Antithrombotic therapy in idiopathic infertility

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ABSTRACT

Idiopathic infertility is an emerging condition among couples, who face difficulties in accomplishing their family plan, in which no organic cause of reproductive failure can be found. Since 1978 the role of assisted reproductive techniques (ARTs) has been established as the best treatment option with increasing success rate in all-cause infertility couples, but still with some limitations and unfavorable outcomes including idiopathic infertility. Aspirin and heparin are commonly used as adjuvant therapy in women with idiopathic infertility undergoing ARTs, however robust evidence proving the efficacy of this therapeutic approach from purposely designed controlled clinical trials is still lacking. A systematic literature search on the use of antiplatelet and/or antithrombotic therapy in idiopathic infertility was performed in PubMed using infertility, heparin and aspirin as search terms, focusing our attention on clinical trials. Despite some trials had shown a benefit of the administration of heparin or aspirin, in terms of increasing pregnancy and live birth rate in women undergoing ARTs, no routine use of these drugs is recommended as adjuvant therapy for unselected women with idiopathic infertility. Routine use of low dose aspirin and heparin in women undergoing ARTs should be discouraged giving the lack of high-quality evidence and potential harm compared to marginal benefits. Their use can be considered after a comprehensive evaluation of risk-benefit ratio of single individual, deriving from a multidisciplinary approach involving experts in hemostasis. However, large multicenter randomized clinical trials are warranted to validate efficacy and safety of such approach in reproductive medicine.

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Introduction

Infertility is a disabling condition with both medical and psychological consequences and is defined as the failure to achieve a successful pregnancy after 12 months or more of regular, unprotected sexual intercourses.[1,2] In western countries increasing age of both partners and the tendency to delay childbearing, represent the most relevant factors that may contribute to conception failure. Treatment strategy starts from the evaluation of detectable and reversible causes in both partners, but in about 30% of all cases, no apparent organic cause can be identified, defining a condition called idiopathic infertility.[3]

In order to increase the fertility rate, several assisted reproductive techniques (ARTs), such as *in vitro* fertilization (IVF) and intracytoplasmic sperm injection (ICSI), have been developed. Unfortunately, success rates remain low: as reported by the European Society of Human Reproduction and Embryology pregnancy rate per transfer was 34.1% and 32.1%, for IVF and ICSI respectively,[4] being implantation failure the most limiting factor.[5] In a recent analysis of data derived from European registries, Griesinger and Larsson drew attention to the possibility of an underestimation of success rates in women undergoing ARTs, since success rates of IVF/ICSI are conventionally reported per treatment cycle or embryo transfer; therefore, treatment attempts of women with a poor prognosis will be over-represented, compared to women with a good prognosis. The authors suggest putting at the center of the analysis the couple, with its own attempts, suggesting using statistical models taking into account the correlation between outcome of cycles within women rather than the total number of cycles.[6]

It is well known that pregnancy poses a high thromboembolic risk, due to a physiological hypercoagulable state, secondary to both an increase in procoagulant factors and a decrease in anticoagulant factors and fibrinolysis.[7] The devel-

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opment and maintenance of placental circulation are critical for a successful pregnancy and rely heavily on the structural modification of spiral arteries and the invasion of trophoblasts. This process involves the remodeling of the maternal spiral arteries to increase their diameter and reduce resistance, allowing for an adequate blood supply to the developing fetus. The invasion of trophoblasts, which are specialized cells originating from the outer layer of the blastocyst, plays a key role in this modification by penetrating the uterine lining and facilitating the transformation of these arteries. This invasion is thought to be supported by the pregnancy-induced procoagulant state, a physiological condition where the blood's ability to clot is enhanced to protect against hemorrhage during childbirth. On the contrary, impaired uterine perfusion with deficient blood flow, may reduce endometrial receptivity and cause embryo implantation failure.[8]

Thrombophilia is a condition characterized by an increased tendency for the blood to clot and a consequent risk of thromboembolism due to changes in hemostatic mechanisms, and therefore has been hypothesized to play a role in infertility. Thrombophilia can be either congenital or acquired. Congenital factors include the factor V Leiden mutation (FVL), the prothrombin (PT) G20210A mutation, and deficiencies in natural anticoagulants such as antithrombin, protein C, and protein S. Among the acquired forms, antiphospholipid syndrome (APS) is most commonly associated with adverse pregnancy outcomes.

The role of thrombophilia in infertility is controversial, with no studies demonstrating a definitive cause-effect relationship. The hypothesis of a causal relationship is supported by the high prevalence of thrombophilic conditions in patients with infertility, although this finding is not consistent across all studies.[9-18]

The underlying pathophysiological mechanisms may involve the clotting of placental vessels, effects of hypo-fibrinolysis on trophoblast migration, or alterations in folic acid metabolism. Despite this, several cohort studies and meta-analyses have shown that the presence of thrombophilic markers, both inherited and acquired, did not result in worse pregnancy rates or implantation failure.[19-29] Studies conducted in this field are primarily observational and exhibit high heterogeneity in protocols, selection of thrombophilic markers, inclusion and exclusion criteria of subjects, timing of initiation and duration of anticoagulant therapy, as well as the types and doses of anticoagulants used.

