REVIEW

Thrombophilia and assisted reproduction technology—any detrimental impact or unnecessary overuse?

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Abstract

Purpose The aim of this study is to provide an overview of the studies investigating a possible association between thrombophilia and assisted reproductive technology (ART) outcome.

Methods This is a literature review.

Results Congenital thrombophilias (CoT) are reported to be associated with pregnancy loss. However, the association between CoT and early pregnancy loss is weak and does not necessarily support causation. CoT are more likely to be associated with late fetal loss. Even though data pooled from case-control and cohort studies suggest an increased risk of ART failure in women with CoTs, there seems no association when the analysis is confined to better quality cohort studies. The evidence supporting anticoagulation to improve ART outcome in CoT carriers is weak. Likewise, studies on antiphospholipid antibodies (APAs) and ART outcome suffer from multiple methodological limitations and a detrimental impact of APA positivity is controversial. Empirical administration of heparin or low molecular weight heparin to women with recurrent ART failures is supported by weak evidence. Importantly, thrombophilias are likely to increase thrombotic complications after ovarian stimulation for ART.

Conclusions Current evidence does not support routinely testing for or treatment of thrombophilia in the setting of ART nor

in couples with implantation failure. A careful personal and family history should be obtained and a risk assessment for thrombotic complications should be made in every woman undergoing ovarian stimulation. If positive, testing for thrombophilia is warranted.

Keywords Assisted reproduction · Thrombophilia · Heparin · Pregnancy loss · Antiphospholipid syndrome

Introduction

The success of assisted reproduction technology (ART), although gradually increased over the years, is far from optimal. Many couples have benefited from this treatment; however, many have also been left frustrated following multiple failed attempts. Couples who fail to conceive after multiple ART cycles often seek treatment options that are new and that have not been offered before [1]. Although some of these options are supported by robust evidence, most suffer from lack of well-designed trials comparing them with other treatment options or no treatment at all.

Investigation and treatment of congenital and acquired thrombophilias have become common practice in management of recurrent implantation failures [2]. The term “thrombophilia” defines any condition associated with an increased risk of thrombosis. Microvascular occlusion at the decidua due to thrombophilia has been suggested as a potential cause of implantation failure in ART cycles. Whether congenital or acquired thrombophilia is an underlying cause of implantation failure, however, remains elusive. Hence, screening for and treatment of thrombophilias in couples undergoing ART is controversial.

Even though most work on the field concerns effect of thrombophilia on ART success, the presence of thrombophilia is also a safety concern. Ovarian stimulation for ART results in

Capsule Current evidence does not support routinely testing for or treatment of thrombophilia in the setting of ART nor in couples with implantation failure.

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a pathological environment in terms of multifollicular growth and supraphysiological levels of sex steroids. These changes increase the risk for thrombosis and thromboembolism. Underlying thrombophilia may augment these risks in affected women. We will review the effect of thrombophilia on pregnancy complications and ART outcomes.

Congenital thrombophilia and pregnancy loss

Congenital thrombophilia is defined as a genetic predisposition to venous thromboembolism (VTE), usually through the absence or alteration of a functional protein in the coagulation cascade. Combined with the hypercoagulable state of pregnancy, thrombophilia has the potential to induce placental thrombosis and cause placental insufficiency with subsequent obstetrical complications. On the other hand, from an evolutionary perspective, thrombophilic gene mutations that lower the risk of hemorrhage may have conferred a survival advantage to the species. Historically, lethal exsanguinations and severe infections have been two major causes of maternal death. The high prevalence of factor V Leiden (FVL) mutation, a relatively common thrombophilic mutation, in the general population suggests that it may indeed serve a purpose for propagation of the mankind. FVL confers lower risk of blood loss and profuse hemorrhage in association with delivery and improves the hemoglobin status. In addition, FVL carriers possibly have a survival advantage during sepsis [3].

