THE ROLE OF THROMBOPHILIAS IN REPRODUCTION: A SWOT ANALYSIS.

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CONDENSATION PAGE

Condensation: Pending new evidence, it would be advisable not to include thrombophilia screening in the initial baseline study of the infertile couple.

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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.

Keywords: thrombophilia, infertility, recurrent implantation failure, anticoagulants, antiphospholipid syndrome.

INTRODUCTION

Reproductive failure (RF) is the inability to conceive or to carry a pregnancy to term[1] and commonly includes infertility, unexplained infertility (UI), repeated implantation failure (RIF), miscarriage, and recurrent pregnancy loss (RPL) (Choudhury and Knapp, 2001; Kuperman et al., 2011). Among women with repeated RF, the rate of thrombophilia is reported to be as high as 50% in selected studies (Lodigiani et al., 2011). In this regard, although the association between thrombophilia and RPL is well-documented (D'Uva et al., 2008), the association between thrombophilia and unexplained infertility or RIF is still a matter of debate and the focus of this review (Han et al., 2021).

Thrombophilia is related to changes in hemostatic mechanisms, characterized by an increased tendency for the blood to clot and a consequent risk of thromboembolism (Martinelli et al., 2010). 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 β2 glycoprotein I (β2GP1). Importantly, although detected in screening, many individuals who carry a thrombophilic trait remain asymptomatic, at least until additional boosting factors arise (Buchholz and Thaler, 2003).

In pregnant women, thrombophilia is associated with an increased risk of venous thrombosis, fetal loss, and gestational complications (Alijotas-Reig et al., 2016; Pierangeli et al., 2011; Simcox et al., 2015), but the role of thrombophilia in infertility is still controversial. Based mainly on the results of observational studies (Bianca et al., 2009; Coulam and Jeyendran, 2009; Deroux et al., 2017; Di Nisio et al., 2011; Hecht et al., 2009; Ivanov et al., 2012), some authors have suggested that thrombophilias could be involved in infertility and, although there is no clear evidence regarding the positive impact of screening and treatment in these patients (Ricci and Simeone, 2008; Favaloro, 2019), they are used in routine clinical practice (Tan et al., 2005). 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) (Malinowski, 2021).

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/Opportunnities/Threats of the screening and treatment of thrombophilia in infertile women according to the reviewed bibliography, and to know the experts' point of view (Barrow, 2016; Bellver et al., 2019; Blockeel et al., 2016; Bosch et al., 2020; Engmann et al., 2016; Espinós et al., 2021; Esteves et al., 2017; Streuli et al., 2018).

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 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.

1. STRENGTHS

1.1 A high prevalence described in infertility.

Inherited thrombophilia was first reported to have an association with RIF by Grandone et al. (Grandone et al. 2001). 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**) (Azem et al., 2004; Behjati et al. 2006; Coulam et al., 2006; Di Micco et al., 2004; Diaz-Nuñez et al., 2019; Fatini et al., 2012; Grandone et al. 2001; Martinelli et al., 2003; Qublan et al., 2006; Sauer et al., 2010; Simur et al., 2009; Vaquero et al., 2006). It has also been described that among the 7% of patients with RIF in oocyte donation, 16% showed positive results for thrombophilia (**evidence 3b**) (Barri et al., 2014).

1.2 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 (Many et al., 2001), some authors suggest that the mechanisms involved in RIF may involve the effects of hypofibrinolysis on trophoblast migration (Ivanov et al., 2012). Patients with RIF experienced reduced plasma fibrinolytic potential compared with fertile controls or patients with the first cycle of IVF (**evidence 2b**) (Coulam and Jeyendran, 2009). 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**) (Coulam et al., 2006).

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) (D'Elia et al., 2014; Enciso et al., 2016; Milenkovic et al., 2020) with decreased enzyme activity and consequent changes in homocysteine concentration (**evidence 2b**) (D'Elia et al., 2014; Enciso et al., 2016; Milenkovic et al., 2020, Rozen, 1997). Folate deficiency and hyperhomocysteinemia can compromise fertility (Dubey et al., 2013) and lead to pregnancy complications by affecting the development of oocytes, preparation of endometrial receptivity, implantation of the embryo, and pregnancy (Milenkovic et al., 2020). A correlation between MTHFR C677T mutation and lower ovarian responsiveness (**evidence 3b**) (Thaler et al., 2006) and male infertility (**evidence 1a**) (Aliakbari et al. 2020) has also been found.

1.3 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 during pregnancy or before the use of oral contraceptives and hormone replacement therapy, patients with haematologic neoplastic disease and women with pregnancy complications (ACOG, 2018; Bates et al., 2016; De Stefano et al., 2002). 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, b**) with positive family history and additional risk factors such prolonged immobilization, obesity, pregnancy complications, and medical co-morbidities (Ormesher et al., 2017). 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 erythematous, even if they have not had any of the above manifestations. Nevertheless, serological aPL profile is emerging as a valuable tool for patient

184 stratification where double/triple positivity identifies patients with the highest risk
185 (Beltagy et al., 2021).

186

187 **1.4 Detection of alterations that affect the health of the patient during pregnancy**

188 Thrombophilic traits are suspected to be associated with approximately 30-40% of
189 obstetrical complications, such as thromboembolic events (DeSancho et al., 2010; Di
190 Prima et al., 2011; Sikouras et al., 2017), placental abruption or placental infarction
191 (Procházka et al., 2007; Livrinova et al., 2015), placenta-mediated pregnancy disorders
192 (Rodger et al.,2016), intrauterine growth retardation (D'Ettore et al., 2011; Saccone et al.,
193 2017), preeclampsia (Larciprete et al., 2003; Heilmann et al., 2011), pregnancy-induced
194 hypertension, and myocardial infarction (Dankova et al., 2017). Although a causal
195 relationship has not been definitively proven (Robertson et al., 2006), its detection could
196 help detect and manage these complications. Moreover, some specific thrombophilias
197 and/or a combination of thrombophilic factors could carry a greater risk and recurrence
198 for a given adverse outcome (**evidence 2a**) (Saccone et al., 2017; Larciprete et al., 2010).