Given the small sample sizes and heterogeneity of results, the evidence is considered to be of very low quality. Furthermore, comprehensive testing for thrombophilia is not globally available, is expensive, and affects accessibility. In the absence of any proof of effective treatment, such investigation is of low value in achieving the desired outcomes.

Giving the lack of strong evidence from available studies, current guidelines do not recommend routinely thrombophilia screening in cases of unexplained infertility or recurrent pregnancy loss. However, it is suggested to perform such a screening for research purposes or in patients with additional risk factors for thrombophilia [previous venous thromboembolism (VTE), or family member with hereditary thrombophilia].[30,31]

We have to discriminate also between *low-risk thrombophilia* such as FVL or FII G202010A heterozygosity, a condition that in absence of family history or without previous VTE doesn't require prophylactic use of heparin during pregnancy, and *high-risk thrombophilia*, such as to antithrombin (AT) deficiency, homozygotes, or double heterozygotes for either FVL or FII202010A, that should require ante-partum administration of heparin.[32,33] Interestingly, a retrospective multicenter family study, involving 52 double heterozygous carriers of FV Leiden and prothrombin G20210A compared to 104 single carrier women for each of the two genetic factors and 104 women without thrombophilia, found no difference for the risk of first VTE during pregnancy and puerperium.[34] Moreover, spontaneous VTE seems not to be more frequent in double heterozygotes than in single heterozygotes or FVL homozygotes, being deep vein thrombosis of the lower limb the most frequent VTE location of double heterozygotes; double heterozygotes women have a higher risk of VTE than single heterozygote.[35] However, in women with a history of thrombosis during pregnancy and puerperium, single mutation of G20210A prothrombin-gene or FVL are associated with higher risk of VTE, and among women with both mutation the risk is even higher than that among women with single mutation.[36] As regard outcomes in women with homozygous FVL mutation, compared to heterozygous and non-carriers, a multicenter retrospective study involving 10 French Hemostatic Unit, showed increased risk of late fetal loss only in women who were homozygous compared with those non-carriers.[37] Indeed, the risk of late fetal loss was similar between heterozygous women compared to non-carriers. A comprehensive evaluation of the role of Factor V Thrombophilia is provided by Kujovic in a review article; factor V Leiden can be found in approximately 20-40% of pregnancy related VTE and linked to increased thrombotic risk during pregnancy and puerperium. The risk of VTE increases progressively from women with heterozygous to homozygous FVL, and is particularly high in combination with other coexisting thrombophilic conditions.[38] Among acquired thrombophilic conditions, antiphospholipid syndrome, a clinical entity characterized by recurrent pregnancy losses and premature birth and persistence of autoantibodies directed against phospholipid-binding proteins, represents a *high-risk thrombophilia*, in which the combined use of heparin and low-dose aspirin is well-known to improve pregnancy outcomes and supported by pathogenetic mechanisms.[39,40]

Therefore, antithrombotic therapy is often prescribed to women undergoing ARTs procedures with the goal of increasing pregnancy and live birth rates but, given the lack of high-quality evidence confirming the benefits of low-molecular-weight heparin (LWMH) or low dose aspirin (LDA) as adjuvant therapies, the indication is still debated. According to current guidelines, LWMH is recommended in pregnant women for prevention of VTE, *e.g.* in cases of severe ovarian hyperstimulation syndrome (OHSS) or antiphospholipid antibody syndrome (APS); in the latter case, in combination with LDA, if there is a history of three or more pregnancy losses. [33] Routine use of antithrombotic therapy is not recommended in unselected women undergoing ARTs and in patients with inherited thrombophilia and recurrent pregnancy loss (RPL).[41]

Aim of our narrative review is to highlight current evidence on the role of antithrombotic therapies, aspirin and heparin, in improving pregnancy outcomes in couples with idiopathic infertility undergoing ARTs.

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Methods

Articles were selected in PubMed after searching for terms *infertility*, *heparin*, *low molecular weight heparin* and *aspirin*; we focused our attention on randomized clinical trials (RCTs).

Studies that have been included in this narrative review are shown in Tables 1[42-48] and 2.[49-63]

Heparin in assisted reproductive techniques procedures

On a molecular basis, heparin is an endogenously produced, linear polysaccharide that consists of repeated units of pyranosyluronic acid and glucosamine residues.[64] Heparins exert an indirect anticoagulant effect, by binding to AT, thus inducing a conformational change in the molecule, which results in an enhanced anticoagulant activity in the order of 1000- to 4000-fold. A pleiotropic effect of heparin was also postulated: heparin seems to interact with cytokines, matrix metalloproteinases, surface membrane proteins and growth factors, to modulate hormones and to induce a concomitant reduction in the expression of the adhesion molecule E-cadherin.[65,66] Given the complex and unique relationship between uterine and embryonic cell surface membranes, and the structural analogy of heparin to heparan sulphate,[67] a beneficial impact of heparin on the implantation process has been suggested, probably derived from the improvement of endometrial receptivity and trophoblast adhesion and invasiveness. Unfortunately, a rigorous demonstration of these phenomena is still lacking.

