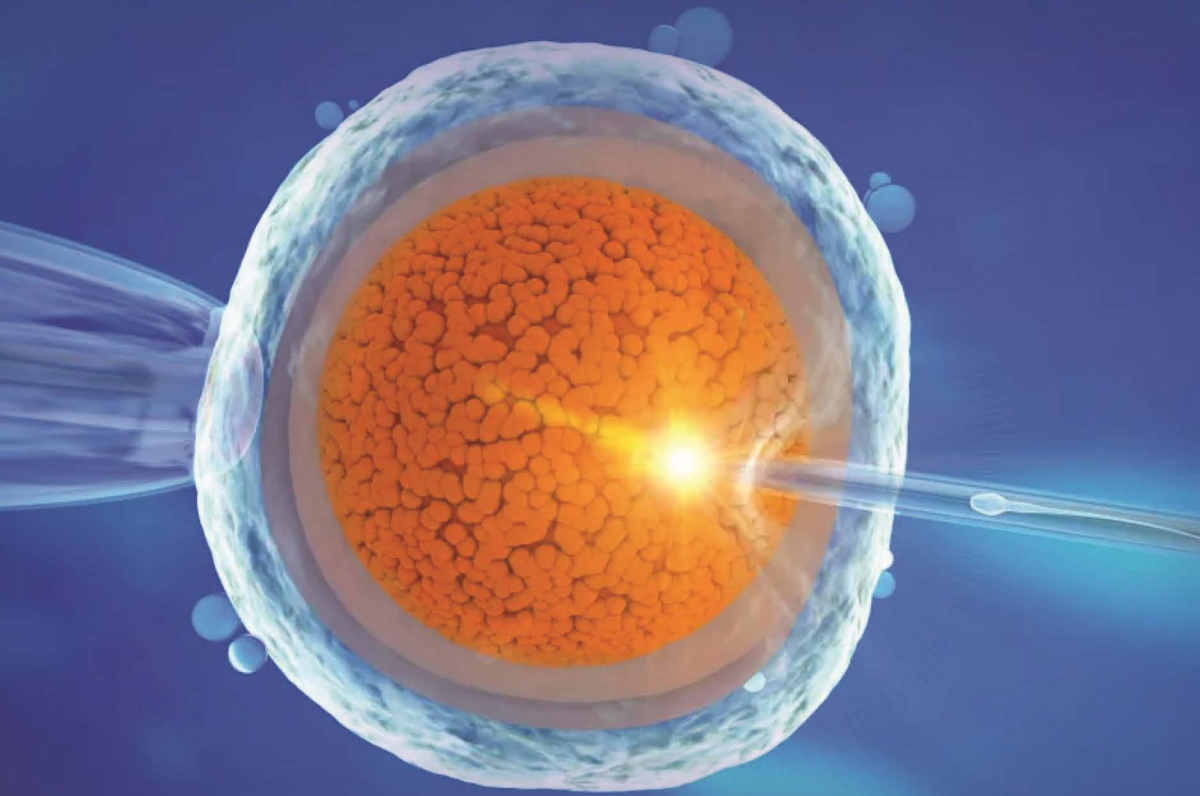
Fertility & ART in Medical Disorders



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Chapter 12

Fertility and Assisted Reproductive Technology in Women on Anticoagulants

Arpita Ray

INTRODUCTION

Infertility affects 15–20% of couples. Advanced medical treatment, delaying childbirth, and increasing uptake of fertility preservation for women undergoing cancer treatment caused a gradual increase in demand of artificial reproductive techniques.