The predominant thrombophilic mutations include FVL mutation, prothrombin gene mutation G20210A (P2), methylene tetrahydrofolate reductase C667T mutation (MTHFR), and deficiencies of the natural anticoagulant proteins C and S, and antithrombin (AT). Almost all of these congenital thrombophilias are inherited in an autosomal dominant fashion.

Large cohort studies show that the relative risk of VTE is increased $\times 80$ in women with a homozygous FVL or P2 gene mutation, whereas the risk is increased $\times 2.7$ and $\times 3.8$ in heterozygotes, respectively [4]. Among obstetrical complications, the strongest association was found to be between congenital thrombophilia and preeclampsia and late fetal loss [5]. In a large cohort study of adverse pregnancy outcomes, the presence of maternal thrombophilia was associated with an increased risk of fetal loss after 14 weeks, fetal growth restriction, placental abruption, and preeclampsia. In contrast, the presence of one or more maternal thrombophilias was found to be protective of pregnancy losses of <10 weeks [6]. However, in a recently published meta-analysis of nine studies (case-control and cohort) including 2147 women, 1305 with and 842 without obstetric complications, women with early recurrent pregnancy loss (RPL) had a statistically significantly increased carrier frequency of F5 mutation, with a common odds ratio (OR) of 1.68 (95 % CI 1.16–2.44) [7]. The above notwithstanding, due to poor quality case-control and cohort study designs, there is often an increase

in the relative risk of pregnancy complications associated with thrombophilia, particularly recurrent early pregnancy loss, but the absolute risk, if there is any, remains very small.

Despite the presence of a possible association between congenital thrombophilias and adverse pregnancy outcomes, anticoagulation has been found to be beneficial only in the setting of antiphospholipid syndrome (APS). The absence of proven safe and effective treatments that will decrease the risk of a future pregnancy loss among women with RPL prevents recommending testing of and treatment for congenital thrombophilias in this setting.

The natural history of the MTHFR mutation in pregnancy has not been well documented. A meta-analysis by Rey et al. concluded that MTHFR was not associated with an increased risk of fetal loss. A subsequent meta-analysis concluded that MTHFR C677T mutation was not associated with early pregnancy loss either [8]. Due to high prevalence of MTHFR mutations in the general population with normal fertility and reproductive outcomes, anticoagulation is not indicated and only supplementation with folic acid should suffice.

Congenital thrombophilia and assisted reproduction technology outcomes

Whether congenital thrombophilia has any impact on the success of ART is a matter of debate among reproductive endocrinologists and reproductive immunologists. Given the similar pathologic mechanisms involved in preimplantation, preclinical, and clinical pregnancy losses, the association between thrombophilia and implantation failure has been sought in several studies but remains elusive. A possible mechanism behind the development of pregnancy complications among thrombophilia carriers is thrombosis of maternal vessels, which could reduce perfusion of the intervillous space leading to placentation failure [8]. Failure of implantation in women undergoing ART may be due to similar mechanisms. Damage of decidual or chorionic vessels, or reduction of trophoblast invasiveness, could prevent embryo implantation.

In a recent meta-analysis, pooled data from eight case-control studies showed a threefold increased risk of ART failure in patients with the FVL mutation (OR 3.08, 95 % CI 1.77 to 5.36); however, an analysis confined to three cohort studies found no significant association (OR 0.62, 95 % CI 0.35 to 1.08). None of the other congenital thrombophilic abnormalities (P2 mutation, AT, protein C, or protein S deficiency) were found to be associated with an increased risk of ART failure [9].

More recently, Steinvil et al. retrospectively analyzed 594 women who underwent ART and had a thrombophilia workup and compared them for prevalence of thrombophilia to two reference groups consisting of 637 fertile women and 17,337 women members of the same healthcare organization with no

history of venous thromboembolism. None of the common thrombophilias tested was found to be significantly associated with the number of prior failed ART cycles or with lower fertility. Rather, women who had activated protein C resistance (APCR) and/or FVL and lupus anticoagulant had significantly higher live birth rates compared to controls [10]. Thrombophilia carrier status was not associated with poorer reproductive outcomes. Data from this large retrospective study confirm that screening for FVL is not indicated in couples undergoing ART.