Nowadays low molecular weight heparin (LMWH) represents the standard of care for thromboprophylaxis and treatment of VTE during pregnancy.[68] Compared to unfractionated heparin, LMWH is characterized by an enhanced ratio of anti-Xa to anti-IIa activity, a reduced ability to activate platelets, and lower risk of bleeding and thrombocytopenia. Additionally, it has an increased bioavailability and half-life.

It is possible to consider two major issues to justify the use of prophylactic dose of LMWH during pregnancy. First, the prevention of venous thromboembolism during pregnancy and puerperium. In particular it is indicated in women at increased risk of developing OHSS and in women who experienced previous unsuccessful ART cycles as described by Grandone *et al.* in RIETE registry.[69] Second, the possibility to increase the likelihood of pregnancy in women undergoing ART cycles, based on the supposed immunomodulating effect of heparin.[70]

As hypothesized in a retrospective analysis by Lodigiani *et al*.,[71] the use of LMWH could improve the invasion of maternal vessels by syncytiotrophoblasts and reduce local microthrombosis at the site of implantation, especially in women aged 36 years and above.

In a randomized placebo-controlled clinical trial, Qublan *et al.* demonstrated the safety and efficacy of LMWH in patients with recurrent IVF failure and thrombophilia, showing not only benefits in prevention of thromboembolism, but also in improving implantation and pregnancy rates.[42] Despite some controversies, linked to heterogeneity among studies, the association of inherited and acquired thrombophilia with failure of ART has been proven.[22]

To confirm benefits of LMWH in improving outcomes in patients with at least two previous failed ART cycles without coagulation disorders or thrombophilia, Urman *et al.* conducted a single-center, open label randomized clinical trial on the use of enoxaparin from the day of oocyte retrieval until negative pregnancy test or until 12 gestation weeks. In this trial, a relative increase of 30% in live birth rates was observed in the interventional group but it resulted not significant (p=0.29).[43] A trend in favor of low-molecular-weight heparin in the subgroup of women with three or more implantation failures, was also observed by Berker *et al.,* but still not significant (p>0.5).[44]

The need for more reliable data and a larger population of patients, induced the group of Lodigiani *et al*. to perform a prospective randomized controlled trial investigating the effects of parnaparin on *in vitro* fertilization outcomes in 247 infertile women, without history of severe thrombophilia (*i.e.,* including antithrombin, protein S, protein C deficiency, homozygous FVL or FIIG20210A or double heterozygous FVL and FIIG20210A) and hormonal or active untreated autoimmune disorders.[45] Unfortunately, the study failed to demonstrate positive effects of prophylactic parnaparin sodium on clinical pregnancy rate (CPR), and even subgroup analysis per age confirmed comparable CPR and live birth rate (LBR) between groups. Similar results were obtained by Siristatidis *et al.,* in a six-center two-arm retrospective cohort study, recruiting 230 patients with two or more unsuccessful IVF/ICSI cycles:[46] no statistically significant differences, regarding clinical pregnancy and miscarriage rates, were found between intervention group, who received, in addition to standard therapy, LMWH at a dose of 3500 IU daily after embryo transfer, and control group. Therefore, authors concluded that routine use of LMWH should not be recommended in this category of patients.

Another promising treatment, that still needs further research and larger RCTs, is the coadministration of LMWH and prednisolone, whose utility seems to be related to the beneficial effect on the implantation process, improving immunotolerance towards the embryo and reducing the inflammation associated to embryo-transfer. A preliminary report by Siristatidis *et al*.[72] showed improved pregnancy outcomes with addition of prednisolone to LMWH, but the subsequent cohort study (that lacks randomization because patients preferred to receive both drugs), only confirmed a positive trend favoring the co-administration of the aforementioned drugs without achieving statistical significance.[47]

In order to clarify the role of heparin and its benefit in women with inherited thrombophilia and recurrent pregnancy loss, Quenby *et al.* conducted a large international randomized controlled trial, whose results have been recently published.[48] LMWH was administered to the intervention group (163 women) at the time of a positive urine pregnancy test until delivery, while the control group (158 women) received no additional therapy. No significant differences in live birth rates were found between groups. However, LMWH appeared to be safe, with low rate of side effects reported in intervention group.

Among studies, despite LMWH was used at different doses and starting time, no relevant side effects were reported; a relevant limit of the above-mentioned studies is also represented by different inclusion and exclusion criteria and the paucity of patients, so that benefits of LMWH could have been underestimated in the intervention group.

Table 1. Randomized and quasi randomized trials evaluating low molecular weight heparin on assisted reproductive techniques procedures.

