CASE REPORT

Lower limb ischemia in a thrombophilic woman during ovarian stimulation for assisted reproduction techniques

Ischemia critica all’arto inferiore in soggetto trombofilico sottoposto a iperstimolazione ovarica

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KEYWORDS
Hormone therapy; Assisted reproduction protocol; Controlled ovarian stimulation; Thrombophilic subject; Factor V Leiden-related thrombophilia.

Summary
Introduction: Women receiving hormone therapy as part of assisted reproduction protocols are at increased risk for thrombosis. Controlled ovarian stimulation may be a risk factor for thrombotic events, and thrombophilic subjects are more prone to develop thrombosis during hormone therapies.

Materials and methods: We report a case of arterial thrombosis of the iliaco-femoropopliteal axis, which occurred in a young woman with Factor V Leiden-related thrombophilia, who was receiving recombinant follicle-stimulating hormone and leuprorelin in preparation for in vitro fertilization and embryo transfer, and pharmacological thromboprophylaxis with enoxaparin.

Results: The thrombosis resulted in critical limb ischemia whose clinical evolution is described.

Discussion: Further research is needed to identify the best strategy for reducing the thrombotic risk associated with assisted reproduction protocols and to determine whether these women should receive pharmacological thromboprophylaxis.

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Introduction

The association between thrombophilia and female infertility due to pregnancy loss is well known both for inherited thrombophilia and acquired thrombophilia [1], while the association between thrombophilia and unexplained female sterility is still matter of discussion in particular for women who underwent repeated in vitro fertilisation (IVF) and embryo transfer (ET) failures [2]. Some authors found an association between thrombophilia and/or hypofibrinolysis and repeated failures to assisted reproduction techniques (ART) [3] while other authors did not [4]. A thrombotic risk is associated with hormonal therapies. Also, IVF procedures involve the controlled pharmacological stimulation of ovarian follicles using gonadotrophin releasing hormones and exogenous gonadotrophins, inducing several haemostatic changes [5,6]. So, ovarian controlled stimulation may be a risk factor for thrombotic events and of course thrombophilic subjects are more prone to develop a thrombosis during hormonal therapies [7]. Because thromboembolic disease as a complication of ovarian stimulation is generally considered to be a rare event, ovarian stimulation may cause life-threatening thromboembolic complications in venous or arterial districts. Venous thromboembolism seems to be more frequent than arterial thromboembolism [8] and upper limb deep vein thrombosis is the most common venous thrombosis [7]. However also arterial thrombosis have been reported in the literature.

We here report a single case of arterial lower ischaemia of a young thrombophilic women during pharmacological thromboprophylaxis.

Case history

A 38-year-old woman with nicotin abuse, of 64 kg, felt a lower limb pain, like an ischialgia, without edema, increasing during exercise and associated with a light cyanosis. The pain was not reduced by analgesic treatment for 2 days performed with paracetamol 1 g twice daily and non-steroidal anti-inflammatory drugs (NSAIDs) (i.e., nimesulide 100 mg twice daily). She was next to ART and indication to IVF-treatment was due to severe oligospermia of her partner. Therefore an intracytoplasmic sperm injection (ICSI) was planned and based on pharmacological ovarian hyperstimulation and on IVF and embryo implantation. Hormonal therapy was based on the administration of recombinant follice-stimulating hormone (FSH; i.e. alpha-follitropin 300 U daily for 1 days) and leuprorelin 3.75 mg for IVF-ET. In particular symptoms (i.e. ischialgia, without edema, increasing during exercise and associated with a light cyanosis) started at day 9 of FSH-stimulation. At this time, 17-beta-estradiol value was 1,800 pg/mL and the last ultrasound pelvic scan showed 9 ovarian follicles without ascites or other signs of ovarian hyperstimulation syndrome. Hemoglobin, hematocrit and platelet count were all normal.

Because the patient was carrier of heterozygosity for Factor V Leiden (FVL) gene variant and had had a previous pulmonary embolism at the age of 18 years and other thrombotic events (table 1), she was performing thromboprophylaxis with enoxaparin 100/ kg (i.e. 6,000 U daily). Also, her mother was carrier of heterozygosity for FVL and had had a pulmonary embolism because a post-traumatic immobility (right leg fracture) during thromboprophylaxis with enoxaparin 4,000 U daily at the age of 62 years (table 2). The patient previously performed other three unsuccessful ART and also in these occasions she performed thromboprophylaxis with enoxaparin 6,000 U daily without complications.