199 In women with primary APS, when >1 antiphospholipid antibody is present, an increased
200 risk of obstetric complications and lower live birth rate (LBR) have been described
201 (**evidence 2a**). In addition, anti-β2 glycoprotein-I is associated with the lowest LBR and
202 highest incidence of preeclampsia, intrauterine growth restriction (IGR), and stillbirth,
203 compared with the presence of anticardiolipin antibodies or lupus anticoagulant alone
204 (Larciprete et al., 2003). UI and RIF screening could therefore help identify
205 asymptomatic patients who could present risks of obstetric complications of
206 thrombophilic origin.

1.5 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 (Tanacan and Beksac, 2019; Abrahamyan, 2017). In women with ≥3 RIF, a meta-analysis **(evidence 2a)** (Potdar et al., 2013) that included one study of women with at least one thrombophilia (Qublan et al., 2008) and two studies of women with unexplained RIF (Urman et al., 2009; Berker et al., 2011) 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.

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 (Qublan et al., 2008). 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 (Chen et al., 2017; Chighizola et al., 2016; Kutteh et al., 1997; Sher et al., 1994; Stern et al., 2003; Ying et al., 2012). 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**) (Simopoulou et al., 2017). As it has recently been suggested (Di Micco et al., 2020; Tanacan and Beksac 2019), 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.

2. WEAKNESS

2.1 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)** (D'Elia et al., 2014; Dobson et al., 2007; Marci et al., 2012; Patounakis et al., 2015; Ricci et al., 2011; Rudick et al., 2009; Steinvil et al., 2012) and meta-analysis (**evidence 2a**) (Deroux et al., 2017; Simopoulou et al., 2019; Tan et al., 2016).

In the meta-analysis of Tan et al. (Tan et al., 2016) 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 (Di Nisio et al., 2011).

2.2 Lack of consensus in the thrombophilia panel to be studied

There is no standard protocol to identify thrombophilia (Dankova et al. 2017) (Table 5), and the lack of studies reveals appropriate thrombophilia markers for RF (Martinelli et al., 2010). 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 (Jerrard-Dunne et al., 2003), and most case-control studies have been undergone in non-Asian countries so their results cannot be extrapolated to other ethnic groups.

2.3 Economic burden

A positive cost-benefit ratio does not support the routine thrombophilia screening in RF (Fábregues et al., 2004; Salvagno et al., 2007). 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 (Wormer et al., 2018).

2.4 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**) (Han et al., 2021).

2.5 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) (Han et al., 2021).

2.6 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 (Arachchillage and Makris, 2019). 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 (Martel et al., 2005).

2.7 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 (Snell et al., 2009).

3. OPPORTUNITIES

3.1 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 (Hamdi et al., 2012). 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.

3.2 Consider studies with improved designs

The overall prevalence of thrombophilic traits in the general population is low (10%) (Colucci and Tsakiris, 2017; De Stefano et al., 2002). 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 (Villani et al., 2019).

3.3 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 (Kofinas et al., 2018; Kosar et al., 2011). 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 (McLaughlin et al., 2018). 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**) (Xu et al., 2015).

4. THREATS

4.1 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 (Favaloro, 2019).

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**) (Xu et al., 2021)[108], this test should not be performed routinely (Middeldorp, 2011).

4.2 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 (Colucci and Tsakiris, 2020). 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 (Royal College of Obstetricians and Gynaecologists Guidelines, 2015).

4.3 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 (Andreoli et al., 2017; Añón-Oñate et al., 2021) 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.

4.4 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 (De Stefano et al., 2002). Thus, a positive screening could represent a considerable delay in initiating other reproductive treatments or discarding the testing of other more probable diagnoses (Quaas and Dokras, 2008).

4.5 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 (Shlomo et al., 2017). Some congenital malformations have been described very sporadically in pregnant women taking LMWH (Deruelle et al., 2016), and gastroschisis has been positively associated with the use of aspirin in early pregnancy (Draper et al., 2008).

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 anticoagulants with no evidence-based, proven benefit. Following recent recommendations (Malinowski, 2021), 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).

Authors' roles

All authors have contributed to the conception and design, analysis and interpretation of data, drafting the article and revising it critically for important intellectual content, and to the final approval of the version to be published.

Conflict of interest

The authors declare that there were no conflicts of interest.

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REFERENCES

1. Abrahamyan, G., 2017. Results of preparation and implementation of IVF program in patients with thrombophilia and history of failed IVF. Georgian Med News. (268-269), 17-23.
2. ACOG Practice Bulletin No. 196, 2018. Thromboembolism in Pregnancy. Obstet Gynecol. 132(1), e1-e17.

3. Aliakbari, F., Pouresmaeili, F., Eshghifar, N., Zolghadr, Z., Azizi, F., 2020. Association of the MTHFR 677C>T and 1298A>C polymorphisms and male infertility risk: a meta-analysis. Reprod Biol Endocrinol. 18(1), 93.

4. Alijotas-Reig, J., Ferrer-Oliveras, R., Esteve-Valverde, E., Ruffatti, A., Tincani, A., Lefkou, E., Bertero, M.T., Espinosa, G., Coloma, E., de Carolis, S., Rovere-Querini, P., Canti, V., Picardo, E., Fredi, M., Mekinian, A., EUROAPS Study Group., 2016. Inherited thrombophilia in women with poor aPL-related obstetric history: prevalence and outcomes. Survey of 208 cases from the European Registry on Obstetric Antiphospholipid Syndrome cohort. Am J Reprod Immunol. 76(2), 164-171.