Study	Methods	Participants (inclusion criteria)	Intervention	Outcomes	Adverse events
Qublan *et al.*[42]	Single-center, single blind (participants) placebo-controlled randomized trial	Three or more implantation failures; age 19-35 y; negative for anatomic, endocrine, immunologic and genetic causes; positive for at least one thrombophilia	Enoxaparin 40 mg/d sc from day of embryo transfer to delivery or fetal loss, saline placebo sc from day of embryo transfer to delivery or fetal loss	Live birth rate: enoxaparin: 10/42 (23.8%); control: 1/41 (2.8%) p<0.05; implantation rate: enoxaparin: 29/139 (20.9%); control: 8/131 (6.1%) p<0.001. Pregnancy rate: enoxaparin 13/42 (31%); control 4/41 (9.6%), p<0.001)	Bleeding: enoxaparin: 3/42 (7,1%); control: not specified; thrombocytopenia: enoxaparin: 2/42 (4,8%); control: not specified; bruising: not reported
Urman *et al.*[43]	Single-center, open label randomized trial	At least 2 implantation failures; age <39; negative for anatomic, endocrine, immunologic, and genetic causes; thrombophilia excluded	Enoxaparin 1 mg/kg/d sc, from the day of oocyte retrieval negative pregnancy test or until 12 gestation weeks; no treatment with LMWH	Live birth rate: enoxaparin: 26/75 (35%); control: 20/75 (27%) p=0.29. Clinical pregnancy rate: enoxaparin: 34/75 (45.3%); control: 29/75 (38.7%) p=0.41. Subgroup with at least 3 implantation failures (IR): enoxaparin: 22%, control: 16%, p=0.41	Bleeding: not reported; thrombocytopenia: enoxaparin: 0/75 (0%); control: not specified; bruising: reported some bruising at injection site in the enoxaparin group (No. not specified).
Berker *et al.*[44]	Open label quasi-randomized control trial (consecutive clinician and treatment assignment)	Two implantation failures; negative for anatomic, endocrine, immunologic, and genetic causes; thrombophilia excluded	Enoxaparin 40 mg/d sc from day of oocyte retrieval and until 12 gestation weeks or negative pregnancy test; no treatment with LMWH	Live birth rate: enoxaparin: 34/110 women (31%); control: 32/109 (30%); p>0.5. Subgroup with 3 or more implantation failures: enoxaparin 15/48 women (31%); control 10/48 women (23%); implantation rate: enoxaparin N/A (23%); control N/A (21%); subgroup with 3 or more implantation failures: enoxaparin: 23/109 (21%); control: 16/101 (16%)	Not reported
Lodigiani *et al.*[45]	Single center, randomized, prospective, controlled, stratified, open label and phase III study	Women between 18-40 years, undergoing a cycle of IVF, negative for hormonal or active untreated autoimmune disorders; severe thrombophilia excluded	Parnaparin (4250 IU or 6400 IU depending on body weight under/over 60 kg), once a day for the whole cycle; no treatment with LMWH	Clinical pregnancy rate: parnaparin 21.5%, control 26.7% (p=0.389). Live birth rate: parnaparin 18.5%, control 20.6% (p=0.757). Subgroup analysis: Clinical pregnancy rate: women ≤35 y: (22.5% *vs* 38.8%, p=0.124); 36-38 y: (21.8% *vs* 17.3%, p=0.631); 39-40 y: (19.4% *vs* 23.3%, p=0.762): Live birth rate: women ≤35 y (16.3% *vs* 32.7%, p=0.099); 36-38 y (20.0% *vs* 13.5%, p=0.443); 39-40 y (19.4% *vs* 13.3%, p=0.731).	Bleeding or thrombocytopenia 0/247 (0%); bruising: small bruises around the LMWH injection sites (No. not specified).

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Study	Methods	Participants (inclusion criteria)	Intervention	Outcomes	Adverse events
Siristatidis *et al.*[46]	Six-center two-arm retrospective cohort study	Women between 25-40 years, history of two or more failed fresh IVF/ICSI cycles, absence of coagulation and/or autoimmune disorders, endocrine or metabolic disorders, thrombophilia excluded	Enoxaparin 3500 UI/day from the embryo transfer to pregnancy test or until the third trimester of pregnancy; no treatment with LMWH.	Clinical pregnancy rate: (33/133 - 24.8% *vs* 20/97, 20.6% p=0.456) Live birth rates: (23/133 - 17.3% *vs* 14/97 - 14.4%, p=0.560).	LMWH side effects: 0% in both groups
Siristatidis *et al.*[47]	Three-center two-arm retrospective cohort study	Women younger than 45 years, with history of at least two failed fresh IVF/ICSI cycles followed by embryo transfer, absence of coagulation and/or autoimmune disorders, endocrine or metabolic disorders, thrombophilia excluded	Enoxaparin 1 mg/kg/day and prednisolone 5 mg/day per os, on the first day of injections (stimulation) until the pregnancy test or to the 12th (prednisolone), and to the 34th (enoxaparin) gestation week	Clinical pregnancy rates: 17/57 (29.8%) *vs* 11/58 (19%), p=0.175. Live birth rates: [15/57 (26.3%) *vs* 9/58 (15.5%), p=0.154]	No side effects reported
Quenby *et al.*[48]	International open label, randomized controlled trial	18-42 years women, with inherited thrombophilia and history of recurrent miscarriage, attempting to conceive or less than 7 weeks pregnant	LMWH; enoxaparin 40 mg or inhixa, dalteparin 5000 IU, tinzaparin 4500 IU, nadroparin 3800 IU until labor; doses were not adjusted to bodyweight; *vs* no treatment (standard care)	Live birth rate; LMWH 116/162 (72%) *vs* standard care 112/158 (71%) p=0.74. Pregnancy loss; LMWH 46/162 (28%) *vs* standard care 46/112 (29%)	No HIT reported, no increase in minor and major bleeding in both groups. Easy bruising; LMWH 45% *vs* standard care 10%.