It is important to identify the need for thromboprophylaxis in high-risk women who are undergoing controlled ovarian stimulation. It is also important to identify the group of women who are already on anticoagulants and need fertility treatment. They will need a multidisciplinary approach to their treatment involving a hematologist assessing optimum drug suitable while they are going through treatment and embarking on pregnancy, a maternal medicine specialist making these women aware of the risk associated with pregnancy and the impact on the fetus, if any, and a fertility expert addressing the risk associated with in vitro fertilization (IVF) drugs and venous thromboembolism (VTE) risk. Pulmonary embolism of deep vein thrombosis occurs in 0.5–2.2/1,000 deliveries. It depends on the population studied.[1-8]

THROMBOPROPHYLAXIS IN PATIENTS UNDERGOING ARTIFICIAL REPRODUCTIVE TREATMENT

There are no definite guidelines or accepted protocols on thromboprophylaxis in relation to IVF treatment. In a recent systematic review,[9] it is shown that the risk of VTE during pregnancy post IVF is double (odds ratio 2.18; 95% CI 1.63–2.92) in comparison to spontaneously conceived pregnancy. It is also noted that there is a very high risk in women who developed ovarian hyperstimulation; it has been noticed that there is up to 100-fold increase in the risk. An absolute risk of 1.7% is noted.

Only evidence-based guideline is issued by the Swedish Association of Obstetrics and Gynecology. This guideline was revised in 2018. They have used grading of recommendations using assessment development and evaluation system while publishing the guideline.

It is important to have a risk assessment system for any woman who is embarking on IVF treatment. The clinician should take a detailed personal

and family history of the woman. It is important to have the opinion of a hematologist in high-risk cases. Periconceptional counseling also needs to be mentioned in high-risk cases.

Risk Associated with Anticoagulant Therapy during Pregnancy

It is important to remember the risks associated with anticoagulant therapy to the fetus. Vitamin K antagonists can cause teratogenicity and it is embryotoxic. It is important to discontinue vitamin K antagonist before 6 weeks of gestation. This will avoid the risk of warfarin embryopathy as well as pregnancy loss, fetal bleeding, and neurological developmental issues.[10-12] Any woman who potentially can be pregnant or trying for pregnancy should not take oral direct factor Xa and thrombin inhibitors (e.g., rivaroxaban and apixaban).[13-16]

The embryogenic effect of these drugs is still unknown, and it is best to avoid them.

Fondaparinux[17] has been reported to be used in pregnancy, in patients with severe heparin allergy. However, these reports are in the second trimester or late pregnancy.

Low molecular heparin, unfractionated heparin, and danaparoid (heparinoid) are pregnancy safe and, therefore, can be used in pregnancy for preventative and therapeutic purposes.

However, there are reports of heparin-induced thrombocytopenia and heparin-induced osteopenia. Low molecular heparin has a better safety profile and is widely used in pregnancy.

It should be used cautiously in patients with renal impairment.

Risk Period of a Thromboembolic Episode in Relation to In Vitro Fertilization

This question was addressed in a recent systematic review by Sennström et al.[9] It was seen in six studies[18-23] that, usually, venous thromboembolic events occur within 3–112 days following embryo transfer. A study by Chan and Ginsberg[20] observed a shorter interval (mean 18 days) in the ovarian hyperstimulation syndrome (OHSS) group than without it (mean 57 days). Four studies[20,24-26] showed that the reported gap from embryo transfer to an antepartum thromboembolic episode was between 3 and 28 days.

Risk of Thromboembolism in In Vitro Fertilization Complicated with Ovarian Hyperstimulation Syndrome

A systematic review published by a Swedish group[9] observed that in a study by Rova et al.,[18] women with post-IVF pregnancy who developed OHSS and were hospitalized had a 1.7% increased possibility of a thromboembolic episode

in the first 12 weeks. There was a 100-fold increase in risk than background non-IVF population.[18] Hansen et al. showed that there is a 14-fold increase in the risk of VTE when high-risk cases (women with polycystic ovarian disease are a major risk factor for OHSS) were excluded and compared with non-IVF pregnant population.[27]

Recommendations from the Swedish Association of Obstetrics and Gynecology[28,29]

Management of IVF patients and risk assessment for thromboprophylaxis:

