

The role of thrombophilias in reproduction: A swot analysis

Francisco Fabregues^{a,*}, Juan Antonio García-Velasco^b, Joaquín Llácér^c, Antonio Requena^c, Miguel Ángel Checa^{d,e}, José Bellver^{f,g,h}, Juan José Espinós^{e,i}

^a Institut Clinic Gynecology, Obstetrics and Neonatology (ICGON), Hospital Clinic, C/Villarroel 160, Barcelona 08036, Spain

^b IVI RMA Madrid, Avda. del Talgo 68, Madrid 28023, Spain

^c Ginefiv-Generalife, Calle José Silva 18, Madrid 28043, Spain

^d Hospital del Mar-Parc de Salut Mar, Paseo Marítimo 25-29, Barcelona 08005, Spain

^e Fundació Fertty, Ausiàs March 25, Barcelona 08010, Spain

^f Departamento de Pediatría, Obstetricia y Ginecología, Facultad de Medicina, Universidad de Valencia, Spain

^g Instituto Valenciano de Infertilidad (IVI-RMA) Valencia, Plaza de la Policía Local, 3, Valencia 46015, Spain

^h Fundación FIVI, Instituto de Investigación Sanitaria La Fe (IIS La Fe), Valencia, Spain

ⁱ Universidad Autónoma de Barcelona. Campus de la UAB, Plaza Cívica, s/n, Bellaterra (Barcelona) 08193, Spain

ARTICLE INFO

Keywords:

Thrombophilia
Infertility
Recurrent implantation failure
Anticoagulants
Antiphospholipid syndrome

ABSTRACT

Thrombophilia is a group of inherited or acquired coagulation disorders that have been associated with reproductive failure. However, there are still no clear recommendations on whether its inclusion in the initial study of the infertile couple or patients with recurrent implantation failure is necessary. In this discussion paper, based on a SWOT (strengths, weaknesses, opportunities, threats) analysis, the different aspects of the repercussions of thrombophilia screening and treatment in reproduction are evaluated. To avoid possible subjectivity in the analysis and results of this study, researchers followed Oxford criteria for the evaluation of evidence.

The results from the evaluation of the reviewed bibliography seem to indicate that, pending new evidence, it would be advisable not to include thrombophilia screening in the initial baseline study of the infertile couple. There is no evidence to support a clear association between thrombophilia and implantation failure or infertility. Thrombophilia testing in this setting may increase cost, with minimal potential benefit and lead to inappropriate use of anticoagulants with possible deleterious adverse effects. Future well-designed studies are needed to assess the possible benefit of anticoagulant therapy in infertile thrombophilic patients with implantation failure.

Introduction

Reproductive failure (RF) is the inability to conceive or to carry a pregnancy to term¹ and commonly includes infertility, unexplained infertility (UI), repeated implantation failure (RIF), miscarriage, and recurrent pregnancy loss (RPL) [25,62]. Among women with repeated RF, the rate of thrombophilia is reported to be as high as 50 % in selected studies [67]. In this regard, although the association between thrombophilia and RPL is well-documented [31], the association between thrombophilia and unexplained infertility or RIF is still a matter of debate and the focus of this review [55].

Thrombophilia is related to changes in hemostatic mechanisms, characterized by an increased tendency for the blood to clot and a consequent risk of thromboembolism [72]. It can be congenital or acquired. Main congenital factors include factor V Leiden (FVL)

(homozygous or heterozygous), prothrombin (PT) G20210A mutation (Pm) (homozygous or heterozygous), and deficiencies of the endogenous anticoagulants, antithrombin (AT), protein C, and protein S. Among acquired thrombophilia, the most common diagnosis implicated in adverse pregnancy outcomes is the antiphospholipid syndrome (APS), that includes the detection of lupus anticoagulant (LAC), anticardiolipin antibodies (ACA), and antibodies interacting with β_2 glycoprotein I (β_2 GP1). Importantly, although detected in screening, many individuals who carry a thrombophilic trait remain asymptomatic, at least until additional boosting factors arise [20].

In pregnant women, thrombophilia is associated with an increased risk of venous thrombosis, fetal loss, and gestational complications [4,79,98], but the role of thrombophilia in infertility is still controversial. Based mainly on the results of observational studies [17,28,34,40,56,58], some authors have suggested that thrombophilias

* Corresponding author.

E-mail address: fgasol@clinic.cat (F. Fabregues).

<https://doi.org/10.1016/j.ejogrb.2022.10.024>

Received 17 May 2022; Accepted 25 October 2022

Available online 31 October 2022

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Table 1

Recommendations for thrombophilia screening and thrombophilaxis in reproductive failure.

