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POLICY AND PRACTICE

Venous thromboembolism associated with medically assisted reproduction (MAR): British fertility society policy and practice guidance for assessment and prevention

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ABSTRACT

The association between Medically Assisted Reproduction (MAR) and thromboembolic complications has been reported widely in multiple published studies. Although venous thromboembolism (VTE) is not thought to be a common complication of MAR, it is associated with high morbidity and is often preventable. Since VTE usually occurs after completion of MAR treatment and is often managed outside of the treating fertility unit, these complications are likely to be underreported and there may be limited awareness of the risks among clinicians. As we continue to see a rise in the total number of MAR treatment cycles, particularly in women over 40 years of age, along with a steady increase in the number of fertility preservation cycles for both medical and social indications, it is likely that we will see an increase in absolute numbers of VTE complications. Currently, there is a lack of management guidance and reporting of VTE events associated with assisted conception treatment. The aim of this guidance is to provide clinicians with information on VTE risk factors, guidance on assessing VTE risk and the best practice recommendations on risk reducing strategies for individuals at risk of VTE undergoing ovarian stimulation and embryo transfer cycles.

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Introduction

Thromboembolism (TE) is defined as a condition in which a thrombosis forms in a vein or an artery, most commonly in the deep veins of the legs or pelvis [deep vein thrombosis (DVT)] which can progress to the pulmonary arteries leading to pulmonary embolism (PE) (NICE, 2020 (updated 2023)). Although its incidence increases with age, venous thromboembolism (VTE) is a reproductive health risk for women and remains a leading cause of maternal death in the UK (Knight et al., 2018). The estimated incidence in all women aged 30–34 years and 35–39 years is 25 (95% CI 11 to 56) and 39 (95% CI 20 to 74) per 100,000 person years respectively for DVT alone and 21 (95% CI 9–50) and 13 (95% CI 4–40) per 100,000 person years for PE ± DVT (ESHRE Capri Workshop Group, Eichinger et al., 2013; Naess et al., 2007). In pregnancy and the puerperium, the risk is higher with an absolute incidence of 107 per 100,000 person-years (95% CI 93–122 per 100,000 person-years) (Sultan et al., 2012).

The most common MAR treatments performed today are in vitro fertilisation (IVF) with fresh embryo transfer (IVF-ET*), Frozen embryo transfer (*FET) and oocyte or embryo cryopreservation for fertility preservation. IVF usually involves stimulation of ovaries using exogenous gonadotropins leading to a rise in endogenous oestradiol. Exogenous oestrogens are used for endometrial preparation in medicated cycles for FET. The association between IVF and venous thromboembolic complications has been reported widely in multiple published studies, both in the context of ovarian hyperstimulation syndrome (OHSS) but importantly, also without it (Filipovic-Pierucci et al., 2019; Rova et al., 2012). Since VTE usually occurs after completion of the IVF-ET/cryopreservation/FET cycle and is often managed outside of the treating fertility unit, these complications are likely to be

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underreported and there may be limited awareness of the risks among clinicians.

The total number of MAR treatment cycles has substantially increased in the UK and globally, particularly in women over 40 years of age (Human Fertilisation and Embryology Authority, 2021). Although VTE is not thought to be a common complication of MAR treatments, it is associated with high morbidity and mortality and is often preventable (RCOG, 2015a). Apart from the single national guideline on prophylaxis in IVF created by the Swedish Association of Obstetrics and Gynaecology (Lindqvist et al., 2014), there is a lack of management guidance and reporting of VTE events associated with MAR treatments. The aim of this guidance is to provide clinicians with information on VTE risk factors, guidance on assessing VTE risk and best practice recommendations on risk reducing strategies for individuals at risk of VTE undergoing ovarian stimulation and embryo transfer cycles.

Aims of this guidance

The purpose of this guidance is to:

- provide a risk assessment tool (VTE score) and appropriate prophylaxis guidance for patients undergoing MAR treatments, including for oocyte preservation.
- identify a number of underlying medical conditions that increase the risk of VTE in those undergoing MAR treatments.
- highlight certain malignancies and benign diseases with an increased risk of VTE where oocyte/embryo cryopreservation may be offered.
- recognise lifestyle factors that increase the risk of VTE during ovarian stimulation, like increased BMI and smoking.
- discuss possible adjustments to ovarian stimulation protocols to try to mitigate the risk of VTE.
- highlight the need for a multidisciplinary team approach in the care of patients with underlying risk factors for VTE.

Scope of this guidance

This document is aimed at the multidisciplinary team providing care to individuals who are undergoing ovarian stimulation and/or embryo transfer cycles for MAR, including for the treatment of infertility, oocyte cryopreservation, oocyte donation and gestational carriage. Guidance is provided herein on assessing and reducing the risk of VTE in individuals over the age of 16 years.

What does this guidance not cover?

This guidance does not cover the following:

- Preconception assessment for those not receiving ovarian stimulation and/or embryo transfer i.e. expecting unassisted pregnancy or MAR without these interventions e.g. natural cycle intrauterine insemination (IUI).
- Those who are pregnant as a result of natural conception Reducing the Risk of Thrombosis and Embolism during Pregnancy and the Puerperium (Green-top Guideline No. 37a) | RCOG (RCOG, 2015a).
- Individuals admitted to hospital with VTE (Overview | Venous thromboembolic diseases: diagnosis, management and thrombophilia testing | Guidance | NICE (NICE, 2018) or Thrombosis and Embolism during Pregnancy and the Puerperium: Acute Management (Green-top Guideline No. 37b) | RCOG (RCOG, 2015b).
- The use of low molecular heparin as an adjuvant/add-on in MAR.
- Prophylaxis dosing regimens, as type of Low molecular weight heparin (LMWH) varies, hence local guidelines should be followed.

Methods

The proposal for this guidance was submitted to the BFS policy and practice chair who presented the proposal to the executive. The executive was informed of the participants of the guidance development group and agreed unanimously that the proposal was sound and advised to proceed.

We followed the GRADE approach (Grading of Recommendations Assessment, Development and Evaluation) for the development and review of recommendations in this guidance. The initial steps involved formulating the PICO questions (Population, Intervention, Comparison and Outcomes) and examining the literature to identify whether evidence reviews have been published or recent evidence can be obtained; Population (women undergoing fertility treatment), Intervention (VTE risk assessment, prophylaxis) Comparison (general population) and Outcomes (cases of venous and arterial thromboembolism reported in the literature and the reported mortality rates). We identified, retrieved and reviewed the relevant published evidence. The Cochrane Library (including the Cochrane Database of Systematic Reviews, the Cochrane Central Register of Controlled Trials and the Database of Abstracts of Reviews of Effects [DARE]), EMBASE, the ACP Journal Club and

MEDLINE, including in-process and other non-indexed citations, were searched from inception to January 2023 inclusive to identify all relevant randomised controlled trials, limited to systematic reviews and meta-analyses published in English. The principal search terms used were: 'thromboprophylaxis', 'dalteparin', 'clexane', 'enoxaparin', 'tinzaparin', 'low molecular weight heparin', 'unfractionated heparin', 'thrombophilia', 'venous thromboembolism', 'arterial thromboembolism', 'deep vein thrombosis', 'pulmonary embolism' and 'assisted reproductive technology', 'assisted reproduction', 'IVF', 'in vitro fertilisation', 'ICSI', 'intra cytoplasmic injection' and 'assisted conception'.

