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ORIGINAL ARTICLE

Antithrombotic therapy during in vitro fertilization (ivf)

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ABSTRACT

The use of antithrombotic agents during IVF is widely considered for the prevention and treatment of thrombotic complications, but also for their possible beneficial effects on pregnancy outcome. Women who develop OHSS are recommended to receive LMWH for at least 3 months. An assessement of thrombotic risk should be offered to all women undergoing IVF

Heparin emerges as a promising agent in IVF, not only for its antithrombotic effects but also for its cytoprotective effect on trophoblast implantation and growth through the increase of HB-EGF secretion, the reduction of TNF-a-induced apoptosis of endometrial cells and the increase of matrix metalloproteinase-2 activity (MMP-2)

Further RCTs are needed in order to evaluate the efficacy and safety of antithrombotic agents in IVF, to identify patient groups that may benefit more from its administration as well as to establish guidelines for the timing, duration, and dose of LMWH.

KEY WORDS IVF, LMWH, thrombosis, pregnancy outcome

Since its first application in 1978 , in vitro fertilization (IVF) has been the most frequently used method of assisted reproduction, aiming to address the ever-increasing rates of infertility in the modern world. (1) The introduction of new techniques and new pharmacological approaches has led to an increase in the success rates of patients undergoing IVF (2); however, only one-third of IVF procedures result in pregnancy, and many women experience repeated failures over multiple IVF cycles, mainly due to implantation disorders. (3)

Thrombophilia, hereditary and acquired, is a known risk factor for secondary infertility, while its role is also being investigated in cases of repeated IVF failures. The successful use of antithrombotic agents, specifically low molecular

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weight heparin (LMWH) in pregnancies of patients with acquired thrombophilia, suggested its application also in the field of assisted reproduction, with encouraging results. The use of LMWH appears to increase success rates in repeated implantation failures after IVF, but also in pregnancy complications related to the placenta or delayed intrauterine growth, regardless of the presence of thrombophilic or autoimmune disorders, thus attributing to heparin potential cytoprotective actions duringthe processes following fertilization. (3,4,5)

Pregnancy as well as the postpartum period are characterized as hypercoagulable states, since during these periods there is a 4-5 times greater risk of thromboembolic events than the general population. (6) In the case of IVF, exogenous administration of gonadotrophins during the ovarian stimulation phase leads to a rapid increase in estradiol levels and changes in the concentrations of coagulation and anticoagulant factors, with the risk of venous thromboembolic disease being up to 3 times greater compared with a spontaneous pregnancy. (3,4)

The observed changes concern the increase in the concentration of coagulation factors (fibrinogen, factor V and VIII, vWF), d-dimers and markers of endothelial damage, such as thrombomodulin, and the decrease of natural inhibitors (protein C and S, antithrombin), while in global coagulation tests (thromboelastography) a significant reduction in clotting time is observed. (3,4) The coexistence of inherited or acquired thrombophilia, oocyte retrieval procedures, immobility, and repeated exposure to hormonal agents in cases of failure obviously further increase the thrombotic risk. (3)

Thrombotic complications during assisted reproduction are mainly venous and less often arterial, with deep vein thrombosis of the upper extremity being a frequent manifestation, due to the drainage of estrogen-rich intra-abdominal lymph into the major thoracic duct. (4)

A special clinicalentity is theovarian hyper-stimulation syndrome (OHSS), a serious systemic complication of controlled ovarian stimulation, characterized by swelling of the ovaries, very high concentrations of estradiol, increased vascular permeability and leakage of fluids into the third space. (7) The more pronounced changes in the concentrations of procoagulant and anticoagulant factors in the case of OHSS, combined with intravascular volume contraction and subsequent hemoconcentration, lead to a steep increase in thrombotic risk, with 1 in 128 women with OHSS developing a thromboembolic event. Therefore, women who develop OHSS are recommended to receive anticoagulation with LMWH for at least 3 months. (3,4,7)