Therefore, although the pain was likely to be an ischialgia and because previous vascular events reported by the patient were related to venous thromboses and not arterial thrombosis, a vascular ultrasound scan of lower limb vessels with color-Doppler flow-examination was performed 2 days after starting treatment with NSAIDs. The procedure showed full thrombosis of iliacofemuropopliteal arterial axis without distal flow into distal peripheral arteries of leg and foot. The patient also performed a lower limb angiography to evaluate the feasibility of revascularization by means of percutaneous angioplasty (PTA) to restore blood flow, but the full thrombosis of iliacofemuropopliteal axis was confirmed and the feasibility to perform PTA or surgery was ruled out. Thus, a pharmacological treatment with low unfractioned
heparin 35,000 U daily with an aPTT range of 1.5–2.5 was started and associated to a treatment with iloprost 2 ng/kg/min. Seven-day treatment resulted in a light improvement of blood flow to the lower limb as assessed by a new ultrasound scan of lower limb vessels with color-Doppler flow-examination. However, the local haemodynamic evidence and personal symptoms revealed the occurrence of a severe claudicatio intermittens with its related morbidity and reduced quality of life. On the other hand, oocyte retrieval was not performed because the clinical outcome of lower limb ischemia was not foreseeable. Data about fertilization rate and next pregnancy outcome are lacking.

**Discussion**

Arterial thromboembolism may be a complication of pharmacological ovarian stimulation for ART. Several cases of strokes or carotid/vertebral thrombosis have been reported while acute coronary syndromes, intracardiac thrombosis and aorta or iliacofemoral thrombosis with following lower limb ischemia are more rarely described [8]. Common risk factors (i.e. smoking, hypertension, diabetes, dyslipidaemia) are sporadic and thrombophilia may be associated [8].

Thrombotic events occurring in women undergoing ART are usually associated to ovarian hyperstimulation syndrome while they have rarely been described in patients with controlled ovarian stimulation as in the case that we reported. Follicles number and 17-beta-oestradiol levels were in fact within expected range and there were no other signs of ovarian hyperstimulation as ascites.

Currently, thrombophilia testing to evaluate thrombotic risk in women undergoing ART is not suggested by international guidelines and pharmacological thromboprophylaxis is not recommended. In our case, the patient had previously been treated with enoxaparin because of the presence of personal and familiar history of pulmonary embolism and because carrier of heterozygosity for FVL. This case report underlines the importance of the timing of diagnosis and in particular the difficulty of reaching an early diagnosis. Also, our case indicates the risk to perform pharmacological ovarian stimulation in women with previous thrombotic disease with or without thrombophilia and provides evidence that thromboprophylaxis should be considered for women undergoing ART during pharmacological ovarian stimulation. Any type of thrombotic disorder of arterial or venous district, in fact, may be associated to a life-threatening complication and it may increase subsequent morbidity and/or mortality in particular if pregnancy is obtained by ART. In these cases, in which major vascular complications may occur, it might be advisable to refrain from ART in order to avoid further complications during a possible pregnancy. Further studies are needed in order to assess the best approach to thrombotic risk and the opportunity of pharmacological thromboprophylaxis in women undergoing ovarian stimulation for a ART.

**Conflict of interest**

The authors have no conflict of interest to disclose.

**References**

[1] D’Uva M, Di Micco P, Strina I, Ranieri A, Alviggi C, Mollo A, et al. Etiology of hypercoagulable state in women with recurrent fetal loss without other causes of miscarriage from Southern Italy: new clinical target for antithrombotic therapy. Biologics 2008;2(4):897–902.

[2] Di Micco P, D’Uva M, Lodigiani C, Rota LL. Thrombophilia and repeated in vitro fertilisation and embryo transfer failure: an open issue. Thromb Haemost 2010;103(2):472–3.

[3] Coulam CB, Jeyendran RS, Fishel LA, Roussev R. Multiple thrombophilic gene mutations are risk factors for implantation failure. Reprod Biomed Online 2006;12(3):322–7.

[4] Martinelli I, Taioli E, Ragni G, Levi-Setti P, Passamonti SM, Battaglioli T, et al. Embryo implantation after assisted reproductive procedures and maternal thrombophilia. Haematologica 2003;88(7):789–93.

[5] Bar J, Orvieto R, Lahav J, Hod M, Kaplan B, Fisch B. Effect of urinary versus recombinant follicle-stimulating hormone on platolet function and other hemostatic variables in controlled ovarian hyperstimulation. Fertil Steril 2004;82(6):1564–9.

[6] Biron C, Galtier-Dereure F, Rabesandratana H, Bernard I, Aguilar-Martinez P, Schved JF, et al. Hemostasis parameters during ovarian stimulation for in vitro fertilization: results of a prospective study. Fertil Steril 1997;67(1):104–9.

[7] Chan WS, Ginsberg JS. A review of upper extremity deep vein thrombosis in pregnancy: unmasking the 'ART' behind the clot. J Thromb Haemost 2006;4(8):1673–7.

[8] Girolami A, Scandellari R, Tezza F, Paternoster D, Girolami B. Arterial thrombosis in young women after ovarian stimulation: case report and review of the literature. J Thromb Thrombolysis 2007;24(2):169–74.