To ensure that this guidance was ratified by the society, it also underwent consultation with the BFS Executive Committee and Membership (BFS Policy and Practice Guidance, 2021- https://www.britishfertilitysociety.org.uk/practice-policy/). Guidance was modified based on the feedback.

Grading of evidence

A recommendation for good practice point (GPP) is made based on the consensus of the guidance development group. The Royal College of Obstetricians and Gynaecologists grading of evidence was used (RCOG, 2020).

General risk of thromboembolism in IVF treatment

The true incidence of VTE complications among all IVF cycles started is unknown. Limited literature suggests that IVF is associated with both arterial and venous embolism, although the incidence of arterial TE (ATE) complications is much lower than for venous (Filipovic-Pierucci et al., 2019; Sennström et al., 2017). A nine to tenfold increase in VTE risk has been reported in the first trimester of pregnancies conceived through IVF with fresh embryo transfer compared to naturally conceived pregnancies (Olausson et al., 2020; Rova et al., 2012; Sennström et al., 2017). A French nationwide cohort study reported that even after an unsuccessful IVF cycle, the incidence of VTE appears to be increased (Filipovic-Pierucci et al., 2019). The Swedish cohort studies showed no increased risk in the first trimester after frozen embryo transfer (FET) (Olausson et al., 2020).

There are five clinical components to IVF cycles: ovarian stimulation, prevention of early ovulation, final oocyte maturation, oocyte retrieval and luteal phase support (unless no embryo transfer is planned in the concurrent cycle). FET cycles are simpler and can either use the natural ovarian cycle or external hormones for endometrial preparation. In hormonally medicated cycles, there are usually three components: prevention of follicle development, endometrial preparation and luteal support. Both IVF-ET and FET cycles may use hormone pre-treatment to schedule the subsequent menstrual period. Each phase is associated with VTE risks and these will be discussed in turn below.

Pre-treatment and the risk of TE

Pre-treatment in IVF in order to schedule cycles may use a combined oral contraceptive pill (COCP) or a progestogen, usually for around two weeks, and is commenced in the menstrual cycle prior to starting ovarian stimulation/oestradiol for endometrial preparation in FET cycles. There are no studies examining the risk of VTE with short-term use of COCP or progestogens as pre-treatment, or if they increase any VTE risk of the subsequent treatment cycle. In users of the COCP for contraception, the risk of VTE was highest during the first three months of use (van Hylckama Vlieg et al., 2009) and changes in coagulation pathways were noted within this time (Zia et al., 2015).

The VTE risk associated with COCP use for contraception is dependent on the dose of oestrogen and type of progestogen. COCPs containing the synthetic oestrogen ethinyl oestradiol plus a third generation progestogen have up to twice increased risk of VTE in comparison to those containing a second generation progestogen; desogestrel (adjusted odds ratio (aOR) 4.28, 95% CI 3.66 to 5.01), gestodene (aOR 3.64, 95% CI 3.00 to 4.43), drospirenone (4.12 aOR, 95% CI 3.43 to 4.96), and cyproterone (aOR 4.27, 95% CI 3.57 to 5.11) versus levonorgestrel (aOR 2.38, 95% CI 2.18 to 2.59) and norethisterone (aOR 2.56, 95% CI 2.15 to 3.06), and norgestimate (aOR 2.53, 95% CI 2.17 to 2.96) (Vinogradova et al., 2015).

Published data assessing the risk of VTE in women prescribed progestogen-only contraception or progestogens for therapeutic indications are limited. A meta-analysis of eight observational studies found the use of progestogen-only contraception was not associated with an increased risk of VTE compared with non-users of hormonal contraception (Mantha et al., 2012). Several studies have reported increased incidence of VTE in women taking high-dose oral norethisterone for therapeutic indications (Kuhnz et al. 1997; Mansour, 2012; Vasilakis et al., 1999). Norethisterone (NE) and its ester norethisterone acetate (NETA) can be readily aromatised by cytochrome P450 mono-oxygenases in the adult liver to ethinylestradiol (EE) and

it is estimated that 1 mg orally administered NE/NETA metabolises to 4–6 μg EE (Kuhnz et al., 1997; Mansour, 2012). Several studies have shown a differential association of VTE risk with type of progestogen in postmenopausal women taking HRT (Canonico et al., 2007; Canonico et al., 2011). Norpregnane derivatives (e.g. levonorgestrel and NE) are associated with a significant increase in VTE risk, while natural progesterone and pregnane derivatives (e.g. medroxyprogesterone/MPA, dydrogesterone) appear not to be. How applicable these studies are to younger people undergoing MAR is debatable. However, since risk factors for VTE are additive and for individuals who are already classified as 'very high risk', even a short duration of steroid hormones can be detrimental.

Ovulation prevention and the risk of VTE

Early ovulation can be prevented by giving a gonadotrophin releasing hormone (GnRH) antagonist or by pituitary downregulation with a GnRH agonist, the latter usually being commenced in the middle of the luteal phase of the cycle before stimulation. GnRH agonist treatment leads to a transient increase in follicle stimulating hormone (FSH), which can briefly stimulate follicular growth and a subsequent a rise in serum levels of oestrogen. No specific data was identified regarding the risk of VTE with GnRH agonist or antagonist use in ovarian stimulation cycles. Increased risk of developing VTE has been reported in association with use of GnRH agonists in men undergoing treatment for prostate cancer (Ehdaie et al., 2012; Klil-Drori et al., 2016; Van Hemelrijck et al., 2010). However, in women, a GnRH agonist is commonly used for menstrual suppression during cancer treatment and was found not to have any prothrombotic risks (American College of Obstetricians and Gynecologists, 2021; Chiusolo et al., 1998).

Ovarian stimulation (OS) and the risk of VTE

The relationship between ovarian stimulation and thrombus formation was first published in the Lancet in 1965 in women undergoing ovulation induction treatment (Mozes et al., 1965) and since then several studies have demonstrated this association (Baumann & Diedrich, 2000; Chan & Dixon, 2008; Stewart et al., 1997). Ovarian stimulation results in supra-physiological endogenous levels of oestradiol; though not as high as in pregnancy, the peak oestradiol levels can be over 20 times higher than baseline levels (Chan, 2009; Hansen et al., 2012; Nelson, 2009). The stimulation phase during IVF treatment appears to induce effects on the coagulation system similar to those observed during pregnancy, COCP use and with HRT (Bremme et al., 1994; Curvers et al., 2001; Lox et al., 1995, 1998). During OS, there is a rise in several pro-coagulation factors: factor V, fibrinogen, von Willebrand factor, the coagulation activation markers prothrombin fragment $1+2$ and D-dimer, and a major increase in plasma microvesicles, (Nelson, 2009; Olausson et al., 2016; Westerlund et al., 2011). The content of these microvesicles, which have been associated with conditions of arterial disease, have been identified as becoming more prothrombotic during OS compared to during downregulation (Olausson et al., 2020). In addition to this, there is a reduction in fibrinolysis with reduced tissue plasminogen activator and plasminogen activator inhibitor type I, along with reduced levels of the natural anticoagulants antithrombin and protein S (Chan, 2009). Furthermore, high oestrogen levels also induce changes in the haemostatic system that impair the efficacy by which activated protein C down-regulates coagulation (Curvers et al., 2001).

