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REVIEW

In vitro Fertilization Procedures with Embryo Transfer and Their Association with Thrombophilia, Thrombosis and Early Antithrombotic Treatments

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Abstract: In vitro fertilization (IVF) procedures have been frequently associated with antithrombotic treatments, in particular, to aspirin or low-molecular-weight heparin (LMWH). The rationale of this treatment is based on the increase of thrombotic risk occurring in this clinical context. Indeed, both prothrombotic changes of coagulation parameters specifically related to IVF procedures as well as the presence of potential thrombophilic alterations may concur to increase the risk in these women. Furthermore, the presence of thrombophilia has been suggested as a potential cause of recurrent IVF failures. Therefore, antithrombotic treatments have been historically planned to prevent thrombotic disorders during pharmacological ovarian stimulation and/or to increase a successful rate of pregnancy and live births after IVF with embryo transfer. However, up to date, the role of inherited and\or acquired thrombophilia is still debated as well as a univocal therapeutic approach is lacking in women with infertility. The administration of antithrombotic drugs differs in several studies and even the dosages of aspirin and\or low-molecular-weight heparin are different. This review focuses on underlining current evidence on the role of thrombophilia and thromboprophylaxis in women selected for IVF with embryo transfer.

Keywords: sterility, in vitro fertilization, thrombophilia, low-molecular-weight heparin, aspirin, ovarian hyper-stimulation syndrome

Background

In vitro fertilization (IVF) procedures with embryo transfer (ET) reach only one-third of achieved pregnancy, as the majority of them fails.[1] The main reasons for IVF failures are related to defects in implantation. Therefore, a relevant part of these patients may be affected by repeated IVF failures.[2] Several reasons have been hypothesized for recurrent IVF failures and the presence of molecular thrombophilia and\or the use of any antithrombotic drugs such as aspirin or low-molecular-weight heparin (LMWH) are still a matter of discussion in this clinical setting.[2] From a methodological point of view, in fact, the association of molecular inherited or acquired thrombophilia with secondary sterility (ie, recurrent pregnancy loss) is well known. On the other hand, the association of thrombophilic defects with primary sterility has been suggested by several articles but not confirmed by other reports.[2,3] On this way, in the last few years, the effect of LMWH administered during the IVF procedures has been extensively studied in several studies.[4] Indeed, the effect of LMWH on trophoblast biology has not been extensively studied, but the available data suggest a possible beneficial effect of LMWH on embryo implantation. Moreover, because of the significant impact on live

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birth rates of LMWH in women with thrombophilia, this kind of treatment has been considered as a potential therapy for several patients ongoing IVF-ET, in particular in those with recurrent implantation failures.[5] In a parallel manner, since more and more experiments have established that aspirin play an important role in female infertility, several reports also tested its utility in IVF procedures.[6]

This review summarizes actual knowledge and perspectives regarding the presence of thrombophilia and the use of antithrombotic drugs during IVF-ET procedures, focusing on clinical aspects regarding the use of thromboprophylaxis to prevent VTE in this clinical setting.

Methods

For this review, we researched articles from MEDLINE, starting from 2001 until present. The articles were selected after searching for the terms sterility, recurrent\repeated in vitro fertilization failures, recurrent implantation failures (RIF), thrombophilia, ovarian hyper-stimulation syndrome, low-molecular-weight heparin, aspirin.

Only studies which did not exclusively consider the presence of thrombophilia as potential cause of unexplained primary female infertility and\or RIF were included. This selection may represent a study limitation. However, actually, thrombophilia is not considered as the most frequent cause of primary female infertility. Therefore, this study limitation may be useful for the interpretation of clinical data concerning thrombophilia and antithrombotic treatment in IVF procedures.