- There is no need for routine thromboprophylaxis in patients without any risk factors.
- Patients with OHSS and pregnancy should continue with thromboprophylaxis at least until 16 weeks of pregnancy. Individual organizations should have their individual risk scoring system for risk assessments. We have added the Hem-ARG guidelines scoring system **(Table 1)**.
- Thromboprophylaxis should be continued at least until 4 weeks after the resolution of ovarian hyperstimulation if the pregnancy test is negative.
- Preconceptional counseling and discussion about thromboprophylaxis to be offered if the risk score is >2 **(Table 1)**.
- If any patient needs thromboprophylaxis during pregnancy, then that should be initiated at the beginning of controlled superovulation with recombinant follicle-stimulating hormone (FSH)/human menopausal gonadotropin (HMG)/biosimilar products and estrogen supplementation.
- Scheduling of cycle with combined contraceptive pills or estrogen supplementation should be avoided in patients who need thromboprophylaxis.
- Individualized plan to be generated with the help of a hematologist for very high-risk patients during controlled superovulation.
- Thromboprophylaxis is to be stopped 24 hours before egg retrieval and started 24 hours after egg retrieval.
- Frozen embryo transfer should be considered in a natural cycle instead of a medicated cycle. Risk assessment needs to be done as per risk assessment criteria. Once the pregnancy test is positive, the thromboprophylaxis protocol is to be followed in either low dose or high dose based on risk scores.
- ED stocking can be recommended at any point during treatment.
- *1 point:* Thromboprophylaxis not needed.
- *2 points:* Thromboprophylaxis postpartum once daily for at least 7 days, this includes thromboprophylaxis for a transient risk factor.
- *3 points:* Thromboprophylaxis once daily for 6 weeks postpartum.
- *≥4 points:* Thromboprophylaxis once daily throughout pregnancy and at least for 6 weeks postpartum.

TABLE 1: Summation of added risk points decides management according to the condition [thromboprophylaxis and in vitro fertilization (IVF) guideline issued by the Swedish Society of Obstetrics and Gynecology[29]].

1 point	*2 points*	*3 points*	*4 points*	*Extremely high risk*
Het FV Leiden	Protein S deficiency	Hom FV Leiden	Prior VTE	Mechanical aortic valve
Het prothrombin mutation	Protein C deficiency	Hom pro-thrombin mutation	APS without VTE	Condition warranting continuous thrombopro-phylaxis
Obesity	Immobilization	More than one throm-bophilia defect	OHSS	APS with VTE
Cesarean section				Recurrent VTE
Age > 40 years				Antithrombin deficiency
Preeclampsia/ abruption placenta				
Hyperhomo-cysteinemia				
Inflammatory bowel disease				

(APS: antiphospholipid syndrome with lupus anticoagulant or cardiolipin antibodies; FV: factor V; Het: heterozygote; Hom: homozygote; OHSS: ovarian hyperstimulation syndrome; VTE: venous thromboembolism)

Notes: (1) Obesity [body mass index (BMI) >28 kg/m^2 in early pregnancy] at booking to the antenatal clinic. (2) VTE in a first-degree relative <60 years. (3) Homocysteine >8 µmol/L in pregnancy. (4) Thromboprophylaxis should be provided during the period of strict immobilization or if the patient has a cast. (5) Patients with previous VTE, or APS without VTE, automatically receive 4 points independent of other risk factors. (6) OHSS—high risk during the entire first trimester. (7) Women in this group are classified as at very high risk of VTE, independent of other risk factors. (8) Warfarin, novel oral anticoagulant (NOAC), low-molecular-weight heparin (LMWH). Not including low-dose acetylsalicylic acid (ASA). (9) Risk factors only in the postpartum period.

- "Very high risk" thromboprophylaxis twice daily (=double dose) throughout pregnancy and at least for 12 weeks postpartum **(Table 2)**.