Human chorionic gonadotrophin for final oocyte maturation and the risk of TE

Human chorionic gonadotrophin (hCG) is commonly used for triggering final oocyte maturation. hCG exaggerates the pro-thrombotic changes already accrued during ovarian stimulation (Nelson, 2009) and in fact, it is rare to experience VTE prior to administration of the hCG trigger (Chan & Dixon, 2008; Chan, 2009). Following hCG administration, levels of fibrinogen and factors II, V, VII, VIII and IX have been found to be elevated with activation of the fibrinolytic system occurring within 2 days, peaking at day 8, and remaining elevated at day 10 even in the absence of OHSS (Kodama et al., 1996). The duration of these changes and their clinical significance in the absence of subsequent pregnancy is unknown: this is discussed further in a later section of this guidance.

No data were identified for VTE risks associated with giving a bolus of GnRH agonist to trigger final oocyte maturation instead of hCG in cycles using a GnRH antagonist to prevent early ovulation. This protocol minimises OHSS risk (Itskovitz-Eldor et al., 2000) and is discussed in the section on IVF protocol adaptations to reduce the risk of VTE below.

Oocyte retrieval and the risk of VTE

Prolonged surgery, reduced mobility and dehydration all increase the risk of VTE (Department of Health, 2018).

Most patients undergoing MAR are well and mobile, and oocyte retrieval (transvaginal or transabdominal) is generally a short (under 30 minute) day-case procedure. The patient is usually positioned in lithotomy or semi-lithotomy, which carries a significantly lower risk of VTE than procedures performed in supine position (0.60% vs 1.28%, $p < 0.0001$) (Dyer et al., 2013). Therefore, the risks of VTE associated with the procedure are minimal for the majority of patients. VTE risk can be reduced further with use of graduated elastic compression (GEC) class 1 stockings (light compression, exerting a pressure of 14–17 mmHg) or intermittent pneumatic compression (IPC) if the procedure is anticipated to be longer than 30 minutes (NICE, 2018), or for those with additional risk factors. The use of either of these measures is not routinely required for patients with low background risk for VTE.

There are limited measures that can be taken to secure haemostasis should excessive internal bleeding from needle puncture sites at oocyte retrieval occur. Immediate or later laparoscopy/laparotomy to secure haemostasis is a rare but recognised complication. Tranexamic acid, an antifibrinolytic agent, has been shown to reduce the incidence of bleeding in elective surgery (Ker et al., 2012) without increasing the incidence of vascular occlusive events (Kozek-Langenecker et al., 2017). This has not been validated for patients undergoing oocyte retrieval, but intraoperative tranexamic acid could be considered if there is active pelvic bleeding of concern.

Luteal support in IVF and the risk of VTE

Progesterone, dydrogesterone (in countries where it is available), sometimes with concomitant oestradiol) or, less commonly, hCG, is used for luteal support following oocyte retrieval when concurrent embryo transfer is planned (van der Linden et al., 2015). The prothrombotic changes already initiated by ovarian stimulation and hCG trigger may be further compounded by these hormones. We identified no papers presenting evidence relevant to this nor on the risk of VTE in pregnancies supplemented by progesterone, although a recent review of dydrogesterone used in MAR or for recurrent miscarriage was reassuring (Ott et al., 2022).

Pregnancies conceived through IVF and the risk of VTE

Pregnancy itself is characterised as a hypercoagulable state and IVF is a recognised risk factor for VTE in the first trimester of pregnancy (RCOG, 2015a). A meta-analysis estimated that in pregnancies following a full IVF cycle, that is, ovarian stimulation with embryo transfer in the same cycle (IVF-ET), the antenatal risk of VTE doubles (odds ratio 2.18, 95% CI 1.63–2.92), compared with the background pregnant population (Sennström et al., 2017). In a cohort study of almost 1 million deliveries over a 10-year period in Sweden, the incidence of first trimester VTE in relation to an IVF-ET cycle was 0.2%, representing a 10-fold increase compared with the background population (Rova et al., 2012). There does not appear to be an increased risk of VTE after the first trimester of pregnancy (Rova et al., 2012).

Multiple pregnancy, irrespective of the method of conception, is a known risk factor for VTE with an adjusted risk ratio of 2.8 (95% CI, 1.9 to 4.2) compared with singleton pregnancies (Virkus et al., 2014).

FET cycles and the risk of VTE

Cryopreserved embryos can be transferred in natural or medicated cycles; the latter uses exogenous oestrogen to prepare the endometrium for embryo transfer, often after pituitary downregulation. Oestradiol valerate and oestradiol hemihydrate are commonly used in medicated cycles with exogenous natural progesterone added for luteal support. Data on the risk of VTE following a medicated FET cycle is sparse. Most of the VTE risks with oestradiol have been assessed in postmenopausal women using HRT and have shown a dose dependent increase in relative risk (Renoux et al., 2010; Smith et al., 2004; Sweetland et al., 2012). Oral oestradiol in this population appears to be associated with a higher risk than transdermal, possibly due to the metabolites of oral oestradiol that are generated by the first pass effect of the liver. The Swedish cohort study comparing 3529 pregnancies following an FET cycle with 935,718 naturally conceived pregnancies found the incidence of VTE was not increased in the first trimester after FET (Rova et al., 2012). The results were the same when the cohorts compared were limited to women giving birth to their first child (Olausson et al., 2020). However, neither study differentiated between medicated and natural FET cycles. A small prospective study of 19 women having medicated FET cycles compared to 15 having natural cycle FET showed that thrombin generation was increased in those receiving oral oestradiol 2 mg times a day (Dalsgaard et al., 2022). Hence data are limited regarding risk of VTE and FET cycles. Natural Cycle FET are anyway preferred method due to reduction in obstetric risks (Zaat et al., 2023).

Duration of hypercoagulable state in the absence of pregnancy

In the absence of a pregnancy after embryo transfer, the duration of the hypercoagulable state following an unsuccessful IVF cycle is unclear. The Danish Cohort study identified no increase in the risk of VTE after an unsuccessful IVF-ET cycle (Hansen et al., 2012). A similarly large French nationwide cohort study demonstrated an increase in VTE (adjusted incidence rate ratio 1.74, 95%CI [1.3–2.34]) (Filipovic-Pierucci et al., 2019; Hansen et al., 2012) although it did not differentiate between VTE events occurring in pregnancies that miscarried before 22 weeks' gestation and those after a negative pregnancy test. VTEs occurring within 90 days of the end of the treatment cycle were included but the distribution of them within that time period was not reported (Filipovic-Pierucci et al., 2019).