5. Andreoli, L., Bertsias, G.K., Agmon-Levin, N., 2017. EULAR recommendations for women's health and the management of family planning, assisted reproduction, pregnancy and menopause in patients with systemic lupus erythematosus and/or antiphospholipid syndrome. Ann. Rheum. Dis. 2017; 76: 476–485.

6. Añón-Oñate, I., Cáliz-Cáliz, R., Rosa-Garrido, C., Pérez-Galán, M.J., Quirosa-Flores, S., Pancorbo-Hidalgo, P.L., 2021. Multidisciplinary Unit Improves Pregnancy Outcomes in Women with Rheumatic Diseases and Hereditary Thrombophilias: An Observational Study. J Clin Med. 10(7), 1487.

7. Arachchillage, D.R.J., Makris, M., 2019. Inherited thrombophilia and pregnancy complications: should we test? Semin Thromb Hemost. 45(1), 50-60.

8. Azem, F., Many, A., Ben Ami, I., Yovel, I., Amit, A., Lessing, J.B., Kupferminc, M.J. Increased rates of thrombophilia in women with repeated IVF failures. Hum Reprod. 2004;19(2):368-370.

438 9. Barri, P.N., Coroleu, B., Clua, E., Tur, R., Boada, M., Rodriguez, I., 2014.
439 Investigations into implantation failure in oocyte-donation recipients. Reprod
440 Biomed Online. 28(1), 99-105.

441 10. Barrow, P., 2016. Revision of the ICH guideline on detection of toxicity to
442 reproduction for medicinal products: SWOT analysis. Reprod Toxicol. 64, 57-63.

443 11. Bates, S.M., Middeldorp, S., Rodger, M., James, A.H., Greer, I., 2016. Guidance
444 for the treatment and prevention of obstetric associated venous thromboembolism.
445 J Thromb Thrombolysis. 41(1), 92-128.

446 12. Behjati, R., Modarressi, M., Jeddi-Tehrani, M., Dokoohaki, P., Ghasemi, J.,
447 Zarnani, A., Aarabi, M., Memariani, T., Ghaffari, M., & Akhondi, M., 2006.
448 Thrombophilic mutations in Iranian patients with infertility and recurrent
449 spontaneous abortion. Annals of Hematology, 85(4), 268-271.

450 13. Bellver, J., Bosch, E., Espinós, J.J., Fabregues, F., Fontes, J., García-Velasco, J.,
451 Llácer, J., Requena, A., Checa, M.A. Spanish Infertility SWOT Group (SISG),
452 2019. Second-generation preimplantation genetic testing for aneuploidy in
453 assisted reproduction: a SWOT analysis. Reprod Biomed Online. 39(6), 905-915.

454 14. Bellver, J., Soares, S.R., Alvarez, C., Muñoz, E., Ramírez, A., Rubio, C., Serra,
455 V., Remohí, J., Pellicer, A., 2008. The role of thrombophilia and thyroid
456 autoimmunity in unexplained infertility, implantation failure and recurrent
457 spontaneous abortion. Hum. Reprod. 23(2), 278-284.

458 15. Beltagy, A., Trespidi, L., Gerosa, M., Ossola, M.W., Meroni, P.L., Chighizola,
459 C.B., 2021. Antiphospholipid antibodies and reproductive failures. Am J Reprod
460 Immunol. 85(4), e13258.

16. Berker, B., Taşkin, S., Kahraman, K., Taşkin, E.A., Atabekoğlu, C., Sönmezer, M., 2011. The role of low-molecular-weight heparin in recurrent implantation failure: a prospective, quasi-randomized, controlled study. Fertil Steril. 95(8), 2499-2502.

17. Bianca, S., Barrano, B., Cutuli, N., Indaco, L., Cataliotti, A., Milana, G., Barone, C., Ettore, G., 2009. Unexplained infertility and inherited thrombophilia. Fertil Steril 92.e4.

18. Blockeel, C., Drakopoulos, P., Santos-Ribeiro, S., Polyzos, N.P., Tournaye, H., 2016. A fresh look at the freeze-all protocol: a SWOT analysis. Hum Reprod. 31(3), 491-497.

19. Bosch E, Espinós JJ, Fabregues F, Fontes, J., García-Velasco, J., Llácer, J., Requena, A., Checa, M.A., Bellver, J. Spanish Infertility SWOT Group (SISG), 2020. Always ICSI? A SWOT analysis. J Assist Reprod Genet. 37(9), 2081-2092.

20. Buchholz, T., Thaler, C.J., 2003. Inherited Thrombophilia: Impact on Human Reproduction. American Journal of Reproductive Immunology. 50, 20-32.

21. Casadei, L., Puca, F., Privitera L, Zamaro V, Emidi E. Inherited thrombophilia in infertile women: implication in unexplained infertility. Fertil Steril 2010;94(02):755–757

22. Checa MA, Bellver J, Bosch E, Espinós, J.J., Fabregues, F., Fontes, J., García-Velasco, J., Llácer, J., Requena, A., 2018. Hysteroscopic septum resection and reproductive medicine: A SWOT analysis. Reprod Biomed Online. 37(6), 709-715.

483 23. Chen, X., Mo, M.L., Huang, C.Y., Diao, L.H., Li, G.G., Li, Y.Y., Lerner, A.,
484 Shoenfeld, Y., Zeng, Y., 2017. Association of serum autoantibodies with
485 pregnancy outcome of patients undergoing first IVF/ICSI treatment: a prospective
486 cohort study. J Reprod Immunol. 122, 14-20.

