Guideline for thromboprophylaxis during in-vitro fertilisation (IVF)

Summary

The incidence of venous thrombosis during spontaneous pregnancy is estimated to 1/1000 pregnancies, and after IVF to 2/1000. The risk of thrombosis in the first trimester in IVF pregnancy increases by 5-10 times, mainly due to an up to 100-fold risk increment during ovarian hyperstimulation syndrome (OHSS) in IVF pregnancies that result in born babies. This increment is present during the entire first trimester. For this reason thromboprophylaxis with low-molecular weight heparin (LMWH) in normal dose (equivalent to Fragmin 5000 E or Innohep 4500 E) is recommended until at least gestational week 13, in women with diagnosed OHSS. In women who prior to pregnancy have been assessed to have a higher risk of thromboembolic complications, according to the HemARG scoring system (risk score ≥4), thromboprophylaxis is recommended during IVF. Prophylaxis should be initiated simultaneously with stimulation with FSH/HMG or estrogen.

Background

There are approximately 19,000 IVF treatments performed annually in Sweden. The risk of both arterial and venous thrombosis increases with ovarian hyperstimulation syndrome (OHSS). The risk of thrombosis in pregnancy decreases by 85-90 % when recommended thromboprophylaxis is used.

SFOG (Swedish Association of Obstetrics and Gynecology) requested in 2010 that HEM-ARG (A working and reference group for haemostatic disorders in Obstetrics and Gynecology) would provide evidence based guidelines on this subject. Concise guidelines regarding thromboprophylaxis in IVF had previously not been available in Sweden. The first version of the guidelines was published in 2015. These guidelines are continuously revised, the latest revision occurred in May 2018. The GRADE system (Grading of Recommendations Assessment Development and Evaluation) should be used and the method accounted for.

Guidelines

1. Thromboprophylaxis is not indicated in patients without known risk factors undergoing IVF treatment without complications.

   GRADE ⊕⊕◯◯. Strong recommendation.

2. *Pregnant patients diagnosed with OHSS* should continue thromboprophylaxis until resolution of OHSS, and at least until gestational week 12+6. If additional risk factors are present, thromboprophylaxis should be continued according to the scoring system in the HEM-ARG guidelines (see Summary Box 1-3).

   GRADE ⊕⊕⊕◯. Strong recommendation.

3. Thromboprophylaxis can be discontinued 4 weeks after resolution of OHSS *in patients that are not pregnant.*

   GRADE ⊕◯◯◯. Strong recommendation.

4. A preconceptional evaluation and decision regarding thromboprophylaxis (risk score ≥2, according to Summary Box 1) during IVF stimulation and pregnancy is recommended.

   GRADE ⊕◯◯◯. Strong recommendation.

5. In patients where thromboprophylaxis is indicated during pregnancy this should be commenced at the initiation of FSH/HMG or estrogen stimulation.

   GRADE ⊕⊕◯◯. Strong recommendation.

6. An individual plan for dosing of thromboprophylaxis (normal dose or high dose) is essential, especially so for patients with "very high risk" of thrombosis (see Summary Box 1-3).

   GRADE ⊕◯◯◯. Strong recommendation.

7. Frozen embryo replacement in women with known risk factors for thrombosis should preferably be done in a natural cycle, and thromboprophylaxis is commenced according to HEM-ARG's score (see Summary Box 1-3).

   GRADE ⊕◯◯◯. Strong recommendation.

Risk score points are assessed using Summary Box 1, and summation of risk score points result in a total risk score, which can be used for planning of thromboprophylaxis (Summary Box 2-3), in accordance with HEM-ARG Report No 79. Stockings for mechanical compression can be freely recommended.

An individual treatment plan should always be prepared in collaboration with an obstetrician experienced in coagulation treatment, prior to IVF.

Summ

Summary Box 1

Summation of added risk points decides management according to Summary Box 2

1 point	2 points	3 points	4 points	”Very high risk”[7]
Het FV Leiden	Protein S deficiency	Hom FV Leiden	Prior VTE[5]	Mechanical aortic valve
Het prothrombin mutation	Protein C deficiency	Hom prothrombin	APS without VTE[5]	Condition warranting continuous thromboprophylaxis[8]
Obesity[1]	Immobilisation[4]	More than one thrombophilic defect	OHSS[6]	APS with VTE
Cesarean section				Recurrent VTE
Hereditary factors[2]				Antithrombin deficiency
Age >40 years				
Preeclampsia				
Hyperhomocysteinemia[3]				
Placental abruption				
Inflammatory bowel disease				
Other major risk factors				

Het: heterozygote, FV: factor V, VTE: venous thromboembolism, Hom: homozygote, APS: antiphospholipid syndrome with lupus anticoagulant or cardiolipin antibodies

1. Obesity (BMI >28 in early pregnancy) at booking to antenatal clinic
2. VTE in a 1st degree relative < 60 years
3. Homocysteine >8 umol/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 risks factors.
6. OHSS=Ovarian hyperstimulation syndrome. High risk during the entire 1st trimester.
7. Women in this group are classified as at very high risk of VTE, independent of other risk factors
8. Warfarine, NOAC, LMWH. *Not including* low-dose ASA.
9. Risk factors only in the postpartum period

Summary Box 2

Management based on risk score (summation of risk points in Summary Box 1)

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

Summary Box 3

Action plan for thromboprophylaxis for patients with conditions entailing very high risk of thromboembolic complications

Condition	Thromboprophylaxis
Recurrent VTE, 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 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 x 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 x 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 resolution of symptoms
Hyperhomocysteinemia	Folic acid 1-5 mg daily and/or vitamin B6 + vitamin B12

APS=antiphospholipid syndrome, TE=thromboembolism, ASA=acetylsalicylic acid, LMWH=low molecular weight heparin

Grading of strength of scientific evidence for the guidelines, according to GRADE

Strong scientific evidence (GRADE ⊕⊕⊕⊕). Low probability that future research will have impact on current view on effect.

Moderately strong scientific evidence (GRADE ⊕⊕〇〇). High probability that future research will have impact on current view on effect.

Limited scientific evidence (GRADE ⊕⊕〇〇). Very high probability that future research will have impact on current view on effect.

Insufficient scientific evidence (GRADE ⊕〇〇〇). Estimated effect very unsure.

Recommendation can be either **strong or weak**, and is based on the strength of the current scientific evidence, and cost-benefit balance for the intervention, both medically and economically.

Abbreviations:

APS	antiphospholipid syndrome
ASA	acetylsalicylic acid
ATE	arterial thromboembolism
CVL	cerebrovascular lesion
DVT	deep venous thrombosis
GRADE	Grading of Recommendations Assessment Development and Evaluation
LMWH	low molecular weight heparin
OHSS	ovarian hyperstimulation syndrome (defined as need for treatment or intensified observation and follow-up)
TE	thromboembolism
VTE	venous thromboembolism