Studies that examined the association between the P2 gene mutation and ART failure [11–16] showed a non-significant overall association (OR 1.48; 95 % CI, 0.71–3.06), and the risk was similar between heterozygotes and homozygotes compared with normal controls.

An association between MTHFR mutation and ART outcome was evaluated in several studies [12, 13, 15–18]. There was no association between MTHFR carrier status and ART outcomes. Both homozygotes and heterozygotes performed similarly. Two studies involving 435 women prospectively assessed the impact of P2 and MTHFR gene mutations on the chance conception in patients undergoing ART [12, 19]. Neither of these thrombophilic mutations increased the risk of failure.

In summary, the relationship of congenital thrombophilia with ART outcome is dubious. Based on the available evidence, we can conclude that testing for and treatment of congenital thrombophilia are not indicated in patients undergoing ART in the absence of a personal or family history of VTE. Anticoagulation with heparin or low molecular weight heparin (LMWH) in women with implantation failure warrants further investigation in larger trials.

Acquired thrombophilia and assisted reproductive technologies

In addition to the abovementioned congenital thrombophilias, a number of acquired conditions increase the risk of thrombosis. These include APS, heparin-induced thrombocytopenia, paroxysmal nocturnal hemoglobinuria, myeloproliferative disorders, particularly polycythemia vera and essential thrombocytosis, paraneoplastic syndrome, pregnancy, and increased estrogen levels. While some of these conditions, such as myeloproliferative disorders, are very rare and require specific treatment, some others are transient, e.g., heparin-induced thrombocytopenia or oral contraceptive use. Thus, APS remains as a chronic thrombophilia, which can be relevant for ART for several reasons. Firstly, increased serum estradiol levels during ovarian stimulation and the luteal phase can further increase the already elevated risk of thrombosis in patients with APS. Secondly, increased coagulability can

hamper embryo implantation and early pregnancy development process possibly through vascular occlusion.

The latter opinion is, at least to some extent, inspired by the association between APS and RPL. However, even though APS is generally recognized as a cause of RPL, whether there is truly a causal relationship is controversial. The Obstetric Task Force of the 14th International Congress on Antiphospholipid Antibodies reviewed the literature in 2014 and they identified 46 studies on APA and RPL [20]. Twenty-seven of the 46 studies reported an association between APA positivity and RPL, but these were mostly small-sized studies. Twelve of the 46 (26 %) did not include a control group. Moreover, 26 of the 46 (56 %) were conducted before the First International Consensus on APA [21]. The consensus statement involved an update of the Sapporo criteria for diagnosis of APS. Importantly, the revised Sapporo criteria defined APA positivity as readings over 40 GPL or MPL or a value greater than three standard deviations. Moreover, APA should be persistently positive, when tested 12 weeks apart, because transient APA positivity was not found to be associated with thromboembolic events [22]. While most studies used arbitrary cut-off values for APA positivity, only few used the abovementioned criteria. Thirty-eight of the 46 studies (83 %) did not confirm APA positivity on a second occasion. Varying definitions of RPL used in the studies further complicated the situation, and the Task Force concluded that “the association between RPL and APA remains inconclusive and the findings of treatment trials are at best inconsistent and at worst misleading....” [20].

Furthermore, recent human and animal studies suggest that APS can lead to pregnancy loss through complement activation and inflammatory response rather than thrombosis [23]. While unfractionated and low molecular weight heparin could prevent complement activation and fetal loss in mice, other anticoagulants, such as hirudin or fondaparinux, were unable to do so despite their anticoagulant effects [24]. Heparins are thought to be effective through their anticomplement rather than anticoagulatory effects.