LMWH, low molecular weight heparin; ARTs, assisted reproductive techniques; IVF, *in vitro* fertilization; ICSI, intracytoplasmic sperm injection; HIT, heparin induced thrombocytopenia.

Heparin can be described as a potential multitarget drug (active in coagulation cascade, endometrium-embryo interface, immune system), with potential benefits for those women with a high-risk thromboembolic profile (obesity, smoking, hypertension, congenital or acquired thrombophilia).

Based on the above reported studies and clear lack of evidence of its effect, heparin is not currently recommended in patients with idiopathic infertility undergoing ARTs. Furthermore, in the subgroup of patients with inherited thrombophilia and RPL, routine use of heparin is not recommended; despite authors discouraged also routine screening for inherited thrombophilia in patients with RPL.[48]

Aspirin in assisted reproductive techniques procedures

Aspirin is a drug of the family of non-steroidal anti-inflammatory drug, that irreversibly inhibits the enzyme cyclo-oxygenase (COX) in platelets, preventing the synthesis of thromboxane (TXA2), a molecule able to induce vasoconstriction and platelet aggregation; COX is also responsible for the suppression of prostacyclin (PGI2) production in endothelium, which acts as a potent vasodilator and antiplatelet agent. Despite high doses of aspirin suppress both the enzymes, it has been demonstrated in pregnancy that low-doses of the drug (50 mg daily), can reduce the synthesis of thromboxane without affecting prostacyclin production, with an overall effect in favor of vasodilatation and inhibition of platelet aggregation.[73] Therefore, low dose aspirin may improve ovarian and uterine blood flow, enhancing folliculogenesis and endometrial receptiveness and consequently improving implantation and pregnancy rates in women undergoing ARTs. However, the use of aspirin in this setting remains controversial because of the lack of well-established evidence.[63]

Some benefits of aspirin administration were found in selected groups of women, for example in those with impaired uterine perfusion (pulsatility index PI<3) or thin endometrium (<8 mm).[74] Weckstein and Hsieh, indeed, demonstrated no increase in endometrial thickness in the aspirin treated group. However, there was a statistically significant increase in implantation rates in the aspirin-treated group (24% *versus* 9%) and in implantation rates and clinical pregnancy rates in the aspirin-treated group when the final endometrial thickness was <8 mm.[58,59] An improvement in uterine blood flow with satisfactory pregnancy rates, was also detected in women undergoing frozen embryo transfer (FET) with normal thickness but impaired uterine perfusion. Wada *et al.* highlighted a higher pregnancy rate in women treated with long regimen aspirin, from the first day of hormonal replacement therapy for 4 days (range 2-8 days), rather than from 13th day of stimulation; no benefit was achieved in woman with normal perfusion.[61]

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On the contrary, aspirin did not improve uterine and ovarian blood flow, ovarian responsiveness, implantation, or pregnancy rates in women undergoing their first IVF cycles without being evaluated for endometrial thickness or ovarian flow.

In a randomized, double-blind placebo-controlled clinical trial, involving women undergoing IVF with infertility due to tubal factors, Rubinstein et al. found that low dose aspirin may lead not only to an improvement in uterine and ovarian blood flow velocity, but also to an increase in implantation and pregnancy rates.[60]

Another cause of infertility can be represented by poor response to hormone stimulation treatments, a condition characterized by low recruitment of mature follicles or repeated high basal levels of FSH. Lok *et al*. evaluated the effect of low dose aspirin in a group of women with this kind of issue. Unfortunately, in this setting, antiplatelet treatment was not effective in improving either ovarian or uterine blood flow or ovarian responsiveness.[52]

No benefit was shown in unselected patients undergoing IVF or ICSI, either with the administration of 80 or 100 mg daily of aspirin, started at time of ovarian stimulation and perceived until pregnancy test, clinical pregnancy or delivery.[53-55]

Table 2. Randomized and quasi randomized trials evaluating aspirin on assisted reproductive techniques procedures.

