Rationale Use of Thromboprophylaxis to Prevent Venous Thromboembolism (VTE) in Women Ongoing Assisted Reproductive Technologies

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Abstract

Assisted Reproductive Technologies (ART) procedures because haemostatic changes due to hormonal treatment and biological prothrombotic changes during ovarian hyperstimulation and following pregnancy may be associated to increases risk of VTE. In recent years several articles discussed the needful support of LMWH not only to reduce VTE incidence in this clinical setting but also to increase the rate of successful pregnancy after ART. There are not guidelines to suggest antithrombotic treatment in both cases nor in regular patients nor in thrombophilic patients. Yet during ART procedures may be present additional prothrombotic condition that may suggest us to evaluate to add antithrombotic treatment to prevent VTE.

Introduction

Assisted reproductive technologies (ART) are associated with an increased risk to develop venous thromboembolism (VTE) if compared to spontaneous pregnancy. VTE may occur after a spontaneous conception nearly in 0.1% of pregnant women [1,2] while in women undergoing ART this incidence may reach a three-four fold increase [3]. Several prothrombotic mechanisms seem to be involved and the most relevant of them are related to the pharmacological ovarian hyperstimulation. This medical treatment, needful to have an increased oocytes number to be recruited for ART is able to increase the procoagulant status [4] as showed by several authors. Yet, although this trend to hypercoagulable state and to thrombotic disorders is well known, pharmacological thromboprophylaxis to prevent VTE in women next to ART is not suggested by international guidelines [5]. A critical problem in real life management of VTE risk of this clinical setting is related also to the duration of VTE risk because frequently thrombotic events occur early in first trimester of pregnancy after ART [6]. Similarly screening to detect thrombophilia in order to plan primary thromboprophylaxis for VTE in women next to ART is not suggested routinely by international guidelines as for recurrent pregnancy loss [7]. Here we report a short review of the usefulness of thromboprophylaxis to prevent VTE in women ongoing ART.

LMWH and VTE in ART

In vitro fertilization (IVF) cycles with following successful pregnancy were very recently reported associated with increased incidence of VTE compared to unsuccessful IVF cycles or with spontaneous pregnancy [8,9]. Moreover this risk seems to be significantly higher during the first trimester [9]. The increase in thrombotic risk of this clinical setting is present because a complex interaction between gene and environmental risk factors. A fundamental role is played by pharmacological ovarian stimulation that induces a 100- fold increase of clotting power [4,10] as testified by several markers of hypercoagulation and also because induced haemoconcentration. These pharmacological and pathophysiological prothrombotic conditions are associated to other thrombotic risk factors as age, BMI, thrombophilias and smoking [11,12]. Yet, from an epidemiological point of view an increased rate of upper limb DVT seems to occur in women that perform ART and this associated may be present because slow blood flow in superior vena cava system [13,14]. The gene environmental interaction and the association of multiple prothrombotic conditions in the occurrence of VTE after ART is are confirmed also by the evidence that nearly
50% of cases occur despite thromboprophylaxis with LMWH [13]. However, the occurrence of VTE in women after ART is associated to a not-high rate of pulmonary embolism in particular when diagnosis and treatment start early. The most common used and studied drugs are low molecular weight heparin and also in this condition suggested dose regimens are 1 mg/kg twice daily [13].

**VTE Prophylaxis with LMWH after ART**

Several authors suggest treatment of low doses of low molecular weight heparin in women ongoing ART for several reasons (e.g., the presence of a thrombophilic condition, the reported reduced rate of incidental VTE, increased rate of following pregnancy and so on) but an open suggestion by international guidelines is not present [1,14]. Probably this lacking clinical indication is due to the absence of randomized clinical trials with predefined goals both on VTE prevention or successful pregnancy after ART. Available studies concerning the incidence of VTE during thromboprophylaxis with LMWH in women ongoing ART reported a very low incidence of VTE in several studies [15,16] both for thrombophilic and not-thrombophilic women [15,16]. On the other hand retrospective analysis by the RIETE registry showed that VTE occurs to thromboprophylaxis in several times [13]. Moreover, several studies showed that the administration of prophylactic doses of LMWH in women ongoing ART may increase the rate of successful pregnancy [15,16] in particular in women older than 35 year; unfortunately this data was not confirmed by others authors. Yet, from a clinical point of view, the PADUA score is suggested to screen inpatients that need for pharmacological thromboprophylaxis [17].

A pharmacological thromboprophylaxis for inpatients is suggested, in fact, by international guidelines if patients show several thrombotic risk factors [18] and women ongoing ART frequently showing their anamnesis the presence of several thrombotic risk factor as hormonal treatment, surgical approach, bed rest after surgery, presence of thrombophilic condition and so on.

So the main clinical question is the following: should we ignore these clinical prothrombotic risk factors or should we consider these prothrombotic risk factors in order to choose if VTE with LMWH may be helpful in this clinical setting to prevent VTE? For this reason another point that needs to be discussed is concerning the timing of LMWH prophylactic regimen. Also in this case data available in the literature may seem confused because all studies reported mixed populations that contemporaneously need to prevent VTE and to increase successful pregnancy after ART. For this reason some authors suggest to starting prophylactic doses of LMWH during pharmacological ovarian hyperstimulation [15] while others reported good results also giving prophylactic doses of LMWH after embryo transfer [19].

So, better addressed trials are needed to focus the best clinical approach.

**Conclusions**

ART procedure may be associated with increased risk of VTE for several reasons starting from hormonal treatment and biological haemostatic changes of treated patients to the following successful pregnancy. The needful support of LMWH to prevent VTE incidence is not supported by international guidelines nor for regular patients nor for thrombophilic women but LMWH is probably implicated also in biological changes that may favorite ART procedures per se. Because during ART procedures may be present other additional prothrombotic condition clinicians should be performing a thorough clinical evaluation to establish if an additional antithrombotic treatment of LMWH is needed. There are not data onto the optimal time to start antithrombotic treatment for LMWH.

**References**