Organization	Year	Guideline/Committee opinion	Recommendation	Rationale
Thrombophilia screening				
CFAS	2020	RIF in IVF	Testing for inherited or acquired thrombophilia in patients with RIF not recommended	Insufficient evidence that either inherited or acquired thrombophilias are increased in RIF patients
ACOG and ASRM	2019	Infertility workup for the women's health specialist	Thrombophilia testing should not be routinely ordered	Adapted from ASRM Choosing Wisely: ten things physicians and patients should question
SMFM	2019	Choosing Wisely: 15 things physicians and patients should question	Don't test women for MTHFR Mutations	Genetic variants C677T and A1286C have been associated with mild decrease in enzymatic activity, which in the setting of reduced folate levels are a risk factor for hyperhomocysteinemia. Although hyperhomocysteinemia is a risk for CVD and VTE, its cause is multifactorial and independent of MTHFR genotype. Despite earlier (mostly case-control) studies that found an association between the MTHFR genotype and adverse outcomes, recent studies of more robust design have not replicated these findings.
ACMG	2017	Choosing Wisely: five things patients and providers should question	Don't order MTHFR testing for the risk assessment of hereditary thrombophilia	The common MTHFR gene variants, 677C > T and 1298A > G, are prevalent in the general population. Recent meta-analyses have disproven an association between presence of these variants and VTE
ASRM	2015	Choosing Wisely: 10 things physicians and patients should question	Don't routinely order throm- bophilia testing on patients undergoing a routine infertility evaluation	This testing is not a part of the infertility workup. Furthermore, the testing is costly, and there are risks associated with the proposed treatments, which would also not be indicated in this routine population. There is no indication to order these tests, and there is no benefit to be derived in obtaining them in someone that does not have any history of bleeding or abnormal clotting and in the absence of any family history
ESHRE	2013	VTE in women: a specific reproductive health risk	Screening for thrombophilia is unlikely to be cost-effective	Routine screening is not appropriate because of the rarity of the conditions and the high-cost screening
Thromboprophilaxis in RF				
CFAS	2020	RIF in IVF	ASA should not be routinely offered in RIF Empirical LMWH for RIF patients should be limited to research	ASA: There are no RCTs evaluating aspirin alone, and only one RCT evaluating aspirin as a combination treatment. The sparsity of studies on low-dose ASA in patients with RIF makes it impossible to make a recommendation. LMWH: Studies are few, populations studied are heterogeneous, and study results are inconsistent
ESHRE	2020	Ovarian stimulation for IVF/ ICSI	Use of ASA before and/or during ovarian stimulation is not recommended in the general IVF/ICSI population or for poor Responders	Existing evidence suggests that adjuvant ASA before and/or during ovarian stimulation does not improve ovarian response in terms of number of oocytes retrieved and outcomes of clinical or ongoing pregnancy, or live birth rates following IVF treatment. Evidence could not be formulated on the outcome of OHSS due to poor study quality
ASH	2018	Management of VTE in the context of pregnancy	-For unselected women undergoing ART, panel suggests against prophylactic antithrombotic therapy to prevent VTE - For women undergoing ART who develop severe OHSS, panel suggests prophylactic antithrombotic	No evidence of a benefit with antithrombotic interventions (ASA or heparins) on other outcomes (e.g., implantation, pregnancy, live births) No evidence for net health benefit from using antithrombotic interventions for prevention of VTE in unselected women (absolute incidence of symptomatic VTE in unselected women is < 1 %) using ART. VTE risk, however, seems sufficiently high in women with severe OHSS and with OHSS requiring hospitalization (risk 2.5 to 6.6 % in severe OHSS) to suggest that desirable consequences of prophylaxis would outweigh undesirable consequences, even though direct data showing benefit to intervention are lacking.
NICE	2013	Fertility problems	Further research is needed to assess the efficacy of adjuvant luteal phase support treatments such as low-dose ASA and heparin	These interventions are starting to be used in clinical practice in the absence of any RCT evidence of benefit, and even where there is RCT evidence of no benefit. Their use has potential dangers to the treated women It is important that the clinical efficacy of these agents is formally established so that clear statements about whether they should be recommended or are contraindicated could be made.

CFAS: Canadian Fertility and Andrology Society; ACOG: American College of Obstetricians and Gynecologists; ASRM: American Society for Reproductive Medicine; SMFM: Society for Maternal-Fetal Medicine; ACMG: American College of Medical Genetics and Genomics; ESHRE: European Society of Human Reproduction and Embryology; ASH: American Society of Hematology; NICE: National Institute for Health and Care Excellence; RIF: repeated implantation failure; CVD: cardiovascular disease; MTHFR: Methylene tetrahydrofolate reductase; VTE: Venous Thromboembolism; IVF: in vitro fertilization; OHSS: ovarian hyperstimulation syndrome; RCT: randomized controlled trial; ASA acetylsalicylic acid; LMWH: low molecular weight heparin. Adapted from: Malinowski AK. The Pathophysiology of Hypercoagulability and Infertility. *Semin Reprod Med.* 2021;39(1–02):34–61.

Table 2

Oxford Centre for Evidence-based Medicine (CEBM)-Levels of Evidence (March 2009).].

Levels of evidence	Type of study
1a	Systematic reviews (with homogeneity) of randomized controlled trials
1b	Individual randomized controlled trials (with narrow confidence interval)
1c	All or none randomized controlled trials
2a	Systematic reviews (with homogeneity) of cohort studies
2b	Individual cohort study or low quality randomized controlled trials (e.g. <80 % follow-up)
2c	“Outcomes” Research; ecological studies
3a	Systematic review (with homogeneity) of case-control studies
3b	Individual case-control study
4	Case-series (and poor quality cohort and case-control studies)
5	Expert opinion without explicit critical appraisal, or based on physiology, bench research or “first principles”

Note: A minus sign “-” may be added to denote evidence that fails to provide a conclusive answer because it is either (a) a single result with a wide Confidence Interval; OR (b) a Systematic Review with troublesome heterogeneity.

Available at: <http://www.cebm.net/oxford-centre-evidence-based-medicine-levels-evidence-March-2009/>

could be involved in infertility and, although there is no clear evidence regarding the positive impact of screening and treatment in these patients [52,86], they are used in routine clinical practice [105]. Nowadays, information on the clinical relevance of thrombophilic defects is increasing, and evidence-based indications for thrombophilia screening and thromboprophylaxis are necessary as controversy exists among the recommendations of the different societies (Table 1) [68].