Study	Methods	Participants (inclusion criteria)	Intervention	Outcomes	Adverse events
Schisterman *et al*.[49] (EAGeR trial)	Multi-center, randomized, double-blind, placebo-controlled, trial	1228 women with previous one or two pregnancy losses at any point in gestation, without history of infertility/sub-infertility	IVF protocol; aspirin 81 mg + folic acid 400 mcg *vs* placebo + folic acid 400 mcg, daily up to 6 menstrual cycles and, if pregnant, until gestational week 36	Live birth rate: among all participants RR 1.10 (95% CI 0.98-1.22), among women with a single recent loss (RR 1.17, 95% CI 1.01-1.37)	Serious adverse events: aspirin 7/615 (1.14%); placebo 5/613 (0.82%). Other adverse events: aspirin 24/615 (3.90%); placebo 8/613 (1.31%)
Radin *et al.* [50] (secondary analysis on EAGeR trial)	"	"	"	Per-cycle risk of anovulation. Anovulation occurred in 12.2% of all cycles. Anovulation rate; aspirin group 13.4%, placebo group 11.1% (RR: 1.16, 95% CI: 0.88, 1.52)	"
Sjaarda *et al*.[51] (secondary analysis on EAGeR trial)	"	"	"	Confirmed pregnancy, live birth, and pregnancy loss rates stratified by tertile of preintervention serum hsCRP. Aspirin increased live birth rate among high-hsCRP women to 59% (RR 1.35; 95% CI 1.08-1.67); it did not affect clinical pregnancy or live birth in the low (live birth: 59% aspirin, 54% placebo) or midlevel hsCRP tertiles (live birth: 59% aspirin, 59% placebo).	"
Lok *et al*.[52]	Single-center, randomized, double-blind, placebo-controlled trial	60 women poor responders; cancellation of previous IVF cycles because of poor follicular recruitment or high basal levels of FSH	IVF protocol; aspirin 80 mg *vs* placebo daily, beginning at the time of GnRHa treatment, until hCG administration/ cancellation. TV-US to assess size, number of follicles and endometrial thickness, intraovarian and uterine artery PI	Cycle cancellation rate; 33.3% placebo *vs* 26.7% aspirin, p 0.39, dose and duration of gonadotropins (p=0.12). Number of follicles recruited; 3.5 aspirin *vs* 3.0 placebo p=0.70. Number of oocytes retrieved; 4 aspirin *vs* 3 placebo p=0.32. Intraovarian PI and uterine PI measured at baseline or on the day of hCG administration; no difference observed (p>0.5).	Not reported

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Study	Methods	Participants (inclusion criteria)	Intervention	Outcomes	Adverse events
Päkkilä *et al.*[53]	Multi-center, randomized, double-blind, placebo-controlled, trial	374 women; fewer than four previous ovarian stimulation	IVF (=235), ICSI (=120), both (n=19). Aspirin 100 mg *vs* Placebo, daily, initiated at the time of gonadotropin stimulation until delivery if pregnancy occurred, or menstruation	Number of oocytes (aspirin 12.0± 7.0 *vs* placebo 12.7±7.2), number embryos (5.82±4.35 aspirin *vs* 5.99±4.66 placebo), number of top-quality embryos (5.82±4.35 aspirin *vs* 5.99±4.66 placebo), number of embryos transferred (1.64±0.64 aspirin *vs* 1.63±0.71 placebo). Clinical PR per ET (25.3% aspirin *vs* 27.4% placebo) or clinical PR per cycle initiated (23.7% aspirin *vs* 25.5% placebo). Birth rate per ET (18.4% aspirin *vs* 21.1% placebo). p non-significant	Not reported
Urman *et al.*[54]	Single-center, randomized control trial	300 women undergoing their first ICSI cycle (IVF cycles excluded)	ICSI. Aspirin 80 mg daily, initiated at the time of gonadotropin stimulation, until negative pregnancy test or clinical pregnancy, *vs* no treatment	Duration of stimulation, gonadotropin consumption, peak estradiol, n. of oocytes retrieved, fertilization and cleavage rate, number of ET; similar in the 2 groups. Implantation rate (15.6% aspirin *vs* 15.1% no treatment), clinical pregnancy rate (39.6% aspirin *vs* 43.4% no treatment); p>0.5	Ectopic pregnancy rate (9.1% aspirin *vs* 1.6% no treatment, p>0.5). Abortion rate (14.5% aspirin *vs* 11.9% no treatment)
Dirckx *et al.*[55]	Single-center, prospective, randomized, double-blind placebo-controlled trial	193 women starting a first or second IVF/ICSI cycle	IVF/ICSI. Aspirin 100 mg or placebo daily, initiated before stimulation and continued until clinical pregnancy	Clinical pregnancy rate (32% aspirin *vs* 31% placebo P=0.916; OR 1.033; 95% CI 0.565-1.890)	No serious events regarding gastrointestinal symptoms or bleeding No difference in miscarriage rate between groups
Waldenström *et al.*[56]	Single center, randomized prospective trial	1380 consecutive IVF cycles (44% first, 26% second, 13% third, 16% 4-8 cycles respectively); 1022 patients. Main indications; tubal factor, endometriosis, hormonal factor, male factor and unknown (25%)	IVF. Aspirin 75 mg daily *vs* no treatment, was given from the day of ET until pregnancy test and it was discontinued regardless the result	Birth rate per ET (27.2% aspirin *vs* 23.2% placebo, OD 1.2 95% CI, 1.0-1.6). Pregnancy rate (37.6% aspirin *vs* 32.1% no treatment, OD 95% C1.31.0-1.6)	Miscarriage (20.9% aspirin *vs* 36% no treatment, OD 1.2, 95% IC 0.8-2), extrauterine pregnancy (2.4% aspirin *vs* 4.9% no treatment, OD 0.5, IC 95% 0.2-1.3)