487 24. Chighizola, C.B., DeJesus, G.R., Branch, D.W., 2016. The hidden world of
488 antiphospholipid antibodies and female infertility: a literature appraisal.
489 Autoimmun Rev. 15, 493-500.

490 25. Choudhury, S.R., Knapp, L.A., 2001. Human reproductive failure I:
491 immunological factors. Hum Reprod Update. 7(2), 113-134.

492 26. Colucci, G., Tsakiris, D.A. Thrombophilia screening revisited: an issue of
493 personalized medicine. J Thromb Thrombolysis 2020;49, 618–629.

494 27. Colucci, G., Tsakiris, D.A., 2017. Thrombophilia Screening: Universal, Selected,
495 or Neither? Clin Appl Thromb Hemost. 23(8), 893-899.

496 28. Coulam, C.B., Jeyendran, R.S., 2009. Thrombophilic gene polymorphisms are
497 risk factors for unexplained infertility. Fertil Steril. 91(4 Suppl), 1516–1517.

498 29. Coulam, C.B., Jeyendran, R.S., 2009. Thrombophilic gene polymorphisms are
499 risk factors for unexplained infertility. Fertil Steril. 91(4 Suppl), 1516-1517.

500 30. Coulam, C.B., Jeyendran, R.S., Fishel, L.A., Roussev, R., 2006. Multiple
501 thrombophilic gene mutations are risk factors for implantation failure. Reprod
502 Biomed Online. 12(3), 322-327.

503 31. D'Elia, P.Q., dos Santos, A.A., Bianco, B., Barbosa, C.P., Christofolini, D.M.,
504 Aoki, T., 2014. MTHFR polymorphisms C677T and A1298C and associations
505 with IVF outcomes in Brazilian women. Reprod Biomed Online. 2, 733–738.

506 32. D'Uva, M., Di Micco, P., Strina, I., Ranieri, A., Alviggi, C., Mollo, A., Fabozzi,
507 F., Cacciapuoti, L., di Frega, M.T.S, Iannuzzo, M., De Placido, G., 2008.
508 Etiology of hypercoagulable state in women with recurrent fetal loss without other
509 causes of miscarriage from Southern Italy: new clinical target for antithrombotic
510 therapy. Biologics. 2(4), 897–902.

511 33. Dankova, I.V., Aleksandrovna, M.O., Borisovna, T.T., Anatolyevna P.L., 2017.
512 Genetic and hemostasiological predictors of IVF pregnancy. Gynecological
513 Endocrinology: the Official Journal of the International Society of Gynecological
514 Endocrinology. 33(sup1), 32-35.

515 34. Dankova, I.V., Aleksandrovna, M.O., Borisovna, T.T., Anatolyevna, P.L.,
516 Olegovich, M.D., Valeryevna, C.O., Evgenyevich, R.N., 2017. Genetic and
517 hemostasiological predictors of IVF pregnancy. Gynecological Endocrinology:
518 the Official Journal of the International Society of Gynecological Endocrinology.
519 233(sup1), 32-35.

520 35. De Stefano, V., Rossi, E., Paciaroni, K., Leone, G., 2002. Screening for inherited
521 thrombophilia: indications and therapeutic implications. Haematologica, 87,
522 1095–1108.

523 36. Deroux, A., Dumestre-Perard, C., Dunand-Faure, C., Bouillet, L., Hoffmann, P.,
524 2017. Female Infertility and Serum Auto-antibodies: A Systematic Review. Clin.
525 Rev. Allergy Immunol. 53, 78–86.

526 37. Deruelle, P., Denervaud, M., Hachulla, E., Ducloy-Bouthors, A.S., Valat, A.S.,
527 Puech, F., Trillot, N., Hatron, P.Y., Subtil, D., 2016. Use of low-molecular-weight
528 heparin from the first trimester of pregnancy: a retrospective study of 111
529 consecutive pregnancies. Eur J Obstet Gynecol Reprod Biol. 127(1),73-78.

530 38. DeSancho, M.T., Berlus, N., Christos, P.J., Rand, J., 2010. Risk factors for clinical
531 manifestations in carriers of Factor V Leiden and prothrombin gene mutations.
532 Blood Coagul Fibrinolysis. 21(1), 11-15.

533 39. D'Ettore, A., Fusco, R., Esposito, M., Pareto, A.E., 2011. Thrombophilia and
534 autoimmune diseases in pregnancy: Implications for pregnancy outcomes.
535 Giornale Italiano di Ostetricia e Ginecologia. 33, 34-36.

536 40. Di Micco, P., D'Uva, M., Strina, I., Mollo, A., Amato, V., Niglio, A., & De
537 Placido, G., 2004. The role of D-dimer as first marker of thrombophilia in women
538 affected by sterility: implications in pathophysiology and diagnosis of
539 thrombophilia induced sterility. J Transl Med. 2(01), 38

540 41. Di Micco, P., Russo, V., Mastroiacovo, D., Bosevski, M., Lodigiani, C., 2020. In
541 vitro Fertilization Procedures with Embryo Transfer and Their Association with
542 Thrombophilia, Thrombosis and Early Antithrombotic Treatments. J Blood Med.
543 11:185-190.

544 42. Di Nisio, M., Rutjes, A.W.S., Ferrante, N., Tiboni, G.M., Cuccurullo, F., Porreca,
545 E., 2011. Thrombophilia and outcomes of assisted reproduction technologies: a
546 systematic review and meta-analysis. Blood. 118(10), 2670–2678.