This study aims to assess whether there is evidence to show that the screening and treatment of thrombophilias may offer advantages in the reproductive results of infertile patients.

Methods

In this study, a SWOT analysis was carried out to assess the Strengths/Weaknesses/Opportunities/Threats of the screening and treatment of thrombophilia in infertile women according to the reviewed bibliography, and to know the experts' point of view [10,13,18,19,22,47–49,104].

A bibliographic search aimed at “Thrombophilia” AND “Reproductive Medicine” OR “Infertility” or “Assisted Reproduction” in the last 10 years was carried out. An Excel spreadsheet for each of the sections of the SWOT was created, which would be available on the [SISGtool.org](http://sisgtool.org) platform. The quality of the selected articles was assessed using the Oxford Centre for Evidence-Based Medicine (CEBM) Levels of evidence (Table 2).

Results

The literature review revealed 152 articles and classified 64 as relevant articles.

Strengths

A high prevalence described in infertility

Inherited thrombophilia was first reported to have an association with RIF by Grandone et al. [53]. They suggested that mutations of FVL and PT alone or combined with acquired factors can induce implantation failure. Later, several case-control studies have reported that congenital and acquired thrombophilias are more prevalent in women with implantation failures and UI (evidence 3b), although not all studies confirm this finding (Table 3) [8,12,29,38,42,51,53,73,84,94,100,110]. It has also been described that among the 7 % of patients with RIF in oocyte donation, 16 % showed positive results for

Table 3

Case-control studies that analyze the prevalence of thrombophilic traits in reproductive failure.

Authors	Population	Outcomes	Level of evidence
[53]	18 women RIF (>3 failed IVF) 24 women successful IVF 214 fertile patients.	27 % thrombophilia (mutations of FVL and PT alone or combined) in RIF vs 0 % successful IVF and 6 % fertile women	3b
[8]	45 women ≥ 4 failed IVF cycles 44 healthy women	Thrombophilia 26.7 % (RIF) vs 9.1 % control (p < 0.05) Thrombophilia 46.9 % (UI) vs 18.2 % control (p < 0.05) Thrombophilia may be a contributing factor in RIF, especially in subgroup with UI No protein C, AT III, or APLA20 (80 %) with elevated D-dimer had thrombophilia vs 7 (50 %) with normal D-dimers (p < 0.05) 27 (69 %) with UI had thrombophilia vs 5 (33 %) of fertile controls investigated for VTE (p < 0.05)	3b
[38]	25 UI (elevated D-dimer) 14 UI (normal D-dimer) 15 fertile women investigated for VTE	Thrombophilia 26.7 % (RIF) vs 9.1 % control (p < 0.05) Thrombophilia 46.9 % (UI) vs 18.2 % control (p < 0.05) Thrombophilia may be a contributing factor in RIF, especially in subgroup with UI No protein C, AT III, or APLA20 (80 %) with elevated D-dimer had thrombophilia vs 7 (50 %) with normal D-dimers (p < 0.05) 27 (69 %) with UI had thrombophilia vs 5 (33 %) of fertile controls investigated for VTE (p < 0.05)	3b
[12]	36 UI 65 RPL 62 healthy fertile women	Prevalence of FVL in UI higher than in controls (31 vs 0; p < 0.05) No significant difference between groups in prevalence of MTHFR (50 vs 39 %) or PG (2.8 vs 3.2 %)	3b
Coulan et al., 2006	42 women RIF (≥4 failed IVF) 20 fertile women	74 % combined thrombophilias in RIF vs 20 % controls (P = 0.0004). Higher rates of PAI-1 4G/5G mutations in RIF vs Controls (p = 0.007)	3b
[84]	90 women ≥ 3 failed IVF 90 women successful IVF 100 fertile patients	Thrombophilia (Mut Factor V, Prothrombin 2, MTHFR, def. Prot C, S y AT III y ACL) 68 % (RIF) vs 25 % in the other groups	3b
ĐUva et al., 2007	20 UI 20 RPL 20 healthy controls	75 % in UI homozygous for MTHFR mutation vs 15 % controls (p < 0.05) Total plasma homocysteine sig. higher for UI vs Controls (p < 0.05)	3b
[14]	31 patients with UI 26 with IF 30 with recurrent spontaneous abortion 32 healthy oocyte donors (controls)	Frequency of APCR higher in IF than in controls (4 [15 %] vs 0, p = 0.035) Frequency of LAC nonsignificantly higher in IF group than in controls (3 [12 %] vs 0, p = 0.056)	3b
Coulan et al., 2009	92 women UI 60 fertile control women	Only the frequency of MTHFR C677T differed between groups (64 % vs 22 %; p < 0.01) UI greater number of polymorphisms UI than controls (34 % vs 20 %, p < 0.001)	3b
[17]	32 UI 130 RPL	Difference between groups in heterozygous FV H1299R (p = 0.001) and homozygous MTHFR C677T (p = 0.02) mutations	3b
[94]	1,325 women UI 676 women RIF 789 women RPL 205 fertile control women.	8 % and 9 % APAs in UI and RIF 11 % RPL 0 % fertile women	3b

(continued on next page)

Table 3 (continued)