CONCLUSION

Venous thromboembolism risk is associated with IVF treatment. It is important to take detailed personal and family history before starting any fertility treatment. Risk assessment of each case using a scoring system

TABLE 2: Action plan for thromboprophylaxis for patients with conditions entailing a very high risk of thromboembolic complications.

Condition	*Thromboprophylaxis*
Recurrent VTE, ongoing oral anticoagulation therapy, and possibly patients with sequelae after previous TE	Ongoing oral anticoagulation therapy and possibly patients with sequelae after previous TE. High-dose prophylaxis LMWH is initiated prior to conception or as soon as pregnancy is confirmed and is continued at least until 6 weeks postpartum or until recommencement of previous treatment
Hereditary antithrombin deficiency	High-dose prophylaxis LMWH is initiated prior to conception or as soon as pregnancy is confirmed and is administered according to individual treatment plan. Antithrombin concentrate if complications and at delivery
APS with TE	High-dose prophylaxis LMWH + ASA 75 mg × 1 is initiated prior to conception and continued at least until 12 weeks postpartum
APS without prior TE	Normal dose prophylaxis LMWH + ASA 75 mg × 1 is initiated prior to conception or as soon as pregnancy is confirmed and continued at least until 12 weeks postpartum
Ovarian hyperstimulation syndrome	Normal dose prophylaxis LMWH is given during the entire first trimester and until the resolution of symptoms
Hyperhomocysteinemia	Folic acid 1–5 mg daily and/or vitamin B6 + vitamin B12

(APS: antiphospholipid syndrome; ASA: acetylsalicylic acid; LMWH; low-molecular-weight heparin; TE: thromboembolism; VTE: venous thromboembolism)

helps in identifying high-risk cases. Women with polycystic ovary syndrome (PCOS) should be thoroughly counseled about increased risk of ovarian hyperstimulation and VTE. The risk of antepartum VTE is doubled than control pregnant population and it is due to a 5–10-fold increase in risk during the first trimester. It is also noted that upper extremity VTE is more common after ovarian hyperstimulation; a suggested explanation is the possibility of drainage of inflammatory peritoneal fluid through thoracic ducts.[30,31] However, bigger studies are needed to establish this relationship. Increased estrogen levels during controlled ovarian stimulation may be responsible for hypercoagulability. OHSS patients were found to have increased hemostatic markers in comparison to normal healthy population.[3,32,33] Detailed discussion, multidisciplinary approach, and counseling help to manage the risk and complication effectively. Each fertility unit should have its own evidence-based risk assessment tools and protocol to reduce risk and complication during treatment and promote safe practice.

KEY LEARNING POINTS

- It is important to identify the need for thromboprophylaxis in high-risk women who are undergoing controlled ovarian stimulation.
- Antepartum risk of VTE post IVF is two times higher in comparison to spontaneously conceived pregnancy.
- It is important to have a risk assessment system for any woman who is embarking on IVF treatment.
- It is important to remember the risks associated with anticoagulant therapy to the fetus.
- Venous thromboembolic episode interval was shorter (mean 18 days) in women with OHSS than without OHSS (mean 57 days).
- Patients with OHSS and pregnancy should continue with thromboprophylaxis at least until 16 weeks of pregnancy.
- Thromboprophylaxis should be continued at least until 4 weeks after resolution of ovarian hyperstimulation if the pregnancy test is negative.
- Preconceptional counseling and discussion about thromboprophylaxis to be offered if the risk score is high.

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Fertility & ART
in Medical Disorders

This book will serve as a comprehensive guide to reproductive medicine students and practicing clinicians dealing with cases of infertility in the setting of medical disorders. Management of infertility with known medical disorders such as heart disease, coagulation disorder, renal disease, and women post-transplant, etc. is always a major challenge to the treating clinicians. In this book, the content is written by reproductive medicine specialists experienced in the field of fertility and ART with multidisciplinary input so as to provide the best possible guidance to the treating doctors and the students to manage these complex scenarios.

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