It is also questioned whether the pro-inflammatory effect of APAs could affect fertility through disrupting oocyte development or uterine decidualization. Indeed, several studies examined the relationship between APAs and fertility or ART outcomes. Chighizola and Jesus reviewed 36 studies in 2014 and we could identify three more studies on the subject published since then [25]. A total of 29 studies compared APA positivity between infertile women and a variety of control groups. Only 13 (45 %) reported significantly higher APA positivity rates among infertile women. However, most studies assessed several non-criteria APAs, i.e., other APAs than lupus anticoagulant, anticardiolipin, and antibeta2 microglobulin IgM and IgG antibodies. The clinical relevance of these APAs is currently speculative. Similar to RPL studies, the vast majority of the studies investigating an association between APA and

infertility used arbitrary cut-off levels not conforming the international consensus. Only two studies confirmed APA positivity 6 to 12 weeks apart [25].

Regarding APA and ART outcome, only two of the 14 studies reported a significant association between APA positivity and ART failure. However, neither the indication for APA screening was mentioned nor the cut-off levels for APA positivity conformed international consensus criteria in these two studies. A third study reporting a positive association between APA and ART outcome included only eight women who tested positive for anticardiolipin antibody after failing two ART cycles and 32 women without anticardiolipin antibodies as controls [26]. While the Sapporo criteria APAs were not found to affect ART outcome, antithrombin IgA antibody positivity (defined as >99th percentile) was found to be detrimental. Obviously, the sample size of eight prevents any firm conclusions.

In a prior review of APA and ART outcome, which essentially included the same studies, Di Nisio et al. separately pooled data from case-control studies and cohort studies [27]. Case-control studies compared APA positivity between women with failed ART cycles (cases) and women without failed ART cycles (controls). However, the controls included different populations, i.e., women with spontaneous pregnancy, women who conceived in the first ART cycle, or “healthy women.” Likewise, the cases also varied with regard to the number of failed ART cycles. Overall, the odds of testing positive for an APA was 3.33 (95 % confidence interval; 1.77 to 6.26) times higher in women with ART failure (20 studies involving 3542 women). Yet, when the cohort studies, comparing ART outcomes between women with and without APAs, were combined, neither the odds of achieving a pregnancy (0.97, 95 % CI 0.58 to 1.62, 10 studies involving 873 women) nor a live birth (1.17, 95 % CI 0.70 to 1.95, five studies involving 437 women) was found to be different between the groups [27].

There are several possible explanations of the observed discordance between case-control and cohort studies. First and foremost, inclusion of healthy controls and spontaneous pregnancy could have led to a biased comparison. It is reported that APA positivity can occur as a transient epiphenomenon during ovarian stimulation for ART; therefore, the lack of confirmation of persistence of APAs can be regarded a serious limitation of all these studies, leading to overestimation of an effect of APAs on ART outcome [28].

In conclusion, available data do not suggest a firm association between the Sapporo criteria APA positivity and ART outcomes. Whether reported associations between non-criteria APAs and ART outcomes are genuine or reproducible remain to be confirmed. Future studies should standardize (i) APA testing, with regard to both APAs to be tested and cut-off levels for positivity, (ii) study populations, e.g., women undergoing ART versus women with recurrent implantation

failure. Ideally, APA positivity should be confirmed on two separate occasions as suggested in the Sapporo criteria. This would require APA testing 6–12 weeks before ovarian stimulation and can be difficult to accomplish. Even if such studies confirm an association between APA positivity and ART failure, we would need other trials demonstrating an effective treatment, which could restore live birth rates in women with APAs. Until then, routinely testing women undergoing ART for APAs does not seem to be justified.