Authors	Population	Outcomes	Level of evidence
[51]	930 infertile women 240 fertile women	Higher incidences of one or more positive thrombophilic marker and PT mutation in women with UI compared with fertile control	3b
Díaz-Núñez et al. 2019	RIF cases (n = 36)RM cases (n = 43) RIF + RM (n = 76)Control (n = 34)	FXIII higher values in RIF (70 % vs 52 %; p < 0.05)	3b
[110]	59 patients ≥ 2 unsuccessful IVF attempts 20 fertile controls	Increased levels of aPL in unsuccessful IVF No association between inherited thrombophilia and failure to achieve pregnancy	3b
Simur et al. 2008	51 ≥ 3 failed IVF 50 fertile controls	No increased prevalence of FVL, PTM and MTHFR was found compared with the controls	3b
[21]	100 UI 200 fertile women	No sign. difference between groups for any of the genetic polymorphisms analyzed (MTHFR C677T, PG, FVL G1691A)	3b

RIF: repetitive implantation failure; UI: unexplained fertility; IVF: in vitro fertilization; RM: recurrent miscarriage; RPL: recurrent pregnancy loss; APCR: activated protein C resistance; LAC: lupus anticoagulant; FVL: Factor V Leiden; aPL: antiphospholipid antibody.

thrombophilia (evidence 3b) [9].

Plausibility of a pathophysiological link between thrombophilia and impaired implantation and infertility

Although the mechanisms by which thrombophilic gene mutations impact the frequency of RPL are thought to be mainly related to clotting of placental vessels [69], some authors suggest that the mechanisms involved in RIF may involve the effects of hypofibrinolysis on trophoblast migration [58]. Patients with RIF experienced reduced plasma fibrinolytic potential compared with fertile controls or patients with the first cycle of IVF (evidence 2b) [28]. In this regard, women with implantation failure have shown a significant increase in the total number of mutated thrombophilic genes and the plasminogen activator inhibitor-1 (PAI-1) mutations (evidence 3b) [29].

The influence of thrombophilia on UI also seems to implicate folic acid metabolism.⁴⁷ The gene MTHFR encodes the 5-MTHFR enzyme, which is involved in folate metabolism, and C677T/A1298C polymorphisms of this gene have been significantly associated with UI (particularly in association with FVL mutation) [30,46,76] with decreased enzyme activity and consequent changes in homocysteine concentration (evidence 2b) [30,46,76,90]. Folate deficiency and hyperhomocysteinemia can compromise fertility [45] and lead to pregnancy complications by affecting the development of oocytes, preparation of endometrial receptivity, implantation of the embryo, and pregnancy [76]. A correlation between MTHFR C677T mutation and lower ovarian responsiveness (evidence 3b) [108] and male infertility (evidence 1a) [3] has also been found.

Identify patients who could benefit from anticoagulant treatment

In patients with UI and a higher prevalence of thrombophilic traits, screening for thrombophilia could identify women who could benefit from anticoagulant therapy to improve pregnancy outcomes and prevent thromboembolism.

All potential candidates to anticoagulant therapy are patients with previous venous thromboembolism (VTE), all asymptomatic individuals who are first degree relatives of a patient with clinically diagnosed thrombophilia, and asymptomatic women with a family history of VTE

Table 4

a: Risk of venous thromboembolism in pregnancy by type of inherited thrombophilia; b: Recommendations for prenatal thrombophilia testing.

a: Thrombophilia	Odds ratio (95 % CI)*
Factor V Leiden – homozygosity	33.4 (9.8–120.1)26.4 (1.2–559.3)8.3
Prothrombin G20210A – homozygosity	(5.4–12.7)6.8 (2.5–18.8)4.8
Factor V Leiden – heterozygosity	(2.1–10.6)4.7 (1.3–16.9)3.2
Prothrombin G20210A – heterozygosity	(1.5–6.9)0.7 (0.2–2.5)
Protein C deficiency	
Antithrombin deficiency	
Protein S deficiency	
MTHFR C677T – homozygosity	
b: Thrombophilia	Indications for Testing**
Inherited thrombophilia	Personal history of VTE Family history of a diagnosed inherited thrombophilia ^a IUFD (when all other causes have been excluded, severe IUGR, or severe placental pathology) ^b
Acquired thrombophilia	Personal history of VTERecurrent pregnancy loss (≥2 losses at 10 wk)Severe preeclampsia (requiring delivery < 34 wk)Placental insufficiency/IUGR (requiring delivery < 34 wk)

IUFD: intrauterine fetal demise; VTE: venous thromboembolism; IUGR: intra-uterine growth restriction.

** Adapted from: Louis-Jacques AF, Maggio L, Romero ST. Prenatal Screening for Thrombophilias: Indications and Controversies, an Update. Clin Lab Med. 2016;36 (2):421–34.

*The associated risk for VTE is different according to genotype, being higher among the carriers of natural anticoagulant deficiencies and homozygotes for factor V Leiden. Adapted from James AH. Venous thromboembolism in pregnancy. Arterioscler Thromb Vasc Biol. 2009;29(3):326–31.

^a Need for testing is controversial.

^b The American College of Obstetrics and Gynecology (ACOG) recommends testing for inherited thrombophilias after an IUFD in cases of severe placental pathology, severe IUGR, or a family or personal history of VTE.

during pregnancy or before the use of oral contraceptives and hormone replacement therapy, patients with haematologic neoplastic disease and women with pregnancy complications [2,11,33]. Screening is indicated when it could impact medication management and in patients with a thrombotic risk high enough to benefit from this therapy. Based on recent data, thromboprophylaxis in pregnancy may be recommended in cases with a family history of VTE and antithrombin, protein C, or protein S deficiencies, as well as in women homozygous for FV Leiden (Table 4a and b) with positive family history and additional risk factors such prolonged immobilization, obesity, pregnancy complications, and medical co-morbidities [77]. Both UI and RIF may be considered other indications for thromboprophylaxis or lead to the discovery of different reasons for anticoagulation.