The use of antithrombotic agents during IVF is widely considered today for the prevention of thrombotic complications, but also for their possible beneficial effects on achieving and maintaining a pregnancy. Aspirin, with its antiplatelet and anti-inflammatory effects, has been studied for its effect on successful implantation and pregnancy rates, but with conflicting results. (3) Its administration in combination with LMWH is well studied during pregnancy in women with antiphospholipid syndrome, however its routine use as prophylaxis during IVF procedures requires further investigation and questions regarding the benefit of anticoagulation administration, its duration and its dose have not been definitely answered. (3) LMWH is used for the treatment for thromboembolic complications during assisted reproduction and pregnancy, but also for prophylaxis in women with known thrombophilia and/or a history of thrombosis. However, its role seems to extend beyond the aforementioned, with the discovery and study of the interactions of heparin with growth factors, cytokines and adhesion molecules involved in the process of implantation and growth of the trophoblast. (4)

Pregnancies achieved by IVF are characterized by an increased risk of perinatal complications, such as prematurity, preeclampsia, perinatal mortality and intrauterine growth retardation, which are associated with implantation disturbances during the first trimester of pregnancy. (4) After implantation of the blastocyst in the endometrium, the trophoblast proliferates and differentiates into two forms, villous and extravillous trophoblast. The latter is responsible for the filtration of the placental and spiral arteries, establishing communication with the maternal blood and ensuring the survival of the fetus. Many molecules participate and regulate this process, with heparin binding epidermal growth factor (HB-EGF) playing a leading role. (8)

HB-EGF is produced by the endometrium and placenta of the first trimester of pregnancy and participates in the differentiation of the extrafollicular trophoblast, in the regulation of the motility of the endometrial stromal cells at the site of implantation, while it also exerts a cytoprotective effect, which is confirmed by the reduced expression of in trophoblast from placentas of patients with preeclampsia or antiphospholipid syndrome. (8,9)

LMWH appears to increase the expression of growth factors from the endometrium and exert its protective effect on trophoblast implantation and growth through the HB-EGF pathway. More specifically, in a study by D'Ippolito et al., the use of LMWH in extrafollicular trophoblast cells from women with six first-trimester miscarriages led to an increase in HB-EGF expression, improving trophoblast penetration and growth. (8) Similar results have also been observed in the study by Bolnick et al., where in addition to the increase in HB-EGF secretion in the presence of LMWH, inhibition of the growth factor abolishes the effects of heparin, thus emphasizing the interaction between these two molecules, with requires the integrity of the HB-EGF pathway. (9) In another study, LMWH appeared to exert a dose-dependent effect, promoting trophoblast proliferation, differentiation, and infiltration at low concentrations and inhibiting these at higher concentrations. (10) Additional data support the role of heparin in reducing TNF-a-induced apoptosis of endometrial cells, in increasing the activity of matrix metalloproteinase-2 (MMP-2) which participates in the infiltration of the extravillous trophoblast, but also in the possible its beneficial effect on endothelial function and angiogenesis during pregnancy. (8,9,11)

Evaluating the use of heparin in real-world settings, several studies are found in the literature with increased success rates with the administration of LMWH in patients with recurrent episodes of spontaneous abortion (12) or with two or more implantation failures after EG (5,13). However, the great heterogeneity in the inclusion characteristics of the patients in the studies and the timing and dosing of LMWH administration do not allow safe conclusions to be drawn. (3,14)

In summary, heparin emerges as a promising agent in assisted reproduction, on one hand, with its anticoagulant effect on the prothrombotic changes that take place during IVF processes and particularly in the presence of thrombophilia or OHSS predisposing factors, and on the other hand, with its action beyond its antithrombotic effect, i.e. its cytoprotective effect on trophoblast implantation and growth. Limited data exist regarding the role of antiplatelet therapy with aspirin in IVF. Further studies are needed in order to evaluate the efficacy of antithrombotic agents and their safety in pregnancy, as well as to establish specificr guidelines, for the timing, the duration, and the dose of anticoagulants , as well as for the selection of subgroups of patient that may benefit more from anticoagulation administration. ■

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