The onset of menstrual bleeding following the withdrawal of luteal phase support after recording a negative pregnancy test, marks the end of an unsuccessful cycle of IVF. Usually this indicates that oestradiol levels are back to baseline; however, changes in the coagulation system are detectable 10 days after final oocyte maturation doses of hCG and it is not known how long these persist (Chan, 2009). A study conducted in COCP users demonstrated that fibrinogen levels were back to baseline 1 month after stopping its use whilst factor X concentrations took 8 weeks to return to baseline (Robinson et al., 1991). The authors of this study recommended stopping the COCP a month prior to any major surgery to reduce the risk of VTE (Robinson et al., 1991) and this is now standard practice for elective surgery.

Ovarian hyperstimulation syndrome and the risk of VTE

Ovarian hyperstimulation syndrome (OHSS) is characterised by ovarian enlargement and massive fluid shifts out of intravascular space, leading to ascites, pleural effusions, and haemoconcentration (Kasum et al., 2014). The relationship between OHSS and thromboembolic disorders is well recognized, both in the presence and absence of pregnancy (Hansen et al., 2014; Rova et al., 2012). The association is multifactorial and includes haemoconcentration, activation of the coagulation cascade, rise of thrombin–antithrombin III and plasmin–antiplasmin complexes, and an increase in platelet counts (Belaen et al., 2001). However, in most of the publications, the incidence of OHSS has not been clearly defined and the use of prophylaxis not documented. One study reported the incidence of VTE in OHSS as between 0–11.1% (Wormer et al., 2018). Thromboses are mainly venous (67–75%), but can involve unusual sites such as the upper limbs and neck (Chan & Ginsberg, 2006; Kodama et al., 1996). Arterial thromboses are less common (23–33%) and are mainly intracerebral (Kasum et al., 2014). These are more likely to occur with the onset of OHSS, whereas VTEs can occur 1–2 months after OHSS symptoms have resolved (Olausson et al., 2020). It is not clear if these 'late' VTEs are related to pregnancy or if they are still more likely even when there is no pregnancy. Thrombosis markers remain elevated for over three weeks after onset of OHSS in the event of a pregnancy, and the disturbances in the coagulation system can persist even after the clinical symptoms of OHSS have resolved (Kodama et al., 1996).

The risk of VTE in women who were pregnant as a result of an IVF-ET cycle and hospitalized due to OHSS was 1.7% in the first trimester compared with a 0.017% risk in the background non-IVF pregnant population, a 100-fold increase (Rova et al., 2012). Prevention of OHSS is paramount in reducing the risk of VTE but failing this, those who are pregnant should continue LMWH prophylaxis as per RCOG or local guidelines on management of OHSS and VTE risk reduction in pregnancy (RCOG, 2015a, Royal College of Obstetricians and Gynaecologists, 2016)

Summary

Ovarian stimulation for IVF treatments is a risk factor for VTE. The risk varies at each stage of the IVF cycle, increasing after hCG administration to achieve final oocyte maturation. It is likely that medicated FET cycles using exogenous oestradiol are as well, although those using the natural cycle are not. The highest risk occurs when pregnancy ensues, especially if the cycle was complicated by OHSS, but OHSS even without pregnancy is a risk factor. It is not clear how long the VTE risk persists in the absence of pregnancy, with or without the complication of OHSS. It is likely that there is an effect at least until endogenous oestradiol concentration returns to physiological levels after ovarian stimulation, the cessation of oral oestradiol after an unsuccessful medicated FET cycle or until the resolution of OHSS symptoms. Extrapolating from data regarding the thrombogenic properties of the COCP, VTE risk could last for a month from the end of the exposure to the risk factor(s) and this might be a relevant consideration for those with other risk factors for VTE. Since VTE risks are multifactorial, any pre-

existing/other VTE risk factors must be taken into account when performing a risk assessment.

Recommendations for all individuals undergoing ovarian stimulation or embryo transfer cycles

1. An assessment of VTE risk factors should be undertaken before commencing each treatment cycle of ovarian stimulation and/or embryo transfer and repeated at any point should circumstances change. The risk assessment tool (see Appendix A) should be used to stratify risk and guide prophylaxis interventions (see Appendix B). D
2. Minimise procedure time for oocyte retrieval and encourage early mobilisation and oral hydration. GPP
3. Where there are risk factors for OHSS, appropriate stimulation protocols should be used to reduce this risk. GPP
4. If OHSS occurs, follow the RCOG guidelines, or equivalent local protocol, for the management of OHSS (Royal College of Obstetricians and Gynaecologists 2016). D

Additional risk factors for thromboembolism

There are many pre-existing conditions that increase a patient's risk of VTE. Some comorbidities carry a high risk of VTE whereas others are intermediate or lower. Risk factors are additive and should not be considered in isolation. Pre-existing conditions should be optimised in preparation for pregnancy and/or fertility preservation.

Appendix A gives examples of potential risk factors for VTE but this is not an exhaustive list. Risks for any condition will vary for individuals and advice from a specialist should be sought at the discretion of the lead clinician or if level of risk is unclear. Recent surgery is a risk factor, but the level of risk will depend on the indication, nature and duration. Malignancy, a common indication for oocyte cryopreservation and a risk factor for VTE, is discussed in the section below. These risk factors should be considered as part of risk stratification prior to commencing MAR treatments. Those with additional risk factors for VTE should be considered for further risk reducing interventions which may include prophylaxis.

Pre-existing malignant disease

Oocyte or embryo storage for fertility preservation is an established option for individuals undergoing medical or surgical treatments that can lead to infertility due to premature ovarian insufficiency, and for trans-men, usually prior to commencing hormone treatment. Medically-indicated fertility preservation is most commonly performed in the context of active malignancy, which is itself recognised as a risk factor for VTE. The estimated incidence of VTE in cancer patients is up to 10-fold higher than that in the general population (Blom et al., 2006; Khorana et al., 2013). VTE events occur in 20% of cancer patients (Heit et al., 2002), but the rate varies greatly by cancer site, type (Walker et al., 2013) and chemotherapeutic agent, with fluorouracil, cisplatin and paclitaxel being the most thrombogenic (Khorana et al., 2013). For these patients, the fertility preservation cycle is often performed immediately before chemotherapy and/or may be before or after surgical procedures that may themselves be risk factors for VTE (Somigliana et al., 2014). Furthermore, the presence of a peripherally inserted central catheter (PICC line) for the delivery of chemotherapy significantly increases the risk of VTE with approximately three-quarters of all upper-extremity deep vein thromboses (DVTs) occurring in the presence of indwelling vascular catheters (Flinterman et al., 2008). The risks of central venous catheters (CVCs) are discussed below.

Among cancer patients opting for oocyte or embryo cryopreservation, the most common malignancy is breast cancer which is associated with the lowest incidence of VTE compared to other malignancies (Barcroft et al., 2013; Wun & White, 2009). Gastrointestinal tumours have the highest reported VTE incidence of 2.7–14% (Wun & White, 2009) whilst haematological malignancies like leukaemia and lymphoma have a reported incidence of VTE of 1.8%-7.4% and 3.7% respectively (Wun & White, 2009).