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Study	Methods	Participants (inclusion criteria)	Intervention	Outcomes	Adverse events
Madani *et al.*[57]	Pilot randomized, double-blind placebo-controlled trial	60 women	FET. Aspirin 100 mg *vs* placebo, daily, given at time of initiation of estradiol valerate administration.	Clinical pregnancy (40% aspirin *vs* 16.7% placebo, p=0.042) implantation (17.4% aspirin *vs* 6.8% placebo p=0.031), live birth (40% aspirin *vs* 10% placebo p=0.007) rates. No significant difference in endometrial thickness, PI and RI	Miscarriage/clinical pregnancies (0% aspirin *vs* 40% placebo, p=0,02).
Weckstein *et al.*[58]	Prospective randomized study	28 women who failed to develop an endometrial thickness of at least 8 mm in a previous evaluation cycle	Oocyte donation. Aspirin 81 mg daily, from one week before estrogen treatment to 9 weeks after ET, *vs* no treatment	Clinical pregnancy rates (83% aspirin *vs* 25% no treatment, p<0.05), implantation rates (38% aspirin *vs* 8% no treatment, p<0.01). No change in endometrial thickness and delivery rate between groups (p>0.05)	Not reported
Hsieh *et al.*[59]	Prospective randomized trial	226 infertile women with thin endometrium (≤8 mm, on the day of IUI in the previous cycle)	IUI. Aspirin 100 mg daily from menstrual day 1 through pregnancy test, *vs* no treatment	Better endometrial pattern (46.5% aspirin *vs* 26.2% no treatment, p<0.001), pregnancy rate (18.4% aspirin *vs* 9.0% no treatment p=0.036). Endometrial thickness, PI/RI values of the uterine artery, spiral artery, and ovarian dominant follicle were similar between both groups (p>0.05)	Not reported
Rubistein *et al.*[60]	Prospective, randomized, double-blind placebo-controlled trial	298 infertile women	IVF. Aspirin 100 mg *vs* placebo, daily, from 21st day of their preceding menstrual cycle, continued until twelve week's gestation or negative pregnancy test	Number of follicles (19.8±7.2 aspirin *vs* 10.2±5.3 placebo, p<0.05), number of oocytes retrieved (16.2±6.7 aspirin *vs* 8.6±4.6 placebo, p<0.05), serum E2 levels (2,923.8±1,023.4 aspirin *vs* 1,614.3±791.7pg/mL placebo, p<0.05), uterine PI (1.22±0.34 aspirin *vs* 1.96±0.58 placebo, p<0.05), ovarian PI (1.18±0.31 aspirin *vs* 1.99±0.56 placebo, p<0.05), pregnancy rate (45% aspirin *vs* 28% placebo, p<0.05), implantation rate (17.8% *vs* 9.2%, p<0.05)	Not reported

To be continued on next page

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Tab. 2. Continued from previous page.

Study	Methods	Participants (inclusion criteria)	Intervention	Outcomes	Adverse events
Wada *et al.*[61]	Trial	99 participants; 37 with impaired uterine perfusion (group I); 62 with normal uterine perfusion (group II)	FET. First attempt; group I received aspirin 150 mg (n=26) or 300 mg (n=11) daily, from day 13 of HRT; group II no treatment. Subsequent attempts: women from group I were allocated to start aspirin on day 1 or day 13 of HRT, and 10 women from group II selected to receive aspirin from day 1 of HRT	Group I, cancellation and pregnancy rates in those who received 150 or 300 mg aspirin daily, were similar. In those with cancelled first attempts, good perfusion was achieved in 82 *vs* 20% (p>0.02) of subsequent attempts using aspiring from day 1 *vs* day 13 of HRT. Higher pregnancy rates (47 *vs* 17%) were achieved in those taking aspiring from day 1 of HRT. In group II, pregnancy rates were not statistically different in those who did or did not receive aspiring during their subsequent attempts (10 *vs* 35%)	Not reported
Davar *et al.*[62]	Prospective, randomized trial	128 women with at least two frozen-thawed embryos available; no history of recurrent abortion	FET. Aspirin 80 mg daily or no treatment, until 12 weeks of gestation.	Clinical pregnancy rate (23.8% aspirin group *vs* 19.4% no treatment, p=0,547). No difference in chemical and implantation rate. Endometrial thickness (8.64±1.60 aspirin *vs* 9.29±1.70 no treatment, p=0.028)	Abortion rate in both groups 0%
Kuo *et al.*[63.]		127 women with unexplained infertility/ repeated failure with various ARTs techniques	Aspirin 100 mg daily given in those with impaired uterine perfusion during previous menstrual cycle	Improvement in the uterine blood perfusion (p<0.05) was detected in peri-implantation period of aspirin-treated cycles	Not reported

ARTs, assisted reproductive techniques; IVF, *in vitro* fertilization; ICSI, intracytoplasmic sperm injection; FET, Frozen Embryo Transfer; HRT, hormonal replacement therapy; PI, pulsatility index; RI, resistive index; hs-CRP, high-sensitivity C-reactive protein; GnRHa, gonadotrophin-releasing hormone analogue.