Alteration of Haemostasis in Controlled Ovarian Hyper-Stimulation and Thrombosis

Although the association between pharmacological treatment with gonadotropins and other hormonal drugs were considered to be associated with venous thromboembolism (VTE) only in sporadic cases, a thorough clinical revaluation of this risk has been considered after the report of Erikson et al This study underlined a three-fold increase of venous thromboembolic events in pregnant women after IVF-ET compared to those with spontaneous pregnancy.[7]

The association between pharmacological treatment for female infertility and thrombotic risk were previously considered only when ovarian hyper-stimulation syndrome (OHSS) was detected in patients undergoing IVF-ET.[8] However, more recent studies or case series reported a considerable incidence of thrombotic events even in women without OHSS.[9] In a previous report, cigarettes, age, and increased BMI were associated with a major risk of developing a VTE during IVF procedures.[10] Indeed, during treatment with gonadotropins, alterations of haemostasis have been found. This acquired hyper-coagulable state seems mainly due to the decrease of clotting anticoagulants such as protein C, protein S and antithrombin and to the increase of endothelial markers of vascular damages as thrombomodulin.[11] Moreover, patients undergoing IVF-ET treatments may also be carriers of inherited thrombophilia, characterized by the presence of factor V Leiden and \or prothrombin a20210g and\or MTHFR gene mutations, that could increase the trend toward vascular thrombosis. From a clinical point of view, this trend has been confirmed by a recent study conducted with data from the RIETE registry that reported several cases of VTE occurring in women with recent IVF-ET without OHSS.[8]

Ovarian Hyper-Stimulation Syndrome and Thrombotic Risk

Ovarian hyper-stimulation syndrome (OHSS) is the most severe complication of controlled ovarian stimulation. It leads to fluid shifts into the third space and hemoconcentration. OHSS may be considered an occasional complication of pharmacological treatment of female infertility with exogenous gonadotropins.[12] It may be as high as 25% of all ovarian stimulation and it is associated with very high levels of serum estradiol (ie, >2500–3500 pg/mL) and to the presence of an increased number of ovarian follicles.[12] From a clinical point of view, OHSS is associated with nausea, vomiting, sudden weight increase, ascites and, rarely, to pleural effusion and thromboembolic complications.[13] Thromboembolic complications usually affect the venous system. However, a relevant number of arterial thrombosis have also been reported.[14] The pathophysiology of thrombosis in these cases is multifactorial and mainly related to changes in clotting and fibrinolytic activities and to hemoconcentration due to pharmacological treatment. The increase of prothrombotic markers, in fact, such as d-dimer, prothrombin fragment 1+2 and thrombin-antithrombin complexes have already been described in several reports and even resulted in an association to an increase of hypofibrinolytic markers as TFPI and PAI-1.[8,15] Moreover, decreased levels of protein C, protein S and antithrombin have also been described during OHSS.[8,15]

On the other hand, these molecular changes may interact with possible-inherited conditions such as hereditary thrombophilias (ie, the presence of factor V Leiden and

prothrombin a20210g gene polymorphisms) and\or acquired conditions such as hemoconcentration induced by the extravasation of fluids due to hormonal effects, thus increasing the risk of a vascular thrombosis.

From a statistical point of view, VTE has been more frequently reported than arterial thrombosis. Furthermore, in a relevant number of cases, VTE has even been reported in unusual sites such as the upper limbs and neck.[16]

Thrombophilia in Recurrent IVF Failures

Thrombophilia has been frequently investigated in patients with repeated implantation failures,[17] because the clinical association between alteration of haemostasis with a trend toward hyper-coagulable state and secondary female infertility due to recurrent pregnancy loss is well known.[18] The presence of thrombophilia may induce local vascular impairment with consequent difficulty in embryo implantation. In several studies, Factor V Leiden mutation has been found to be more prevalent in the IVF failure group.[19] Another intriguing study, although in a small population, found a role of MTHFR mutation, homocysteine and folate metabolism in the presence of unexplained primary sterility.[20] However, in other studies, although a considerable number of thrombophilic subjects in selected populations of women with recurrent implantation failures was found, a significantly statistical difference was not found. Therefore, the clinical debate in this field is still open.[3,21–26]

Thrombophilic defects other than factor V Leiden polymorphism, prothrombin a20210g gene polymorphism or MTHFR gene polymorphism have not been found useful in these clinical settings.[3,21–26] On the other hand, contradictory data were found if acquired thrombophilia, as anti-phospholipid syndrome, was considered as the clinical cause of recurrent implantation failures. Female infertility, in fact, has been associated with the presence of several patterns of autoantibodies and anti-phospholipid antibodies have been detected in these patients. However, none of these studies included large populations.[27]