A literature review published in 2014 concluded that the risk of VTE after OS for fertility preservation for malignancy was low in the absence of OHSS or other additional risk factors, since most patients are young, otherwise healthy and with early-stage disease, whilst acknowledging the lack of specific data (Somigliana et al., 2014). The authors concluded that prophylaxis should be reserved for those with risk factors additional to the underlying malignancy. A recently published small retrospective study of 127 cancer patients undergoing OS for fertility preservation identified 4 who had a VTE within 6 months of oocyte retrieval and concluded that the risk of VTE was high in this group (Melo et al., 2022). However, the events occurred between 6 weeks and 6 months after oocyte retrieval, the median time being 3 months. It could be argued that those occurring after 3 months were unrelated to the preceding

fertility preservation cycle, extrapolating from the OHSS associated risk of VTE in pregnancy not persisting beyond 3 months.

Chemotherapy can usually be commenced a couple of days after oocyte retrieval. This means that the menstrual period at the end of the fertility preservation cycle may coincide with a drop in platelets caused by chemotherapy, depending on the agents used. The risk of heavy menstrual bleeding should be considered if prophylaxis use is extended beyond the onset of that menstrual period. Furthermore, oncologists may wish to consider risk of VTE if chemotherapy is commenced soon after a cycle of ovarian stimulation, especially for patients, cancers or chemotherapeutic agents with higher risk of VTE.

Oocyte/embryo cryopreservation in patients with pre-existing non-malignant disease

A growing number of non-malignant conditions are being treated by stem cell transplantation, e.g. sickle cell anaemia, transfusion-dependent thalassaemia and multiple sclerosis. Recipients of stem cell transplants are given gonadotoxic conditioning therapies, including alkylating agents such as cyclophosphamide and busulfan, and total body irradiation, which are associated with up to an 80% risk of premature ovarian insufficiency (Pecker et al., 2018). An increasing number of these patients are undertaking oocyte/embryo cryopreservation prior to the conditioning therapies.

Central venous catheters and risk of VTE

Central venous catheters (CVCs) are commonly used in patients with malignancy or haematological disorders for administration of chemotherapy, transfusion of blood products and the like. Catheter related thrombosis, particularly upper extremity deep vein thrombosis, is a well-known complication of CVCs in general, with a reported incidence ranging from 12–60% (Sriskandarajah et al., 2015) and occurring more commonly in patients with malignant disease (Khorana et al., 2013). The presence of a CVC during an IVF cycle is a potential risk factor for VTE and should be taken into consideration at the pre-treatment VTE risk assessment, or if insertion is planned (e.g. for delivery of chemotherapy/other treatments after oocyte cryopreservation). The duration of VTE risk after oocyte retrieval is unknown, but liaison with the medical team regarding the timing of insertion, especially for patients with additional risk factors for VTE, may be prudent.

Risk stratification for VTE

The risk assessment tool in Appendix A can be used to stratify patients by their level of risk. Patients with pre-existing requirements for long-term anticoagulation should be discussed with their specialist before planning fertility treatment. The presence of multiple low risk factors may equate to high risk of VTE. The involvement of a multidisciplinary team (e.g. haematologist, oncologist, cardiologist, neurologist etc, depending on the underlying condition) may be required for those classified as high or intermediate risk of VTE.

Recommendations

5. Careful discussion and planning should be undertaken with a multidisciplinary team where the risks of VTE are high, especially where these coexist with increased risks of haemorrhage, as in certain haematological malignancies or benign conditions. Some at risk patients may be recommended an intermediate or treatment dose of low molecular weight heparin by their specialist, rather than a prophylactic one. GPP

Modifiable risk factors

Some risk factors for VTE are modifiable. All women who are trying to conceive should be advised to achieve a normal BMI, or reduce weight to be closer to a normal BMI, and to stop smoking (NICE, 2013). Smoking can be stopped within weeks by most with the right support and engagement. However, for those who are overweight or living with obesity, losing enough weight to improve VTE risk profile may take an unreasonable amount of time, which might be critical for some individuals for whom age along with significant delays to treatment may affect live birth rates, or for those undergoing fertility preservation, which is usually urgent.

Immobility is a risk factor even when it is only due to long-distance travel. Whilst most women will access MAR treatments locally, some will travel long distances during or immediately after their cycle, and this should be taken into account in both the risk assessment and the planning of the treatment cycle. Elective surgery with a risk of VTE should not normally be scheduled for 4 weeks before, during or within 4 weeks after an IVF treatment, although this may not be an option for those undergoing fertility preservation for malignant disease.

Recommendations

6. When feasible, modifiable risk factors should be optimised before starting MAR treatment. **GPP**
7. Individuals undergoing ovarian stimulation or medicated embryo transfer cycles should be advised to inform their healthcare provider of this if admission to hospital or a procedure with a risk of VTE is required during treatment or within a month after oocyte retrieval/discontinuing FET hormone treatments respectively. Elective procedures with a risk of VTE should be deferred. Clinicians should consider this situation as analogous to a woman taking HRT or the COCP within the last month. **GPP**
8. Recent MAR treatment should be taken into consideration at the pre-treatment risk assessment if another treatment cycle is planned to start within a month of the previous oocyte retrieval. **D**

IVF protocol adaptations to reduce the risk of TE

There is no current accepted guideline on an ideal IVF protocol for those with increased risk of VTE. Since we accept that high oestradiol levels and OHSS increase the risk of thrombosis it would be safe to assume that keeping oestradiol levels low and minimising the risk of hyperstimulation would be desirable.

Depending on the level of thrombotic risk, the following ovarian stimulation protocols may be considered.

Antagonist cycles with agonist oocyte maturation trigger

The use of GnRH antagonist protocols is associated with lower risk of OHSS, and exchanging hCG for a GnRH agonist to trigger final oocyte maturation is now empirically established in practice with the aim of reducing the risk of ovarian hyperstimulation in high responders (Lambalk et al., 2017; Youssef et al., 2014). Although an agonist trigger may further lower the risk of OHSS, if an embryo transfer is planned in the same cycle, additional exogenous hormone replacement is required to obtain similar live birth rates as with hCG triggers (Humaidan et al., 2005; Kolibianakis et al., 2005). Whilst this may come with a risk of VTE, it is still likely to be significantly lower than that associated with OHSS.

Freeze-all strategy with natural cycle frozen embryo transfer

Another strategy used in OHSS risk mitigation is a freeze all protocol. An antagonist cycle with an agonist bolus for final oocyte maturation followed by storing all embryos has the lowest risk of OHSS. This also avoids the prothrombotic changes associated with hCG use. This strategy allows the option of transferring a frozen embryo in a natural cycle (in patients with regular cycles) reducing the additional risks from exogenous oestrogen. An antagonist cycle with an agonist trigger is also suitable for those storing oocytes/embryos for fertility preservation.