Similarly, persistent phospholipid antibodies (aPL) positivity is a risk for thrombotic and pregnancy complications, and appropriate interventions are suggested. At present, testing for aPL antibodies is usually restricted to patients who have had thrombosis, embolism, or pregnancy complications that may be attributable to APS and to patients with systemic lupus erythematosus, even if they have not had any of the above manifestations. Nevertheless, serological aPL profile is emerging as a valuable tool for patient stratification where double/triple positivity identifies patients with the highest risk [15].

Detection of alterations that affect the health of the patient during pregnancy

Thrombophilic traits are suspected to be associated with

Table 5

Cohort studies that analyze the association between in vitro fertilization outcomes and inherited thrombophilias.

Author	Year	Type of study	Factor analyzed	N (mutation/control)	Age (years)	Outcomes	Results Thrombophilia/control	Level of evidence
Dobson et al.	2007	PC	MTHFR (C677T)	197 (101/96)	35.2/35.5	Clinical pregnancies	No effect on positive pregnancy test or clinical pregnancy rate	2b
Rudick et al.	2009	PC	MTHFR (A1298C) FVL	196 (100/96) 182 (3/179)	32.0/35.4	Implantation rate, Clinical pregnancies	FVL mutation prevalence was very low (1.6 %) and had a preliminarily positive association with pregnancy, suggesting that routine testing in a general IVF population for FVL mutation as a cause of IVF failure and infertility is not indicated.	2b
Marci et al.	2012	RC	MTHFR (C677T)	273 (103/170)	33.8/34.6	Implantation rate, clinical pregnancies	The fertilization rate was significantly higher in the control group, although the implantation rate and clinical pregnancies were similar in both groups.	2b
Ricci et al.	2011	PC	FVL/PGM	480 (30/450)	35.1/36.2	Implantation rate, clinical pregnancies	The results of this study suggest that FVL and PGM presence in asymptomatic women and in the absence of other risk factors do not influence IVF outcome, or represent risk factors for ovarian hyperstimulation syndrome (OHSS), or favour thrombosis after IVF. Screening for FVL and PGM does not appear to be justified to identify the patients at the risk for IVF failure, and/or for OHSS, and/or for thrombotic complications	2b
Steinvil et al.	2012	RC	FVL/APCR PGM	445 (35/410) 511 (16/495)	30.9 (4.1)*	Clinical pregnancies	None of the common thrombophilias tested was found to be significantly associated with the number of IVF cycles or with lower fertility success rate. Rather, women who had APCR and/or factor V Leiden and lupus anticoagulant had significantly higher live birth rates (12.3 % and 12.6 %, respectively) in comparison to women who were tested negative (9.0 % and 9.7 %, respectively).	2b
D'Elia et al.	2014	PC	MTHFR (C677T)	82 (47/35)	32.0/31.0	Clinical pregnancies	The C677T variant was associated with proportions of mature (P = 0.006) and immature (P = 0.003) oocytes whereas the A1298C variant was associated with number of oocytes retrieved (P = 0.044). The polymorphisms, whether alone or in combination, were not associated with normal fertilization, good-quality embryo or clinical pregnancy rates.	2b
Patounakis	2015	PC	MTHFR (C677T) FVL PGM MTHFR (A1298C)	1717 (919/798) 1717 (59/1658) 1717 (50/1667) 1717 (927/790)	35.0 (4.4)*	Implantation rate, clinical pregnancies	There were no statistically significant differences in positive pregnancy test, clinical pregnancy, embryo implantation, live birth, or pregnancy loss in the analysis of 1717 patients attempting their first cycle of IVF.	2b

PC prospective cohort, RC retrospective cohort, FVL factor V Leiden, MTHFR 5,10-methylenetetrahydrofolate reductase, PGM prothrombin gene.

G20210A mutation, APCR activated protein C resistance.

*mean age of all participants.

approximately 30–40 % of obstetrical complications, such as thromboembolic events [36,41,97], placental abruption or placental infarction [66,81], placenta-mediated pregnancy disorders [88], intrauterine growth retardation [37,92], preeclampsia [57,64], pregnancy-induced hypertension, and myocardial infarction [32]. Although a causal relationship has not been definitively proven [87], its detection could help detect and manage these complications. Moreover, some specific thrombophilias and/or a combination of thrombophilic factors could carry a greater risk and recurrence for a given adverse outcome (evidence 2a) [65,92].

In women with primary APS, when >1 antiphospholipid antibody is present, an increased risk of obstetric complications and lower live birth rate (LBR) have been described (evidence 2a). In addition, anti-β2 glycoprotein-I is associated with the lowest LBR and highest incidence of preeclampsia, intrauterine growth restriction (IGR), and stillbirth, compared with the presence of anticardiolipin antibodies or lupus anticoagulant alone [64]. UI and RIF screening could therefore help identify asymptomatic patients who could present risks of obstetric complications of thrombophilic origin.