Yet, specific analysis on patients with recurrent IVF failures and combined thrombophilia for the presence of multiple-inherited defects or with inherited thrombophilia and anti-phospholipid syndrome has not completely investigated as far as the exact percentage of patients with recurrent IVF failures and clotting inhibitors deficiency (ie, antithrombin deficiency and/or protein S deficiency and/or protein C deficiency).[28]

In the last few years, the clinical debate on the presence of thrombophilia in this setting has represented a daily clinical issue, born not only to focus the cause of recurrent IVF failures but also to understand the potential therapeutic role of antithrombotic treatments to improve the outcome of IVF-ET.

Therefore, a number of studies have been focused on the role of LMWH and aspirin in patients with recurrent implantation failure as shown below in a specific paragraph.

Aspirin in IVF Procedures

The improvement of the clinical pregnancy rate is a constant challenge in reproductive medicine, and aspirin is one of most discussed drugs in this context. With the development of knowledge about infertility, more and more experiments have suggested that aspirin may play an important role in female infertility and assisted reproductive technology (ART). Aspirin, indeed, is used with the aim of optimising the outcome of ART and subsequently the chance of live birth in women subjected to ART. The objective of antiplatelets therapy with aspirin is to increase the successful rate of potential pregnancy after embryo transfer and it is based on the useful action that aspirin may exert on cytokines network,[29] cyclo-oxygenase action[30] and prostaglandins production.[31] This anti-inflammatory effect of aspirin is also testified by the decrement of levels of C reactive protein as biomarker of inflammation in several clinical settings. So, the administration of aspirin is associated both to its antithrombotic property for antiplatelet action and to its anti-inflammatory action.

Historically speaking, the pathophysiological hypothesis took place after improvements found in the outcome in unselected pregnant patients with anamnesis of recurrent unexplained foetal growth retardation[32] or recurrent foetal loss.[17]

However, the role of aspirin in women with infertility is controversial according to data available from several clinical studies.[30,33–39] Actual data seem to be positive only if aspirin is administered to increase implantation rates due to its support to intracytoplasmic sperm injection (ICSI) treatment cycles in addition to traditional IVF.[30,39] Moreover, the most appropriate time to start aspirin in women undergoing IVF-ET, the length of its treatment and useful dosages are also constantly matter of discussion in the scientific community. Furthermore, the rate of OHSS did not decrease when aspirin was associated with hormonal treatment in particular conditions such as polycystic ovary syndrome.[33–38]

According to data from a recent meta-analysis on this topic, low-doses of aspirin could improve the pregnancy rate in IVF-ET, with the recommended dose of 100 mg/day.[40] Yet, all the referenced articles, as reviews and met-analyses, require further randomized clinical trials to confirm this clinical evidence. Reported data, in fact, may appear controversial. Of course, a better point of view could appear if treated patients have routine clinical, laboratory and instrumental check during the IVF-ET protocol; in this way an appropriated clinical opinion regarding the use and the advantage of aspirin during IVF procedures may be obtained.

LMWH in IVF Procedures

The use of LMWH in women undergoing ART procedures has been an issue of investigation for a number of years. Historically, its administration was suggested for thrombophilic women that were selected for IVF-ET in order to reduce the risk of VTE.[4] Yet, more recently, the utility of LMWH has also been suggested to increase the rate of implantation achievement in women with recurrent failures to ART procedures.[4,19]

Currently, two different strategies are being covered to administer LMWH in women undergoing IVF-ET: the first with the aim of preventing thrombosis in women with OHSS or with other thrombotic risk factors;[2] the second one to increase the rate of successful pregnancies in patients with recurrent failure to ART procedures.[41] The rationale of administering LMWH in order to prevent VTE during ART procedures is related to the fact that during their pharmacological treatment, patients undergoing IVF-ET, are sequentially subjected to several thrombotic risk factors such as different and repeated hormonal therapies, surgical approach for oocyte retrieval, hypomobility, possible thrombophilia and potential pregnancy.[42,43] This approach could also be confirmed in clinical settings different from female infertility, since the presence of several of these items is even found in different clinical scores such as the PADUA score.[44]