547 43. Di Prima, F. A., Valenti, O., Hyseni, E., Giorgio, E., Faraci, M., Renda, E., De
548 Domenico, R., & Monte, S., 2011. Antiphospholipid Syndrome during pregnancy:
549 The state of the art. J. Prenat. Med. 5, 41–53.

550 44. Diaz-Nuñez, M., Rabanal, A., Expósito, A., Ferrando, M., Quintana, F., Soria,
551 J.M., Matorras, R., 2019. Recurrent Miscarriage and Implantation Failure of
552 Unknown Cause Studied by a Panel of Thrombophilia Conditions: Increased
553 Frequency of FXIII Val34Leu Polymorphism. J Reprod Infertil. 20(2), 76-82.

554 45. Dobson, A.T, Davis, R.M., Rosen, M.P., Shen, S., Rinaudo, P.F., Chan, J., Cedars,
555 M.I., 2007. Methylenetetrahydrofolate reductase C677T and A1298C variants do
556 not affect ongoing pregnancy rates following IVF. Hum Reprod. 22:450–456.

557 46. Draper, E.S., Rankin, J., Tonks, A.M., Abrams, K.R., Field, D.J., Clarke, M.,
558 Kurinczuk, J.J., 2008. Recreational drug use: a major risk factor for gastroschisis?
559 Am J Epidemiol. 167(4), 485-491.

560 47. Dubey, P., Gupta, N., Diwedi, S., 2013. Hyperhomocysteinemia: a risk factor in
561 unexplained infertility. Int J Reprod Contracept Obstet Gynecol. 2(2), 165-171.

562 48. Enciso, M., Sarasa, J., Xanthopoulou, L., Bristow, S., Bowles, M., Fragouli, E.,
563 Delhanty, J., Wells, D., 2016. Polymorphisms in the MTHFR gene influence
564 embryo viability and the incidence of aneuploidy. Hum Genet. 135(5), 555-568.

565 49. Engmann, L., Benadiva, C., Humaidan, P., 2016. GnRH agonist trigger for the
566 induction of oocyte maturation in GnRH antagonist IVF cycles: a SWOT analysis.
567 Reprod Biomed Online. 2016; 32(3):274-85.

568 50. Espinós JJ, Fabregues F, Fontes J, García-Velasco JA, Llácer J, Requena A, Checa
569 MÁ, Bellver J; Spanish Infertility SWOT Group (SISG), 2021. Impact of chronic
570 endometritis in infertility: a SWOT analysis. Reprod Biomed Online. 42(5), 939-
571 951.

572 51. Esteves, S.C., Agarwal, A., Cho, C.L., Majzoub, A., 2017. A Strengths-
573 Weaknesses-Opportunities-Threats (SWOT) analysis on the clinical utility of
574 sperm DNA fragmentation testing in specific male infertility scenarios. Transl
575 Androl Urol. 6(Suppl 4), S734-S760

576 52. Fábregues, F., Tàssies, D., Reverter, J.C., Carmona, F., Ordinas, A., Balasch, J.,
577 2004. Prevalence of thrombophilia in women with severe ovarian
578 hyperstimulation syndrome and cost-effectiveness of screening. Fertil Steril.
579 81(4), 989-995.

580 53. Fatini, C., Conti, L., Turillazzi, V., Sticchi, E., Romagnuolo, I., Milanini, M.N.,
581 Cozzi, C., Abbate, R., Noci, I., 2012. Unexplained infertility: association with
582 inherited thrombophilia. Thromb Res.129(5):e185-188.

583 54. Favaloro, E.J., 2019. Genetic Testing for Thrombophilia-Related Genes:
584 Observations of Testing Patterns for Factor V Leiden (G1691A) and Prothrombin
585 Gene "Mutation" (G20210A). Semin Thromb Hemost. 45(7), 730-742.

586 55. Grandone, E., Colaizzo, D., Lo Bue, A., Checola, M.G., Cittadini, E.,
587 Margaglione, M., 2001. Inherited thrombophilia and in vitro fertilization
588 implantation failure. Fertil Steril. 76(1), 201-202.

589 56. Hamdi, K., Vaezi, M., Dagigazar, B., Mehrzad-Sadagiani, M., Farzadi, L.,
590 Pashaei-Asl, M., 2012. Association between Thrombophilia and Repeated
591 Assisted Reproductive Technology Failures. Adv Pharm Bull. 2(2), 233-237.

592 57. Han, A.R., Han, J.W., Lee, S.K., 2021. Inherited thrombophilia and anticoagulant
593 therapy for women with reproductive failure. Am J Reprod Immunol. 85(4),
594 e13378.

595 58. Hecht, S., Pavlik, R., Lohse, P., Noss, U., Friese, K., Thaler, C.J., 2009. Common
596 677C > T mutation of the 5,10-methylenetetrahydrofolate reductase gene affects
597 follicular estradiol synthesis. Fertil Steril. 91, 56–61.

598 59. Heilmann, L., Schorsch, M., Hahn, T., Fareed, J., 2011. Antiphospholipid
599 syndrome and preeclampsia. Semin. Thromb. Hemost. 37:141–145.

600 60. Ivanov, P., Tsvyatkovska, T., Konova, E., Komsa-Penkova, R., 2012. Inherited
601 thrombophilia and IVF failure: the impact of coagulation disorders on
602 implantation process. Am J Reprod Immunol. 68(3), 189-198.

603 61. Ivanov, P., Tsvyatkovska, T., Konova, E., Komsa-Penkova, R., 2012. Inherited
604 thrombophilia and IVF failure: the impact of coagulation disorders on
605 implantation process. Am J Reprod Immunol. 68(3), 189-198.