Treatment could improve reproductive outcomes in thrombophilic women with RIF

Recently, two retrospective cohort study suggest that evaluation and management of thrombophilia may be beneficial for patients with UI (evidence 3b) with at least one failed cycle [1,107]. In women with ≥ 3 RIF, a meta-analysis (evidence 2a) [80] that included one study of women with at least one thrombophilia [83] and two studies of women with unexplained RIF [16,109] shows that the use of low molecular weight heparin (LMWH) as an adjunct to IVF treatment significantly improved LBR (RR = 1.79, 95 % CI = 1.10–2.90, P = 0.02) (evidence 1a-). The IR for ≥ 3 RIF (N = 674) showed a trend toward improvement (RR = 1.73, 95 % CI 0.98–3.03, P = 0.06) with LMWH (NNT = 8). However, the beneficial effect of LMWH was not significant when only studies with unexplained RIF were pooled. Some authors suggested that despite the lack of statistical significance in unexplained RIF, the relative increase by 30 % in live births with LMWH may be regarded as a clinically significant trend, necessitating further research. Differences in populations analyzed seem to be relevant if subjects with thrombophilia are included in the studies.

Table 6

Characteristics and outcomes of randomized controlled trials with anticoagulants in women with infertility.

Authors (Year)	Type of study (N)	Thrombophilia included	Inclusion criteria	Exclusion criteria	Group 1 (n)	Group 2 (n)	Outcome	Level of evidence
Outcomes of anticoagulation in women with reproductive failure and thrombophilia								
[83]	RCT (N = 83)	PC, PS, AT, ACL, LA	Three consecutive failed IVF/ICSI with at least one coagulation defect	Known etiologies, endometriosis, PCOS, personal and family history of thrombosis	Enoxaparin 40 mg/day, from the day of embryo transfer until delivery (n = 42)	0.9 % NaCl (n = 41)	LMWH: Better IR, CPR, LBR, & abortion rate	1b
Outcomes of anticoagulation in women with reproductive failure and no thrombophilia								
Urman et al [109]	RCT (N = 150)	MTHFR, FVL, PT, PC, PS, AT, activated PC, ACL, LA	At least two fresh IVF failure in women with unexplained infertility	Both acquired and inherited thrombophilia	Enoxaparin 1 mg/kg/day, from the day after oocyte retrieval to 12th week of pregnancy (n = 75)	None (n = 75)	No improvement of CPR, LBR, IR	1b
Berker et al (2011)	RCT (N = 219)	AT, PC, PS, PT, FVL, MTHFR, LA, ACL	Two RIF	Both acquired and inherited thrombophilia	Enoxaparin 40 mg/day, from the day of oocyte retrieval to 12th week of pregnancy (n = 110)	None (n = 109)	Heparin: Higher LBR, CPR, IR, but not significant	1b
Noci et al (2011)	RCT (N = 153)	AT, PC, PS, activated PC resistance, homocysteine, PT, LA, ACL, Ab2GPI	Women planned first IVF/ICSI, age < 40 years	Both acquired and inherited thrombophilia	Dalteparin 2500 IU/day, from the day of oocyte retrieval to 9th week of pregnancy (n = 73)	None (n = 80)	No significant increase in LBR, CPR, IR, abortion rate	1b
Lodigiani et al. (2017)	RCT (N = 266)	AT, PC, PS, activated PC resistance, PT, LA, ACL	Women planned first IVF/ICSI, ages of 18–40 years	Both acquired and inherited thrombophilia	Parnaparin 4250 IU or 6400 IU daily, from the day before stimulation of ovary, until delivery (n = 135)	None (n = 131)	No difference in LBR, CPR, abortion rate	1b

Abbreviations: Ab2GPI, anti-β2glycoprotein 1 antibody; ACL, anticardiolipin; AT, antithrombin; CPR, clinical pregnancy rate; FVL, factor V Leiden; ICSI, intracytoplasmic sperm injection; IR, implantation.

Adapted from: Han AR, Han JW, Lee SK. *Inherited thrombophilia and anticoagulant therapy for women with reproductive failure. Am J Reprod Immunol.* 2021;85(4):e13378.⁵.

Only one placebo-controlled, randomized trial evaluates the efficacy of thromboprophylaxis (using enoxaparin 40 mg/day) in 83 women with a history of ≥ 3 IVF failures, who had at least one thrombophilic defect [83]. This study showed that patients who received LMWH for thromboprophylaxis significantly increased the implantation and pregnancy rates compared with the placebo controls (20.9 vs 6.1 % and 31 vs 9.6 %, respectively; $p < 0.001$ and $p < 0.05$, respectively). In addition, a significant increase in the LBR was observed in the heparin-treated group compared with placebo (23.8 vs 2.4 %, respectively; $p < 0.01$), suggesting that when thrombophilia is confirmed, anticoagulation treatment could improve reproductive outcomes (evidence 1b).

Similarly, some studies have examined the effect of anticoagulants such as heparin or low-dose aspirin (LDA) on the outcome of IVF in women with antiphospholipid antibodies [23,24,63,95,103,114]. Results suggest a potential improvement in implantation and pregnancy outcomes with anticoagulant therapy but with high heterogeneity of studies (evidence 3b). In a recent systematic review addressing the relationship between aPL and infertility and/or the outcome after ART, only 2 studies out of 8 showed a favorable treatment effect (mostly LDASA), especially on LBR (evidence 1a) [99]. As it has recently been suggested [39,107], a specific evaluation and care of thrombophilias could be beneficial for the management and outcome of primary infertility for patients with at least one failed IVF cycle, but this finding has to be confirmed in good quality studies.

Weakness

No differences in the achievement of pregnancy in patients with or without thrombophilias

Remarkably, the presence of thrombophilic markers, both inherited and acquired, have not been associated with worse pregnancy rates or implantation failure in several cohort studies (Table 5) [30,43,70,78,85,91,102] and meta-analysis (evidence 2a) [34,99,106].