In a large prospective randomized trial (aspirin 75 mg daily vs no treatment), including 1380 IVF cycles (1200 women), Waldenström *et al.* found a slight improvement, although not statistically significant, in biochemical, clinical and birth rates in unselected women of the interventional group, receiving aspirin from the day of embryo transfer until pregnancy test.[56] Nevertheless, some biases must be considered: at first the number of IVF cycles, fertilized oocytes, and embryos transferred, were significantly higher in the aspirin-group, which could have contributed to the higher pregnancy rates, second, the assignment of patients to the interventional group rather than the control group, was not completely randomized.[53,56]

Davar *et al.* have recently found no improvement in pregnancy rate in women undergoing FET cycles treated with aspirin 80 mg daily, compared to no treatment; to be noted, endometrial thickness was significantly lower in the aspirin group than in the control group.[62] Otherwise, Madani *et al.* suggested in a small, randomized pilot study, a potential benefit of aspirin treatment in unselected women candidate to FET: compared to placebo group, in the interventional group higher rates of clinical pregnancy, implantation, live birth rate and lower miscarriages were observed. It must be underlined that in the above-mentioned studies, women didn't undergo ovarian stimulation, which exposes to higher levels of estradiol, conferring negative impact on endometrial receptivity and being potentially responsible for implantation failure in IVF. In fact, higher estrogen levels may increase platelet aggregation and coagulation cascade leading to a procoagulant state, then conferring a biological plausibility to the treatment with aspirin in this setting.[57,62]

It is worth mentioning that Schisterman *et al.* demonstrated a higher live birth rate, among women with single recent pregnancy loss, undergoing IVF and taking aspirin as adjuvant therapy along-

side with hormonal stimulation; the study population had no history of infertility or recurrent pregnancy loss (maximum of two previous pregnancy losses).[49] Furthermore, in a secondary analysis conducted by Sjaarda *et al*., aspirin seemed to be more effective in patients with higher levels of C-Reactive Protein, without metabolic syndrome criteria, or ovulation disorders.[51]

Additionally, it has been proven that low-dose aspirin may lead to a reduction in the likelihood of developing pre-eclampsia and a pregnancy with serious adverse outcomes.[75,76] Moreover, it has been shown that the use of aspirin in combination with other drugs, for example steroids, is not associated with proven benefit in routine IVF or ICSI treatment.[77]

In summary, the available literature remains extremely contradictory. First trials had generally low sample size, with consequence of low statistical power. Second, there is high heterogeneity among patients' groups, dose of aspirin administered, timing of therapy and ARTs protocols. For example, the term *low dose aspirin*, refers to several possible dosages, ranging from 80 to 325 mg daily, with no well-established risk-benefit ratio. However, the dose of 80 mg daily, seems to be the lowest with the most favorable activity-ratio between thromboxane and prostacyclin. Moreover, the timing for the initiation (at the luteal phase or during controlled ovarian hyperstimulation), and the total duration of aspirin treatments, differs between trials. To date, no universal consensus regarding the definition of infertility or of poor responders exists. Furthermore, it is not always specified for which reasons patients included in clinical trial underwent ARTs. There is a lack of knowledge about safety issues, because just a minority of all studies included adverse events, but no serious ones were described.

Heparin and aspirin in idiopathic infertility

Just few studies have evaluated aspirin and heparin together as adjuvant therapy in ARTs procedures. Akhtar et al evaluated retrospectively the co-administration of aspirin and heparin in 234 consecutive subjects who had previously performed one or more unsuccessful IVF cycle, with no evidence of improvement in live birth rates.[78] Similar results were found by Kaandorp *et al.* in a randomized trial involving 364 women with history of unexplained recurrent miscarriage, with no differences in terms of live birth rate, between the two intervention groups (receiving respectively aspirin 80 mg daily plus nadroparin 2850 UI/daily or only aspirin 80 mg daily) and the control group (receiving placebo).[79]

Conclusions

According to current research, neither LMWH, aspirin, or their combination is universally recommended for women undergoing ART procedures. The available literature suggests only a minimal advantage in a narrow subset of patients, and antithrombotic medications should only be recommended for infertility management after a thorough risk-benefit analysis by reproductive specialists. It is critical to underline that the extensive use of antithrombotic medicines and thrombophilia testing is unsupported by evidence and should be discouraged. More comprehensive RCTs are needed to investigate the efficacy of antithrombotic medicines in this situation.

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