The possible role of heparin in improving assisted reproductive technology outcomes

Heparin treatment is widely administered in thrombophilia carriers with implantation failure despite the absence of solid proof of effectiveness [2]. Heparin might improve implantation rates in patients undergoing ART through mechanisms not related to anticoagulation, but by improving endometrial receptivity and decidualization of endometrial stromal cells, as well as trophoblast adhesion and invasiveness [29].

We sought the answer to the question whether empirical LMWH could enhance pregnancy rates in women with unexplained recurrent implantation failures, i.e., in the absence of common thrombophilias [30]. One hundred and fifty women with ≥ 2 failed ART cycles were included in this randomized open-label pilot trial. Participants underwent controlled ovarian stimulation with the long protocol and were randomly allocated to receive 1 mg/kg/day LMWH or no treatment in addition to routine luteal phase support (LPS) on the day after oocyte retrieval. LPS and LMWH was continued up to the 12th gestational week in pregnant participants. There were more live birth rates in the treatment group (34.7 vs 26.7 %); however, the difference was short of statistical significance.

Potdar et al. pooled the results of our trial with results of another randomized and one quasi-randomized trial [31]. The other randomized trial included women with thrombophilia and the quasi-randomized trial included women without thrombophilias. The administration of unfractionated or low molecular weight heparin was found to significantly increase live birth rates in women with recurrent implantation failures (rate ratio 1.79, 95 % CI 1.10 to 2.90) [30, 31]. Yet, the quality of evidence is moderate at best, and it cannot be justified to recommend heparin administration to all women suffering from recurrent ART failures [29].

Thrombophilia and complications of assisted reproductive technology

Ovarian hyperstimulation syndrome (OHSS) is a serious and life-threatening complication of ovarian stimulation. The etiology is poorly understood but is thought to involve

the action of vasoactive peptides released from hyperstimulated ovaries leading to increased vascular permeability and shift of intravascular fluid to the third space, resulting in intravascular fluid depletion and increased hematocrit levels. Vascular endothelial growth factor (VEGF) appears to be the key mediator initiating the development of OHSS. Hemoconcentration and activation of the coagulation cascade, increased activity of the thrombin—anti-thrombin and plasmin—antiplasmin complexes, elevated platelet levels, and increased fibrinogen levels have all been reported in patients with OHSS and can induce a hypercoagulable state which requires thrombosis prophylaxis [32]. A major complication of OHSS is the development of both arterial and venous thrombotic events [33]. Increased levels of VEGF, supraphysiological levels of estradiol, and blood hyperviscosity together increase the risk of thrombotic events. The risk may be further augmented by the presence of thrombophilia. In a review of 140 women who had thrombotic complications due to OHSS, 45 % had an underlying thrombophilia [33]. The major thrombophilias included FVL mutation, protein C, protein S, and antithrombin deficiencies, and APS. Anticoagulation is a prophylactic measure that needs to be instituted in women with severe OHSS. The European Society of Human Reproduction and Embryology recommends that all women undergoing ART should be individually assessed for the risk of thromboembolic disorders, taking into account personal history or family history of VTE, concurrent medical conditions, age, obesity, and, if available, laboratory assessment on thrombophilia, and thromboprophylaxis should be instituted with LMWH until the 13th week of gestation in women conceiving in the presence of OHSS [34]. The Society of Obstetricians and Gynaecologists of Canada also recommends the administration prophylactic doses of anticoagulants to women with severe OHSS [35].

Conclusions

The association between congenital and acquired thrombophilia and ART outcomes is dubious. Current evidence does not support routinely testing or treatment for thrombophilia in the setting of ART nor in couples with implantation failure. A careful personal and family history should be obtained and a risk assessment for VTE should be made in every woman undergoing controlled ovarian stimulation. If positive, testing for thrombophilia is warranted. Women presenting with severe OHSS should be given prophylactic heparin or LMWH. Whether heparin, given its possible implantation enhancing effects, should be administered to increase success rates of ART should be investigated in further large-scale randomized trials.

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