

Talking about assisted reproductive techniques and thromboembolic risk: everything we always wanted to know

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The last report on Assisted Reproductive Technologies (ART) showed a steady increase in the annual number of treatment cycles worldwide.¹ The most common techniques of autologous ART - *in vitro* fertilization (IVF) and intracytoplasmic sperm injection (ICSI) - require the use of exogenous gonadotropins with possible adverse effects. It is clear that efforts to address infertility in order to give the chance of the motherhood should be, however, carefully weighed against possible complications. Indeed, exogenous gonadotropins used for controlled ovarian hyperstimulation, induce hypercoagulable state.² When an ovarian hyperstimulation syndrome (OHSS) occurs, the

risk of venous thromboembolism (VTE) can be up to 100-fold higher than that observed in absence of such complication.³ Actually, severe OHSS, that occurs in 0.5-5% of ART cycles, shows quite heterogeneous pathogenetic mechanisms leading to thrombosis through a huge imbalance of coagulation and fibrinolysis.⁴ ART-induced hypercoagulability is mainly due to an increase in plasma levels of several clotting factors and especially factor VIII, leading to an acquired activated protein C resistance. On the other hand, the downregulation of fibrinolysis and lowering levels of endogenous natural anticoagulants, such as protein S, further increase the risk.⁵ All these changes can be detected by global tests as thrombo-elastography-based viscoelastic assays.⁶

VTE may be diagnosed up to several weeks after a controlled ovarian hyperstimulation or OHSS, whereas arterial thrombotic complications usually occur several days after ovulation induction.² Notably, pulmonary embolism (PE) is frequently reported in this setting, independently of the presence of deep vein thrombosis in the lower extremity. Indeed, the risk of PE is approximately threefold higher than that reported during oral contraception.⁷

Increasing age, overweight or overt obesity, in addition to smoking and other individual characteristics further raise the risk.⁵ Controversial data are so far available about whether and to what extent thrombophilia increases the risk.²

More recently, data from several studies have shown that VTE risk in pregnancies following ART is doubled in comparison to that estimated after spontaneous conception, independently of the occurrence of OHSS. VTE risk is tenfold greater in the first trimester in ART pregnancies compared to that recorded in the reference population.⁸ Consistent with these findings, VTE risk appears significantly lower in unsuccessful cycles compared to successful ones.⁹

As for antithrombotic prophylaxis in high-risk women, as well as type and duration of treatment in case of OHSS, robust data are lacking. Furthermore, there are no conclusive studies focusing on the best management of OHSS, although, due to the highest risk of VTE, pharmacological prophylaxis with low-molecular-weight-heparin (LMWH) is recommended.^{2,3} For these reasons, current guidelines

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often do not report any practical suggestions on strategies to reduce the risk - both, arterial and venous - in ART nor give specific advice to guide the intensity and duration of antithrombotic treatment in case of OHSS. This issue is particularly relevant, as maternal age is one of the most frequent indirect risk factors for mortality in western countries and the mean age at first childbirth continues to increase. Most importantly, fewer than a third of mothers who gave birth over the age of 45 receive the recommended care for older mothers (https://www.npeu.ox.ac.uk/assets/downloads/mbr-race-uk/reports/maternal-report-2020/MBR-RACE-UK_Maternal_Report_Dec_2020_v10_ONLINE_VERSION_1404.pdf).

In Italy, one of the most frequent indirect causes of maternal death is ART (11.3% of fatalities), whereas the leading causes of direct deaths in pregnancy are hemorrhage and VTE (<https://www.epicentro.iss.it/en/itoss/maternal-mortality-surveillance>). These data prompted the European Society of Cardiology (ESC) to recommend avoiding fertility treatments in women with class IV of the modified WHO classification of maternal risk and to be cautious in those with modified WHO class III or those who are anticoagulated. Actually, these groups of women have a significantly higher risk of superovulation and therefore of OHSS.¹⁰ At variance with ESC, many other international guidelines do not give particular suggestions on these issues in the absence of *ad hoc* studies. We deem it crucial that international guidelines on reproductive health give reasonable suggestions to provide the best possible counselling, in the light of albeit scarce evidence instead of simply stating that there is no evidence. On the other hand, while waiting for randomized controlled trials in this field, we must be pragmatic and strive to utilize innovative alternative study designs, aimed at offering our women safe strategies to get pregnant and mostly to avoid life-threatening situations for mothers and babies.¹¹

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