606 62. Jerrard-Dunne, P., Evans, A., McGovern, R., Hajat, C., Kalra, L., Rudd, A.G.,
607 Wolfe, C.D., Markus, H.S., 2003. Ethnic differences in markers of thrombophilia:
608 implications for the investigation of ischemic stroke in multiethnic populations:
609 the South London Ethnicity and Stroke Study. Stroke. 34(8):1821-6.

610 63. Kofinas, A., Bell, E., Kofinas, J.D., 2018. Improved Outcomes in ART
611 Pregnancies Complicated by Thrombophilia, Treated with Low Molecular Weight
612 Heparin in Comparison to Spontaneously Conceived Low-Risk, Untreated
613 Pregnancies: A Case Control Study. Obstetrics & Gynecology International
614 Journal. 9:1-5.

615 64. Kosar, A., Kasapoglu, B., Kalyoncu, S., Turan, H., Balcik, O.S., Gümüs, E.I.,
616 2011. Treatment of adverse perinatal outcome in inherited thrombophilias: a
617 clinical study. Blood Coagul Fibrinolysis. 22(1), 14-8.

618 65. Kuperman, A., Di Micco, P., Brenner, B., 2011. Fertility, infertility and
619 thrombophilia. Womens Health (Lond). 7(5), 545.

66. Kutteh, W.H., Yetman, D.L., Chantilis, S.J, Crain, J., 1997. Effect of antiphospholipid antibodies in women undergoing in vitro fertilization: role of heparin and aspirin. Hum. Reprod. 12(6), 1171–1175.

67. Larciprete, G., Gioia, S., Angelucci, P.A., Brosio, F., Barbati, G., Angelucci, G.P., Frigo, M.G., Baiocco, F., Romanini, M.E., Arduini, D., Cirese, E., 2003. Single inherited thrombophilias and adverse pregnancy outcomes. J Obstet Gynaecol Res. 33(4), 423–430.

68. Larciprete, G., Rossi, F., Deaibess, T., Brienza, L., Barbati, G., Romanini, E., Gioia, S., Cirese, E., 2010. Double inherited thrombophilias and adverse pregnancy outcomes: Fashion or science? Journal of Obstetrics and Gynaecology Research. 36, 996-1002.

69. Livrinova, V., Lega, M.H., Dimcheva, A.H., Samardziski, I., Isjanovska, R., 2015. Factor V Leiden, Prothrombin and MTHFR Mutation in Patients with Preeclamsia, Intrauterine Growth Restriction and Placental Abruption. Open Access Maced J Med Sci. 3(4), 590-594.

70. Lodigiani, C., Di Micco, P., Ferrazzi, P., Librè, L., Arfuso, V., Polatti, F., Benigna, M., Rossini, R., Morenghi, E., Rota, L., Brenner, B., Setti, P.E., 2011. Low-molecular-weight heparin in women with repeated implantation failure. Womens Health (Lond). 7(4), 425-431.

71. Malinowski, A.K., 2021. The Pathophysiology of Hypercoagulability and Infertility. Semin Reprod Med. 39(1-02), 34-61.

72. Many, A., Schrieber, L., Rosner, S., Lessing, J.B., Eldor, A., Kupferminc, M.J., 2001. Pathologic features of the placenta in women with severe pregnancy complications and thrombophilia. Obstet Gynecol. 98, 1041–1044.

644 73. Marci, R., Lisi, F., Soave, I., Lo Monte, G., Patella, A., Caserta, D., Moscarini,
645 M., 2012. Impact of 677C > T mutation of the 5,10-methylenetetrahydrofolate
646 reductase on IVF outcome: is screening necessary for all infertile women? Genet
647 Test Mol Biomark. 16, 1011–1014.

648 74. Martel, N., Lee, J., Wells, P.S., 2005. Risk for heparin-induced thrombocytopenia
649 with unfractionated and low-molecular-weight heparin thromboprophylaxis: a
650 meta-analysis. Blood. 106(8), 2710-2715.

651 75. Martinelli, I., Bucciarelli, P., Mannucci, P.M., 2010. Thrombotic risk factors:
652 basic pathophysiology. Crit Care Med. 38(2 Suppl), S3–S9.

653 76. Martinelli, I., Taioli, E., Ragni, G., 2003. Embryo implantation after assisted
654 reproductive procedures and maternal thrombophilia. Haematologica 88(7): 789–
655 793.

656 77. McLaughlin, K., Scholten, R.R., Parker, J.D., Ferrazzi, E., Kingdom, J.C.P., 2018.
657 Low molecular weight heparin for the prevention of severe preeclampsia: where
658 next? Br J Clin Pharmacol. 84(4), 673-678.

659 78. Middeldorp, S., 2011. Is thrombophilia testing useful? Hematology Am Soc
660 Hematol Educ Program. (1), 150-155.

661 79. Milenkovic, J., Milojkovic, M., Mitić, D., Stoimenov, T.J., Smelcerovic, Z.,
662 Stojanović, D., Vujic, S., & Bojanić, N., 2020. Interaction of thrombophilic SNPs
663 in patients with unexplained infertility-multifactor dimensionality reduction
664 (MDR) model analysis. J Assist Reprod Genet. 2020;37(6):1449-1458.

80. Ormesher, L., Simcox, L.E., Tower, C., Greer, I.A., 2017. 'To test or not to test', the arguments for and against thrombophilia testing in obstetrics. Obstet Med. 10(2), 61-66.

81. Patounakis, G., Bergh, E., Forman, E.J., Tao, X., Lonczak, A., Franasiak, J.M., Treff, N., Scott, R.T. Jr., 2016. Multiple thrombophilic single nucleotide polymorphisms lack a significant effect on outcomes in fresh IVF cycles: an analysis of 1717 patients. J Assist Reprod Genet. 33(1), 67-73.