In the meta-analysis of Tan et al. [106] analyzing reproductive outcomes in patients with inherited thrombophilias, there were no significant differences in clinical pregnancy rate (CPR) or IR between the mutation and control groups. Clinical pregnancy was only affected when FVL/APCR mutation was presented (1 cohort study; RR = 1.30, 95 % CI 1.03–1.63, $P = 0.03$) (evidence 2a).

Similarly, in the meta-analysis of Di Nisio et al., although case-control studies suggest that women experiencing assisted reproductive technology (ART) failures are more frequently positive for FVL and antiphospholipid antibodies, the evidence was not supported when only cohort studies were considered (3 cohort studies analyzed FVL and 10 cohort studies analyzed APs). They concluded that thrombophilic traits were not associated with a viable pregnancy, live birth, or higher incidence of negative pregnancy tests (evidence 2a). However, the authors caution that prospective cohort studies were relatively underpowered, and not all studies tested for all major inherited thrombophilias, thereby potentially underestimating risk [40].

Lack of consensus in the thrombophilia panel to be studied

There is no standard protocol to identify thrombophilia [33] (Table 5), and the lack of studies reveals appropriate thrombophilia markers for RF [72]. Current thrombophilia markers were developed to diagnose VTE and their cutoff values need to be set up for women with RF. Moreover, ethnic differences in thrombophilia markers have been described [59], and most case-control studies have been undergone in non-Asian countries so their results cannot be extrapolated to other ethnic groups.

Economic burden

A positive cost-benefit ratio does not support the routine thrombophilia screening in RF [50,93]. In infertile patients, since the possible benefits in reproductive outcomes are not evident, testing for

thrombophilia would seem to be justified in a limited number of patients with precise clinical characteristics and whose risk of complications during pregnancy appears to be substantially raised [112].

Low-quality studies

Another obstacle is the heterogeneity and low quality of the studies. Most studies that analyze the association between infertility and thrombophilias are mainly observational. These studies used diverse research protocols. There was inconsistency in selected inherited thrombophilic markers, inclusion and exclusion criteria of the subjects, the timing of initiation and duration of anticoagulant therapy, as well as the types and doses of anticoagulants (Tables 5 and 6) [55].

Lack of consensus on therapeutic approach

Anticoagulant therapy during pregnancy is complex due to the potential for both fetal and maternal complications. Currently, there is no consensus regarding the treatment to be administered, dose, or treatment duration, and great variability has been found in studies evaluating the use of anticoagulant therapy in women with RIF and thrombophilia (Table 6) [55].

Maternal risks of antithrombotic therapy

Antithrombotic therapy's potential adverse effects are bleeding, local skin reactions, including itching, swelling, and irritation at the injection site [7]. Serious complications, such as osteopenia and Heparin-induced thrombocytopenia (HIT), can be caused by unfractionated heparin (UFH), but these adverse effects are significantly rare in LMWH users [71].

Difficulties in managing bleeding in the first trimester of pregnancy

Administration of anticoagulants increases the risk of bleeding. Pregnant women who require anticoagulants suffer an added level of anxiety regarding excessive bleeding, placental hemorrhage, or implantation bleeding since the management of bleeding in the first trimester is particularly complex and challenging for clinicians [101].

Opportunities

New genetic variants of thrombophilia that could influence the reproductive outcome

It has been suggested that the addition of new diagnostic techniques could achieve results that more definitively clarify the relationship between thrombophilias and RF [54]. Recently developed techniques in genetic screening, mainly next-generation sequencing (NGS), is a possible choice to detect genetic risk variants for thrombophilia in specific populations (Abdi and Osman, 2017) and to detect inherited traits associated with both thrombophilia and RF.

Consider studies with improved designs

The overall prevalence of thrombophilic traits in the general population is low (10 %) [27,33]. Consequently, to establish a precise correlation between this event and infertility, a study with a considerable sample size would have to be conducted, rendering such an endeavor costly and complex. Currently, a large prospective, multicenter, observational study to evaluate pregnancy or ART outcomes in consecutive women with previous RF after spontaneous or assisted conception is underway [111].

Positive side effects of therapy

Thrombophilia may cause significant pregnancy complications, including preeclampsia, placental abruption, IUGR, early and late pregnancy loss, and maternal death that could be prevented by anticoagulation therapy [60,61]. Among the anticoagulants evaluated in studies carried out in pregnant women, the results from clinical trials evaluating LMWH for the prevention of preeclampsia are conflicting [74]. Concerning the use of low-dose aspirin, the available evidence

shows that it is effective in preventing preeclampsia and its complications, mainly if used before gestational week 16 (evidence 1a) [113].

Threats

Overdiagnosis and overtreatment

A recent report that describes an audit of local test findings for a recent period (starting from 2016 to end of June 2018) to analyze the possible ineffectiveness in testing for thrombophilias suggest contemporary futility of genetic testing for thrombophilic traits in the real world, and in particular, in females for indications around pregnancy/fetal morbidity, proposed to be related to poor patient selection in most instances [52].

Regarding treatment, in the absence of well-designed trials comparing routine and prolonged anticoagulant treatment in patients testing positive for thrombophilia, testing for such defects to prolong anticoagulant therapy cannot be justified. Because testing for thrombophilia serves a limited purpose, except for diagnosing APS in women with recurrent miscarriages (evidence 1a) [115], this test should not be performed routinely [75].

