Lancet* 1965;2:1213-5.
6. Stewart JA, Hamilton PJ, Murdoch AP. Thromboembolic disease associated with ovarian stimulation and assisted conception techniques. *Hum Reprod* 1997;12:2167-73.
7. Rao AK, Chitkara U, Milki AA. Subclavian vein thrombosis following IVF and ovarian hyperstimulation: A case report. *Hum Reprod* 2005;20:3307-12.
8. Chan WS, Ginsberg JS. A review of upper extremity deep vein thrombosis in pregnancy: Unmasking the 'ART' behind the clot. *J Thromb Haemost* 2006;4:1673-7.
9. Chipwete SE, Bugren S, Rafla N. Thrombosis post ovarian hyperstimulation. *Fertil Steril* 2009;91:1956.e13-4.
10. Seong SW, Park JH, Shin SK, Jin SA, Park YK, Choi SW, et al. A case with upper extremity deep vein thrombosis after *in vitro* fertilization. *J Cardiovasc Ultrasound* 2010;18:98-100.
11. Dorais J, Jones K, Hammoud A, Gibson M, Johnstone E, Peterson CM, et al. A superior mesenteric vein thrombosis associated with *in vitro* fertilization. *Fertil Steril* 2011;95:804.e11-3.
12. Fleming T, Sacks G, Nasser J. Internal jugular vein thrombosis following ovarian hyperstimulation syndrome. *Aust N Z J Obstet Gynaecol* 2012;52:87-90.
13. Mmbaga N, Torrealday S, McCarthy S, Rackow BW. Acute portal vein thrombosis complicating *in vitro* fertilization. *Fertil Steril* 2012;98:1470-3.
14. Meshksar A, Yadollahi Kholes G, Borhani-Haghighi A. Middle cerebral artery infarction after *in vitro* fertilization: A case report. *Int J Stroke* 2013;8:E26.
15. Hansen AT, Kesmodel US, Juul S, Hvas AM. Increased venous thrombosis incidence in pregnancies after *in vitro* fertilization. *Hum Reprod* 2014;29:611-7.
16. Henriksson P, Westerlund E, Wallén H, Brandt L, Hovatta O, Ekblom A, et al. Incidence of pulmonary and venous thromboembolism in pregnancies after *in vitro* fertilisation:

- Cross sectional study. *BMJ* 2013;346:e8632.
17. Jacobsen AF, Skjeldestad FE, Sandset PM. Ante- and postnatal risk factors of venous thrombosis: A hospital-based case-control study. *J Thromb Haemost* 2008;6:905-12.
 18. Sennström M, Rova K, Hellgren M, Hjertberg R, Nord E, Thurn L, *et al.* Thromboembolism and *in vitro* fertilization – A systematic review. *Acta Obstet Gynecol Scand* 2017;96:1045-52.
 19. Nelson SM. Prophylaxis of VTE in women – During assisted reproductive techniques. *Thromb Res* 2009;123 Suppl 3:S8-15.
 20. Hansen AT, Kesmodel US, Juul S, Hvas AM. No evidence that assisted reproduction increases the risk of thrombosis: A Danish National cohort study. *Hum Reprod* 2012;27:1499-503.
 21. Available from: http://www.nfog.org/files/guidelines/NFOG_Guideline_SWE_160116%20Thromboprophylaxis%20in%20IVF.pdf. [Last accessed 2018 Mar 19].
 22. Royal College of Obstetricians and Gynaecologists. Reducing the Risk of Venous Thromboembolism during Pregnancy and the Puerperium. Green-top Guideline No. 37a. London: RCOG; 2015.
 23. Curvers J, Nienhuis SJ, Nap AW, Hamulyák K, Evers JL, Rosing J, *et al.* Activated protein C resistance during *in vitro* fertilization treatment. *Eur J Obstet Gynecol Reprod Biol* 2001;95:222-4.
 24. Chan WS. The ‘ART’ of thrombosis: A review of arterial and venous thrombosis in assisted reproductive technology. *Curr Opin Obstet Gynecol* 2009;21:207-18.
 25. Romagnuolo I, Sticchi E, Fedi S, Cellai AP, Lami D, Alessandrello Liotta A, *et al.* Is tissue factor pathway inhibitor a marker of procoagulable status in healthy infertile women undergoing ovarian stimulation for assisted reproduction? *Blood Coagul Fibrinolysis* 2014;25:254-8.
 26. Somigliana E, Peccatori FA, Filippi F, Martinelli F, Raspagliesi F, Martinelli I, *et al.* Risk of thrombosis in women with malignancies undergoing ovarian stimulation for fertility preservation. *Hum Reprod Update* 2014;20:944-51.
 27. Girolami A, Scandellari R, Tezza F, Paternoster D, Girolami B. Arterial thrombosis in young women after ovarian stimulation: Case report and review of the literature. *J Thromb Thrombolysis* 2007;24:169-74.
 28. Mahajan N, Naidu P, Gupta S, Rani K. Deep venous thrombosis in a patient undergoing *in vitro* fertilization with oocyte donation. *J Hum Reprod Sci* 2015;8:182-5.
 29. Tsagkas N, Valasoulis G, Zikopoulos K, Zerzi C, Mitselos I, Koutoulakis I, *et al.* Ascites in the puerperium in the context of a woman with turner syndrome who conceived through assisted reproductive technology. *Case Rep Obstet Gynecol* 2015;2015:459679.
 30. Hassa H, Aydin Y, Oge T, Yavuz Tokgoz V. Incompletely evaluated ART leading to ectopic pregnancy and cerebral thrombosis. *Int J Fertil Steril* 2013;7:138-41.