82. Pierangeli, S.S., Leader, B., Barilaro, G., Willis, R., Branch, D.W., 2011. Acquired and inherited thrombophilia disorders in pregnancy. Obstet Gynecol Clin North Am. 38(2), 271-295.

83. Potdar, N., Gelbaya, T.A., Konje, J.C., Nardo, L.G., 2013. Adjunct low-molecular-weight heparin to improve live birth rate after recurrent implantation failure: a systematic review and meta-analysis, Human Reproduction Update. 19 (6), 674–684.

84. Procházka, M., Lubuský, M., Slavík, L., Hrachovec, P., Zielina, P., Kudela, M., Lindqvist, P.G., 2007. Frequency of selected thrombophilias in women with placental abruption. Aust N Z J Obstet Gynaecol. 47(4), 297-301.

85. Quaas, A., Dokras, A., 2008. Diagnosis and treatment of unexplained infertility. Rev Obstet Gynecol. 1(2), 69–76.

86. Qublan, H., Amarin, Z., Dabbas, M., Farraj, A.E., Beni-Merei, Z., Al-Akash, H., Bdoor, A.N., Nawasreh, M., Malkawi, S., Diab, F., Al-Ahmad, N., Balawneh, M., Abu-Salim, A., 2008. Low-molecular-weight heparin in the treatment of recurrent IVF-ET failure and thrombophilia: a prospective randomized placebo-controlled trial. Hum Fertil (Camb). 11(4), 246-253.

689 87. Qublan, H.S., Eid, S.S., Ababneh, H.A., 2006. Acquired and inherited
690 thrombophilia: implication in recurrent IVF and embryo transfer failure. Hum.
691 Reprod. 21(10), 2694–2698.

692 88. Ricci, G., Bogatti, P., Fischer-Tamaro, L., Giolo, E., Luppi, S., Montico, M.,
693 Ronfani, L., Morgutti, M., 2011. Factor V Leiden and prothrombin gene G20210A
694 mutation and in vitro fertilization: prospective cohort study. Hum Reprod.
695 26:3068–3077.

696 89. Ricci, G., Simeone, R., 2008. Thrombophilic screening in clinical practice should
697 be evidence-based. Hum. Reprod. 23(11), 2610–2601.

698 90. Robertson, L., Wu, O., Langhorne, P., 2006. Thrombophilia in pregnancy: a
699 systematic review. Br. J. Haematol. 132(2), 171–196.

700 91. Rodger, M.A., Gris, J.C., de Vries, J.I.P., Martinelli, I., Rey, É., Schleussner, E.,
701 Middeldorp, S., Kaaja, R., Langlois, N.J., Ramsay, T., Mallick, R., Bates, S.M.,
702 Abheiden, C.N.H., Perna, A., Petroff, D., de Jong, P., van Hoorn, M.E., Bezemer,
703 P.D., Mayhew, A.D., 2016. Low-molecular-weight heparin and recurrent
704 placenta-mediated pregnancy complications: a meta-analysis of individual patient
705 data from randomised controlled trials. Lancet. 388(10060), 2629-2641.

706 92. Royal College of Obstetricians and Gynaecologists Green-top Guidelines 37a,
707 April 2015

708 93. Rozen, R., 1997. Genetic predisposition to hyperhomocysteinemia: deficiency of
709 methylenetetrahydrofolate reductase (MTHFR). Thromb Haemost 78, 523–526.

710 94. Rudick, B., Su, H.I., Sammel, M.D., Kovalevsky, G., Shaunik, A., Barnhart, K.,
711 2009. Is factor V Leiden mutation a cause of in vitro fertilization failure? Fertil
712 Steril. 92:1256–9.

713 95. Saccone, G., Berghella, V., Maruotti, G.M., Ghi, T., Rizzo, G., Simonazzi, G.,
714 Rizzo, N., Facchinetti, F., Dall'Asta, A., Visentin, S., Sarno, L., Xodo, S.,
715 Bernabini, D., Monari, F., Roman, A., Eke, A.C., Hoxha, A., Ruffatti, A., Schuit,
716 E., Martinelli, P.; PREGNANTS (PREGNancy in women with ANTiphospholipid
717 Syndrome) working group., 2017. Antiphospholipid antibody profile based
718 obstetric outcomes of primary antiphospholipid syndrome: the PREGNANTS
719 study. Am J Obstet Gynecol. 216(5), 52

720 96. Salvagno, G.L., Lippi, G., Franchini, M., Targher, G., Montagnana, M., Franchi,
721 M., Guidi, G.C., 2007. The cost-benefit ratio of screening pregnant women for
722 thrombophilia. Blood Transfus. 5(4), 189-203.

723 97. Sauer, R., Roussev, R., Jeyendran, R.S., Coulam, C.B., 2010. Prevalence of
724 antiphospholipid antibodies among women experiencing unexplained infertility
725 and recurrent implantation failure. Fertil Steril. 93(7), 2441-2443.

726 98. Sher, G., Feinman, M., Zouves, C., 1 High fecundity rates following in vitro
727 fertilization and embryo transfer in antiphospholipid antibody seropositive
728 women treated with heparin and aspirin. Hum. Reprod. 1994; 9(12), 2278–2283.

729 99. Shlomo, M., Gorodischer, R., Daniel, S., Wiznitzer, A., Matok, I., Fishman, B.,
730 Koren, G., Levy, A., 2017. The Fetal Safety of Enoxaparin Use During
731 Pregnancy: A Population-Based Retrospective Cohort Study. Drug Saf.
732 40(11):1147-1155.

733 100. Sikouras, P., von Tempelhoff, G.F., Rath, W., 2017. Epidemiology, Risk
734 Factors and Risk Stratification of Venous Thromboembolism in Pregnancy and
735 the Puerperium. Z Geburtshilfe Neonatol. 221(4), 161-174.