Creation of an unrealistic scenario (therapeutic illusion)

Thrombophilia screening requires a targeted patient with a specific indication, in which a finding would have implications. Carrying out a thrombophilia examination is often a cause of uncertainty and concern [26]. Due to the lack of evidence regarding the impact of thrombophilia screening in infertile patients and improvement in reproductive outcomes, recommending its routine use may increase demand and general false expectations in these patients with RF. Indiscriminate testing can result in uncertainty on the practicalities of dealing with positive results [89].

Delegating to other specialties to take decisions on fertility problems

In pregnant women with thrombophilia, monitorization in multidisciplinary consultations allows for individualized follow-up and treatment protocols that improve prognosis. In addition, multidisciplinary teams make preconception counseling, obstetric risk stratification, evaluation of pharmacology safety during pregnancy, and control of maternal-fetal complications possible [5,6]. Thrombophilia screening in infertile patients could increase the demand in other specialties (immunology, hematology, etc.) for the proper management of pregnant women without a real need for such intrusiveness.

Underdiagnosis of other causes of infertility

The overall prevalence of thrombophilic traits in the general population being near to 10 % renders the probability of carrying multiple defects not excessively rare [33]. Thus, a positive screening could represent a considerable delay in initiating other reproductive treatments or discarding the testing of other more probable diagnoses [82].

Perinatal outcomes (possible risks inherent to antithrombotic medication such as malformations)

Although exposure to anticoagulants during pregnancy is considered safe and has not been associated with an increased risk of major malformations in general or according to organ systems, the risk for specific malformations cannot be ruled out [96]. Some congenital malformations have been described very sporadically in pregnant women taking LMWH [35], and gastroschisis has been positively associated with the use of aspirin in early pregnancy [44].

Conclusions

Thrombophilia testing in infertility is still controversial. There is no evidence to support a strong association between thrombophilia and infertility. Thrombophilia testing in this setting may increase cost, with minimal potential benefit and lead to inappropriate use of

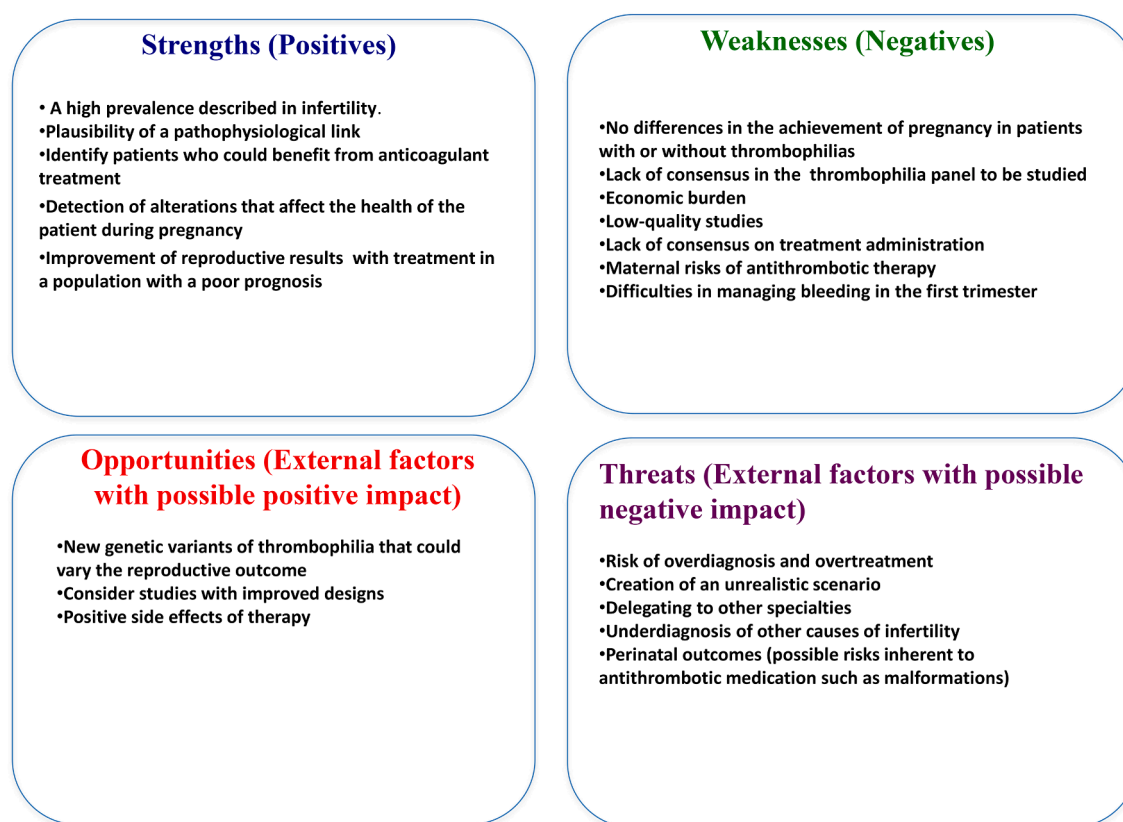


Fig. 1. A SWOT analysis.

anticoagulants with no evidence-based, proven benefit. Following recent recommendations [68], routine testing for inherited and/or acquired thrombophilia in patients with RIF or UI is not recommended, although it could be useful in some instances to identify infertile women who could benefit from anticoagulant therapy. Future well-designed studies are needed to assess the possible benefit of anticoagulant therapy in thrombophilic women with RIF and the possible role of new or multiple thrombophilia traits in infertile couples (Fig. 1).

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Acknowledgements

The author would like to thank Ana Isabel Ortega and Ana Zabala-jaregui, who provided medical writing assistance.

Funding

No funding or sponsorship was received for this study. Support for editorial assistance was funded by IBSA.

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