Mild stimulation

Mild stimulation refers to protocols that aim to stimulate the growth of a small number of follicles and to collect a correspondingly lower number of eggs than with standard protocols (Nargund et al., 2007). This option may be suitable for selected younger women at risk of VTE (where egg quality will be inherently good) and/or for those with male factor or pelvic factor infertility, rather than those with unexplained infertility or when the indication is fertility preservation, where the number of eggs/embryos available for transfer may affect outcome more. There is no exact definition of mild stimulation, but it is accepted that the dose of gonadotrophins used will not exceed 225 units (depending on ovarian reserve) (Zhang et al., 2016). Mild stimulation can be carried out with FSH, hMG, clomiphene or aromatase inhibitors or a combination of clomiphene/letrozole with a low dose of FSH/hMG (Fauser et al., 2010). These protocols may nonetheless be associated with a small risk of VTE. The European Society of Human Reproduction and Embryology (ESHRE) guidance does not support the use of mild stimulation protocols based on live birth and OHSS as primary outcomes: VTE risk was not evaluated (European Society of Human Reproduction and Embryology (ESHRE), 2019).

Modified natural cycle

Modified natural cycle usually refers to egg collection in a natural cycle with added agents to retard premature LH surge such as indomethacin (Nargund et al., 2001), thereby avoiding any rise in oestradiol above normal. Modified natural cycles may also include the use of hCG for final oocyte maturation. Usually only a single oocyte is retrieved, which is associated with a very low live birth rate. The modified natural cycle may be an option for some patients with high VTE risk, but the poor efficacy of this protocol should be weighed against the use of adequate stimulation with the addition of VTE prophylaxis.

DuoStim and back-to-back cycles

'DuoStim' is the process of stimulating the ovaries twice within the same menstrual cycle to retrieve eggs. The VTE risks of the second stimulation course rapidly following the first egg collection should be counted in the VTE risk assessment for the second stimulation. The same should apply for back-to-back IVF/FET cycles. DuoStim cycles or back-to-back IVF/FET cycles should usually be avoided in those at high risk of VTE.

Adjuvant aromatase inhibitors

Aromatase inhibitors are used alongside gonadotrophins in patients with hormone sensitive breast cancer to keep oestradiol concentrations low (Rodgers et al., 2017). There are no studies evaluating any reduction of VTE risk with the addition of aromatase inhibitors to reduce the rise in oestradiol during stimulation. In studies of VTE in breast cancer patients taking tamoxifen or aromatase inhibitors, VTE risk was found to be higher with tamoxifen than with aromatase inhibitors (Blondon et al., 2022; Xu et al., 2019). Use of adjuvant aromatase inhibitors can be considered to lower oestradiol concentrations during ovarian stimulation in freeze-all and fertility preservation cycles.

It is to be noted that if it is deemed safe for a patient at increased risk of VTE to be pregnant, it is usually safe for IVF-ET/FET with additional measures to mitigate VTE risk, which includes seeking advice from a specialist. One cycle optimised for live birth is likely to be preferable to several suboptimal ones, especially in the highest risk individuals on long-term anticoagulation for whom discontinuing this even for a short time to allow safe oocyte retrieval would have a risk of VTE.

Recommendations

9. Where a risk factor for VTE has been identified, consider modification of the standard OS/FET protocol to one that may be associated with a lower risk of TE. **GPP**
10. Where a risk factor for VTE has been identified, ensure good hydration during and/or after oocyte retrieval. **GPP**
11. Where a risk factor for VTE has been identified, single embryo transfer should be recommended. **D**

Pharmacological prophylaxis

The use of pharmacological prophylaxis/treatment must balance the benefits against the risk of bleeding at oocyte retrieval. It must also consider that oestradiol levels steadily rise to their highest on the day of egg collection and that an hCG trigger probably potentiates the risk of VTE in this hyper-oestrogenic environment. Long-acting agents, including aspirin, should be avoided because of their potential to increase bleeding at oocyte retrieval. Low molecular weight heparin (LMWH) is the anticoagulant of choice for prophylaxis/treatment in the peri-operative period for most surgical procedures as with subcutaneous administration in most patients (unless renal function is severely impaired) it has a short half-life of approximately 3–7 hours (Douketis et al., 2012) and is the recommended agent for prophylaxis/treatment in pregnancy (RCOG, 2015a).

The Swedish Association of Obstetrics and Gynaecology recommends omitting the morning dose of LMWH on the day of oocyte retrieval, restarting it the same evening (Lindqvist et al., 2014). In terms of risk of surgical bleeding, the procedure is considered to be similar to epidural catheter insertion or spinal injection, and it would be reasonable to extrapolate the same recommendations about interrupting LMWH injections to balance the risk of bleeding against that of thromboembolism (Douketis et al., 2012). The last dose (prophylactic or as specified in the patient's bridging plan) should be taken at least 24 hours prior to oocyte retrieval. Prophylactic dose LMWH should be restarted after oocyte retrieval, usually aiming for 6–12 hours later and within 24 hours. If prophylactic dose LMWH is planned to commence after oocyte retrieval, it should be within this window. Those taking treatment doses of LMWH should have a bridging plan from their specialist involved in the management of their usual anticoagulation, prior to starting MAR treatments. Bridging plans may vary but as a general guide, the last dose of LMWH pre oocyte retrieval should be half a treatment dose 24 hours beforehand. LMWH can be restarted 6–12 hours after and within 24 hours, following the dosing schedule as specified in the bridging plan. All patients with increased background risks for VTE should be made aware of the increased risk during the time without anticoagulation around oocyte retrieval.

Use of prophylaxis in MAR

Recommendations for prophylaxis should be based on the classification of risk in individual patients (see risk assessment tool in Appendix A). Appendix B provides prophylaxis guidance based on risk classification. Where possible, non-pharmacological risk reducing measures should be used in addition to pharmacological ones,

especially those aimed at reducing the risk of OHSS and VTE around oocyte retrieval.

Recommendations

12. LMWH administered subcutaneously is the anticoagulant of choice when an anticoagulant is required during MAR treatments. **A**

For patients identified as high risk of VTE

13. Those on long-term anticoagulation treatment should have a pre-conception plan for thromboprophylaxis formulated by the specialist involved in the management of their anticoagulation before discontinuing contraception. Those requiring oocyte retrieval will need a bridging plan as well, and should normally be converted to LMWH at the start of their oocyte retrieval/FET cycle. Those at risk of VTE, including those on treatment dose anticoagulation, should be informed that their risk of VTE is highest around oocyte retrieval during the time without anticoagulation (see Appendix A). **GPP**
14. Consider omitting pre-treatment with a progestogen and/or oestrogen. **GPP**
15. For those not taking long-term anticoagulation, start LMWH with the start of potentially thrombogenic hormone treatment i.e. hormone pre-treatment or ovarian stimulation/endometrial preparation with oestradiol, whichever is the sooner, prophylactic dose in some patients (e.g. antithrombin deficiency), and already stated that specialist should advise. **GPP**
16. LMWH should be interrupted for oocyte retrieval to reduce the risk of bleeding. The last dose (prophylactic or as specified in the patient's bridging plan) should be taken at least 24 hours prior to oocyte retrieval. LMWH should be recommenced 6–12 hours after the procedure depending on the risk of bleeding as assessed by the senior clinician responsible for the oocyte retrieval, but no longer than 24 hours later. For those on long-term anticoagulation, the dose of LMWH on restarting should be as specified in the bridging plan. **GPP**
17. Natural rather than medicated cycles should be used for FET if possible, and LMWH commenced with a positive pregnancy test or as soon as practicable after*. **GPP**
18. In the absence of pregnancy after an IVF-ET/oocyte or embryo cryopreservation cycle uncomplicated by OHSS, consider stopping LMWH two to four weeks after the start of the menstrual period marking the end of the cycle. After an unsuccessful medicated FET cycle, consider stopping LMWH 2 to 4weeks after all hormone support has been discontinued. **D**

* Unless requiring long-term anticoagulation.