736 101. Simcox, L.E., Ormesher, L., Tower, C., Greer, I.A., 2015. Thrombophilia
737 and Pregnancy Complications. Int J Mol Sci. 16(12), 28418-28428.

738 102. Simopoulou, M., Sfakianoudis, K., Maziotis, E., Grigoriadis, S.,
739 Giannelou, P., Rapani, A., Tsioulou, P., Pantou, A., Kalampokas, T., Vlahos, N.,
740 Pantos, K., Koutsilieris, M., 2019. The impact of autoantibodies on IVF treatment
741 and outcome: a systematic review. Int J Mol Sci. 20:892.

742 103. Simur, A., Ozdemir, S., Acar H, Colakoglu, M., Görkemli, H., Balci,
743 O., Nergis S., 2009. Repeated in vitro fertilization failure and its relation with
744 thrombophilia. Gynecol Obstet Invest. 67(2), 109-112.

745 104. Snell, B.J., 2009. Assessment and management of bleeding in the first
746 trimester of pregnancy. J Midwifery Womens Health. 54(6), 483-491.

747 105. Steinvil, A., Raz, R., Berliner, S., Steinberg, D.M., Zeltser, D., Levran, D.,
748 Shimron, O., Sella, T., Chodick, G., Shalev, V., Salomon, O., 2012. Association
749 of common thrombophilias and antiphospholipid antibodies with success rate of
750 in vitro fertilisation. Thromb Haemost. 108, 1192–7.

751 106. Stern, C., Chamley, L., Norris, H., Hale, L., Baker, H.W., 2003. A
752 randomized, double-blind, placebo-controlled trial of heparin and aspirin for
753 women with in vitro fertilization implantation failure and antiphospholipid or
754 antinuclear antibodies. Fertil. Steril. 80(2), 376–383.

755 107. Streuli, I., Benard, J., Hugon-Rodin, J., Chapron, C., Santulli, P., Pluchino,
756 N., 2018. Shedding light on the fertility preservation debate in women with
757 endometriosis: a swot analysis. Eur J Obstet Gynecol Reprod Biol. 229, 172-178.

758 108. Tan, B.K., Vandekerckhove, P., Kennedy, R., Keay, S.D., 2005.
759 Investigation and current management of recurrent IVF treatment failure in the
760 UK. BJOG. 112(6), 773–780.

761 109. Tan, X., Yu, Z., Sao, J., Sao, J., Chen, L., Shen, Y., Ding, J., Shi, W., 2016.
762 Association between in vitro fertilization outcomes and inherited thrombophilias:
763 a meta-analysis. J Assist Reprod Genet. 33(8), 1093-1098.

764 110. Tanacan, A., Beksac, M.S., 2019. Spontaneous pregnancies in patients
765 with at least one failed IVF cycle after the management of autoimmune disorders,
766 hereditary thrombophilia, and methylation disorders. JBRA Assist Reprod. 23(4),
767 361-366.

768 111. Thaler, C.J., Budiman, H., Ruebsamen, H., Nagel, D., Lohse, P., 2006.
769 Effects of the common 677C > T mutation of the 5,10-methylenetetrahydrofolate
770 reductase (MTHFR) gene on ovarian responsiveness to recombinant follicle-
771 stimulating hormone. Am J Reprod Immunol. 55, 251–258.

772 112. Urman, B., Ata, B., Yakin, K., Alatas, C., Aksoy, S., Mercan, R., Balaban,
773 B., 2009. Luteal phase empirical low molecular weight heparin administration in
774 patients with failed ICSI embryo transfer cycles: a randomized open-labeled pilot
775 trial. Hum Reprod. 24(7), 1640-1647.

776 113. Vaquero, E., Lazzarin, N., Caserta, D., Valensise, H., Baldi, M.,
777 Moscarini, M., Arduini, D., 2006. Diagnostic evaluation of women experiencing

778 repeated in vitro fertilization failure. Eur J Obstet Gynecol Reprod Biol. 125, 79–
779 84.

780 114. Villani, M., Baldini, D., Totaro, P. 2019. Rationale and design of two
781 prospective, multicenter, observational studies on reproductive outcome in
782 women with recurrent failures after spontaneous or assisted conception: OTTILIA
783 and FIRST registries. BMC Pregnancy Childbirth. 19(1):292.

784 115. Wormer, K.C., Jangda, A.A., El Sayed, F.A., Stewart, K.I., Mumford,
785 S.L., Segars, J.H., 2018. Is thromboprophylaxis cost effective in ovarian
786 hyperstimulation syndrome: a systematic review and cost analysis. Eur J Obstet
787 Gynecol Reprod Biol 224, 117–124.

788 116. Xu, T.T., Zhou, F., Deng, C.Y., Huang, G.Q., Li, J.K., Wang, X.D., 2015.
789 Low-Dose Aspirin for Preventing Preeclampsia and Its Complications: A Meta-
790 Analysis. J Clin Hypertens (Greenwich). 17(7), 567-73.

791 117. Ying Y, Zhong Y-P, Zhou C-Q, et al. A retrospective study on IVF
792 outcome in patients with anticardiolipin antibody: effects of methylprednisolone
793 plus low-dose aspirin adjuvant treatment. J Reprod Immunol. 2012; 94:196-201.

794 118. Yu, X., He, L., 2021. Aspirin and heparin in the treatment of recurrent
795 spontaneous abortion associated with antiphospholipid antibody syndrome: A
796 systematic review and meta-analysis. Exp Ther Med. 21(1), 57.

797

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807 **Figure legends**

808 **Figure 1.** A SWOT analysis