On the other hand, as previously underlined, heparin has also been considered as an adjunct drug in assisted reproduction, in particular during peri-implantation, in order to increase the rate of successful pregnancies.[45–47] LMWHs as tinzaparin and enoxaparin may also modulate the expression of heparin binding epidermal growth factor (HB-EGF) in addition an effect on decidual and endometrial stromal cells has been reported.[48] Furthermore, heparin, similarly to heparin sulfate proteoglycans or HB-EGF, should be involved in blastocyst adhesion, invasion and proliferation.[49] For this reason, LMWH is usually administered at or after oocytes collection or at embryo transfer and then continued once daily.[45–47] So, the effects of the administration of LMWH) in subfertile patients with two or more unexplained unsuccessful IVF-ET has been considered in several studies. Available studies on LMWH in assisted reproduction are characterized by heterogeneous inclusion criteria and a lack of proven effectiveness,[4] although a positive trend has been found in several reports in which patients with RIF were treated with LMWH.[45,47,49,50] On the other hand, in a cohort study, the administration of LMWH with prednisolone in subfertile women with repeated implantation failures does not improve clinical pregnancy rates.[46]

Yet, Lodigiani performed a retrospective observational analysis of patients with at least two IVF/intracytoplasmic sperm injection cycles with implantation failures submitted to further ART cycles with or without administration of LMWH, finding a higher pregnancy rate in patients treated with LMWH compared with controls.[2] Moreover, in another study from the same clinical group, Lodigiani et al underlined a positive effect of parnaparin, administered once a day for the whole cycle, on clinical pregnancy rate in infertile women undergoing in IVF-ET.[51] Similar data have been reported in a study conducted by Berker et al on patients with previous IVF failure treated without success when LMWH was not used and with success after the administration of LMWH.[52]

In conclusion, heparins have been evaluated for their use in patients with recurrent implantation failures and although there is not yet enough evidence to recommend its use to improve pregnancy outcomes in these patients, there is clinical evidence that specific subgroups of these patients with similar clinical characteristics may show increased pregnancy rates if treated with LMWH.

In addition, a further problem is related to the timing of the administration of LMWH, because it was different in all reported studies that showed improved outcomes.

LMWH and Aspirin in IVF Procedures

The association of low dose of aspirin with prophylactic dose of low-molecular-weight heparin in women undergoing ART procedures such as IVF-ET has not been extensively studied[53] by clinical studies, although some authors have suggested it. Several experts are actually evaluating the potential increase of bleeding complication during oocyte retrieval and after embryo transfer, before suggesting any type of extensive clinical experience.

For patients with anti-phospholipid syndrome, a combined antithrombotic treatment has been discussed and suggested.

Indeed, besides antithrombotic actions of both drugs, heparin might even bind to anti-phospholipid antibodies, interfering with the pathophysiological mechanisms of anti-phospholipid syndrome. This may be a crucial point because a specific evaluation and care of thrombophilias and/or autoimmune conditions could be beneficial for the management and outcome of primary infertility for patients with at least one failed IVF cycle.[53]

Conclusion

IVF procedures are associated with an induced hypercoagulable state, especially when OHSS is present or a successful pregnancy is obtained. Other risk factors, such as the presence of thrombophilias and\or anti-phospholipid syndrome may be present. For this reason, antithrombotic treatments are frequently suggested in this clinical setting in order to prevent vascular thrombosis. Furthermore, in some studies, antithrombotic treatments even seem associated with an increased rate of achieved pregnancy. Therefore, in the daily clinical practice, thrombophilia is generally researched in order to select patients at increased risk for VTE, which may mostly benefit from thromboprophylaxis (ie, prevention of VTE as well as to increase the rate of pregnancy after IVF-ET). However, antithrombotic regimens used in all the considered studies are different and further studies are needed to better address this complex clinical condition.

Disclosure

The authors report no conflicts of interest in this work.

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