For patients identified intermediate risk of TE

19. Commence thromboprophylactic dose LMWH 6–12 hours after oocyte retrieval depending on the risk of bleeding as assessed by the senior clinician responsible for the retrieval but no longer than 24 hours later. **GPP**
20. If a medicated FET cycle is planned, LMWH should be given from the start of potentially thrombogenic pre-treatment or with the start of oestrogen therapy, whichever is the sooner. **GPP**
21. In the absence of pregnancy after an IVF-ET/oocyte or embryo cryopreservation cycle uncomplicated by OHSS, or after a medicated FET cycle, consider stopping LMWH when the menstrual period starts and once all luteal phase hormone support has been discontinued. **D**

Risk of VTE with ovulation induction and superovulation

Ovulation induction (OI) is a method for treating anovulatory infertility using antioestrogens, gonadotrophins, or GnRH with the aim of achieving a monofollicular response. Superovulation (SO) aims to achieve one-two follicles greater than 16 mm in diameter on ultrasound in those with regular natural ovulations. This is sometimes offered to couples having intravaginal intercourse as an empirical treatment for unexplained infertility, often in conjunction with intrauterine insemination (IUI). SO-IUI may also be used for those requiring donor sperm, if natural cycle IUI has been discounted. With both OI and SO, peak oestradiol levels rarely go above 2000 pmol/l, as cycles are cancelled and stimulation discontinued when more than three follicles $>$ 16 mm are seen. In the absence of ovarian hyperstimulation, there is currently no evidence of increased risk of VTE with OI (Filipovic-Pierucci et al., 2019) or SO treatments. VTE prophylaxis is therefore not indicated with either of these treatments unless the person develops ovarian hyperstimulation syndrome or requires hospitalisation (please refer to the RCOG Ovarian Hyperstimulation Syndrome *guideline* (Royal College of Obstetricians and Gynaecologists, 2016) or NICE *Venous thromboembolism in over 16s: reducing the risk of hospital-acquired deep vein thrombosis or*

*pulmonary embolism guideline (*NICE, 2018). People with increased risks of VTE, including those on long-term anticoagulation, should be assessed by a specialist prior to starting trying to conceive and should follow those pre-conception recommendations during OI/SO treatment. There is an increased risk of multiple pregnancy with SO and OI treatments, which should be considered when planning either of these treatment options for those with known risk factors for VTE.

Recommendation

22. Ovulation induction (OI) and superovulation (SO) treatments do not require prophylaxis as these are not associated with increased risk of VTE, unless OHSS occurs. Those on long-term anticoagulation should follow the pre-conception/early pregnancy plan advised by their specialist.

MAR treatment adjuvants and the risk of VTE

Treatment adjuvants, adjuncts or 'add-ons' are empirical treatment steps that may be offered on top of standard fertility treatments. It is outside the scope of this paper to discuss the role or otherwise of these controversial treatments. However, some of the commonly used ones have been associated with higher risk of VTE.

Targeting immune dysregulation and maintaining a pre-conceptional anti-inflammatory environment for implantation and pregnancy continuation have been a controversial area in the field of fertility. Intravenous immunoglobulin G (IVIG) treatment has been reported to enhance reproductive outcome mainly in patients with recurrent implantation failures and miscarriages (Li et al., 2013). This practice is still not considered evidence-based and is not supported by the American Society for Reproductive Medicine (ASRM), NICE guidance or the HFEA. In the general context of medical illnesses, case series and other observational studies reported that the thromboembolic incidence rates among IVIG-treated patients have ranged from 0.5% to 17% (Ammann et al., 2016; Caress et al., 2003; Marie et al., 2006; Ramírez et al., 2014). Randomised controlled trials (RCT) also yielded inconsistent risk estimates (Ammann et al., 2016). A metanalysis of RCT concluded that the absolute risk of arterial and venous thrombotic events associated with IVIG treatment is likely to be low (Ammann et al., 2016). Most patients seeking fertility treatments are expected to be young with a low risk of vascular events, yet the risk needs to be assessed in the context of comorbid medical conditions and other risks factors.

Recommendation

23. If empirical adjuvant treatments to MAR are being considered, their potential to increase the risk of VTE must be balanced against their perceived benefit. GPP

Conclusion

VTE is a recognised complication of MAR although the literature provides scarce data on the true incidence. It is a preventable condition with high mortality and morbidity when left untreated. Patient education is paramount for reducing the modifiable risk factors.

There is currently no generally accepted consensus on prophylaxis in relation to IVF treatments and the evidence for recommending prophylaxis is insufficient. The absolute risk of VTE in MAR is overall low and therefore some form of risk stratification is required to determine who warrants pharmacological prophylaxis. The guidance on risk assessment, prophylaxis and risk reducing strategies are drawn up recognising the limited evidence in this area.

An assessment of thrombotic risk should be undertaken before commencing any MAR treatment. Appendix A provides a VTE risk assessment tool for classifying individuals into risk groups. Appendix B provides prophylaxis guidance based on risk classification.

The VTE risk assessment score must be documented in the patient records and all clinicians involved in the patient's care during and immediately after MAR treatment should be aware of it and the factors that could affect VTE risk. A repeat risk assessment should be performed if clinical factors change, such as OHSS develops, or in the event of an ongoing pregnancy. This should be conducted early in view of the increased thrombotic risks associated with first trimester complications such as hyperemesis gravidarum.

Importantly, individuals needing prophylaxis should have clear pathways to access prescriptions and support to ensure compliance.

MAR treatment records are usually kept separately from the patient's other medical records, even when fertility treatment is occurring within a general hospital setting, rather than at a stand-alone fertility centre. Fertility clinics in all settings should therefore consider how the VTE risk assessment score will be shared appropriately with other clinicians, whilst maintaining patient confidentiality. Patient-held VTE risk

assessment scores along with patient education, may be one solution. Greater general clinical awareness of the potential VTE effect of MAR is also needed, especially since these treatments are increasingly common.

Recommendation

24. A risk registry should be set up nationally to record the cases of VTE associated with MAR, which would help inform future development of recommendations.

Disclosure statement

No potential conflict of interest was reported by the author(s).

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Appendix A. Thromboembolism risk assessment tool in IVF

All patients should be risk assessed prior to starting any fertility treatment. Patients should be re-assessed after a positive pregnancy test and/or if they develop OHSS): RCOG guidelines (or local equivalent) should be followed in either situation. If any additional thrombotic risk factors occur within 1 month of triggering final oocyte maturation, the risk assessment should be repeated.

This risk assessment tool should be used for outpatient treatment only. Those admitted during or within 1 month of trigger should be assessed using the local VTE risk assessment tool. Recent or ongoing IVF treatment should be noted as a thrombotic risk factor similar to use of hormone replacement therapy or a combined hormonal contraceptive.

STEP ONE

Review the patient-related factors shown on the assessment sheet against thrombosis risk. The risk factors identified are not exhaustive. Clinicians may consider additional risks in individual patients and offer prophylaxis as appropriate.

STEP TWO

Classify patient as 'high risk', 'intermediate risk' or 'lower risk' of VTE.

STEP THREE

Review the patient-related factors shown against any contraindications and cautions to pharmacological prophylaxis (more than one box can be ticked).

Any tick should prompt clinical staff to liaise with a specialist with expertise in thrombosis and bleeding, and evaluate if bleeding risk is sufficient to preclude pharmacological intervention.

STEP FOUR

Follow the recommended prophylaxis guidance relevant to the risk classification.

Table A1. Risk factors for VTE.

Pre-existing risk factors	Score
Previous venous or arterial thromboembolism[a]	4
Valvular heart disease including prosthetic valves[b]	4
High risk thrombophilia: antithrombin deficiency, protein C or S deficiency	4
Compound heterozygous or homozygous for low-risk thrombophilia: factor V Leiden gene mutation, G20210A prothrombin gene mutation	4
Thrombotic APS (lupus anticoagulant, moderate or high positive anti-ß2 glycoprotein 1 and/or anticardiolipin antibodies)[c]	4
Cancer: varies with type – breast is low risk, most pelvic cancers high risk; myeloproliferative neoplasms high risk[c]	1 to 4
Medical co-morbidities: examples include heart failure, inflammatory /autoimmune conditions (e.g. active SLE, inflammatory bowel disease), nephrotic syndrome, Type 1 diabetes with nephropathy, sickle cell disease, thalassaemia (excluding thalassaemia trait)[c]	3
Obstetric APS, persistent antiphospholipid antibodies[c]	3
Central venous catheter	3
IVF-ET/oocyte or embryo cryopreservation/medicated FET cycle completed within previous 4 weeks	1
Heterozygous for factor V Leiden or G20210A prothrombin gene mutation and no previous VTE	1
Family history of VTE and/or thrombophilia in first degree relative	1
Family history of premature arterial disease	1
BMI $>30\,kg/m^2$	1
Age $>$ 40 years	1
Drugs e.g. chemotherapy, long-term tamoxifen/clomiphene	1
Parity $\geq$ 3	1
Smoker	1
Issues during treatment, ensuing pregnancy or within 28 days of a negative pregnancy test	
Ovarian hyperstimulation syndrome	4
Additional surgical procedure, excluding egg collection	3
Immobility	1
Dehydration	1
Systemic infection (including SARS-CoV-2)	1
Long distance travel (>4 hours within last 4 weeks)	1
Hyperemesis	1

Anyone on long term anticoagulation should have an individualised treatment plan from a specialist.
List not exhaustive.
APS: antiphospholipid syndrome; BMI: body mass index, SLE: systemic lupus erythematosus, VTE: venous thromboembolism.
[a]Any history of VTE or stroke/arterial thromboembolism needs specialist assessment prior to IVF (NB: event within last 3 months is very high risk).
[b]Examples of cardiac valvular disease include mitral/tricuspid stenosis or regurgitation. Those with a prosthetic valve need specialist input prior to IVF, even if not requiring long-term anticoagulation.
[c]Should have specialist/multidisciplinary input prior to IVF.
If total score is 4 or more, treat as 'high' risk.
If total score is 3, treat as 'intermediate' risk.
If total score is less than 3, treat as 'lower' risk and no additional precautions required.

Appendix B. Management of prophylaxis: Summary

Follow RCOG guidelines (or local equivalent) in pregnancy or if OHSS occurs.

High risk
Refer to specialist prior to starting any fertility treatment.
Anyone on long term anticoagulation or requiring treatment dose LMWH during IVF should have an individualised treatment plan from a specialist. This should include a bridging plan for oocyte retrieval.
LMWH is the anticoagulant of choice when prophylaxis/treatment is required during IVF treatments (*see below for cautions and contraindications to LMWH)
Consider modification of the standard IVF protocol to one that may be associated with a lower risk of VTE.
Consider omitting pre-treatment with a progestogen and/or oestrogen. If this cannot be omitted, start LMWH with the start of potentially thrombogenic hormone treatment.
LMWH should be commenced with ovarian stimulation, unless already started with pre-treatment.
LMWH should be interrupted for oocyte retrieval to reduce the risk of bleeding. The last dose (in accordance with the patient's bridging plan, e.g. prophylactic or half treatment dose as appropriate) should be taken at least 24 hours prior to oocyte retrieval.
LMWH should be recommenced 6–12 hours after the procedure depending on the risk of bleeding as assessed by the operator, but no longer than 24 hours later. The dose should be as per the bridging plan.
Natural rather than medicated cycles should be used for FET if possible and LMWH commenced with a positive pregnancy test or as soon as practicable after.
If a medicated FET cycle is used, LMWH should be given from the start of potentially thrombogenic pre-treatment or with the start of oestrogen therapy, whichever is the sooner.
In the absence of pregnancy after an IVF-ET / oocyte or embryo cryopreservation cycle uncomplicated by OHSS, consider stopping LMWH two to four weeks after the start of the menstrual period marking the end of the cycle. After an unsuccessful medicated FET cycle, consider stopping LMWH 2 to 4 weeks after all hormone support has been discontinued.
If OHSS has occurred in the absence of embryo transfer/pregnancy, consider continuing prophylaxis for 4 weeks after resolution of symptoms.
Intermediate risk
Commence LMWH 6–12 hours after oocyte retrieval depending on the risk of bleeding as assessed by the operator but no longer than 24 hours later.
If a medicated FET cycle is used, LMWH should be given from the start of potentially thrombogenic pre-treatment or with the start of oestrogen therapy, whichever is the sooner.
In the absence of pregnancy after an IVF-ET / oocyte or embryo cryopreservation cycle uncomplicated by OHSS, or after a medicated FET cycle, consider stopping LMWH when the menstrual period starts.
If OHSS has occurred in the absence of embryo transfer/pregnancy, consider discontinuing prophylaxis with the start of the menstrual period marking the end of the cycle or with resolution of symptoms, whichever is the later.
Lower risk
Pharmacological prophylaxis is not required (unless OHSS occurs).

*__Contraindications and cautions to prophylaxis with LMWH__ (not exhaustive).

Active bleeding
Thrombocytopenia (platelets <50 x10^9/L)
Uncontrolled systolic hypertension (230/120 mmHg or higher)
New stroke
Known bleeding disorder – requires formal assessment by a specialist prior to IVF
Previous heparin induced thrombocytopenia (HIT) or allergy to LMWH/heparin
Bleeding in pregnancy/presence of subchorionic haematoma