

Reproductive Impact of Thrombophilias and Antiphospholipid Antibodies

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This article provides a review of the American College of Obstetrician and Gynecologists (ACOG) practice bulletin on inherited thrombophilias in pregnancy and the American Society for Reproductive Medicine (ASRM) position on antiphospholipid antibodies and in vitro fertilization (IVF) success.^{1,2}

FOCUSPOINT

Pregnancy is accompanied by changes in both clotting and anticlotting factors.

A major ambivalence occurs in a pregnant woman's clotting mechanisms: trying to avoid hemorrhage during implantation, placentation, and remodeling of spiral arteries, and simultaneously trying to prevent catastrophic hemorrhage after separation of the placenta from the uterine wall following delivery. To meet these hemostatic challenges, pregnancy is accompanied by changes in both clotting and anticlotting factors to enhance hemostasis. Consequently, to prevent hemorrhage, a 10-fold increase in venous thromboembolism (VTE), a leading cause of maternal mortality, occurs during pregnancy and the puerperium.

The reproductive impact of antiphospholipid antibodies (APA) and thrombophilias has been both contentious and confusing; more complicated is the appropriate management, if any. In a 2010 editorial, Lockwood noted that the impetus for testing and treating thrombophilias resulted

from the observation of Kupferminc et al in 1999. He observed:

an increased prevalence of factor V Leiden (FVL), the C677T methylenetetrahydrofolate reductase (MTHFR) polymorphism, and the prothrombin G20210A gene (PG) mutation in 110 women whose prior pregnancies had been complicated by stillbirth, severe preeclampsia, abruptio placentae, or intrauterine growth restriction (IUGR).^{3,4}

The origins of the plethora of testing are of secondary importance to the lack of evidence and potential risk of treatment.

FIRST TRIMESTER OUTCOMES

Antiphospholipids

ASRM classifies APA as the lupus anticoagulant, anticardiolipin antibodies, and antiphosphatidyl serine.² While an association has been demonstrated with recurrent miscarriage, the presence of APA has not been shown to reduce IVF implantation failure; consequently, ASRM believes "therapy is not justified on the basis of existing data."

In a consensus statement, the 11th International Congress on APA classified APA to include anti-beta 2 glycoprotein I antibody of immunoglobulin G (IgG) and/or IgM (Table 1).⁵ This is defined slightly different

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TABLE 1. Revised Classification Criteria for Antiphospholipid Syndrome⁵

Antiphospholipid antibody syndrome (APS) is present if at least one clinical criteria and one laboratory criteria are met*

Clinical Criteria

1. Vascular Thrombosis

One or more clinical episodes of arterial, venous, or small vessel thrombosis, in any tissue or organ. Thrombosis must be confirmed by objective validated criteria (ie, unequivocal findings of appropriate imaging studies or histopathology). For histopathologic confirmation, thrombosis should be present without significant evidence of inflammation in the vessel wall.

2. Pregnancy Morbidity

(a) One or more unexplained deaths of a morphologically normal fetus at or beyond the 10th week of gestation, with normal fetal morphology documented by ultrasound or by direct examination of the fetus, or

(b) One or more premature births of a morphologically normal neonate before the 34th week of gestation because of (i) eclampsia or severe preeclampsia defined according to standard definitions or (ii) recognized features of placental insufficiency, or

(c) Three or more unexplained consecutive spontaneous abortions before the 10th week of gestation, with maternal anatomic or hormonal abnormalities, and paternal and maternal chromosomal causes excluded.

In studies of populations of patients who have more than one type of pregnancy morbidity, investigators are strongly encouraged to stratify groups of subjects according to a, b, or c above.

Laboratory Criteria

1. Lupus anticoagulant (LA) present in plasma, on 2 or more occasions at least 12 weeks apart, detected according to the guidelines of the International Society on Thrombosis and Haemostasis (Scientific Subcommittee on LAs/phospholipid-dependent antibodies).

2. Anticardiolipin antibody of IgG and/or IgM isotype in serum or plasma, present in medium or high titer (ie, >40 GPL or MPL, or >99th percentile), on 2 or more occasions, at least 12 weeks apart, measured by a standardized enzyme-linked immunosorbent assay test (ELISA).

3. Anti-beta 2 glycoprotein I antibody of IgG and/or IgM isotype* in serum or plasma (in titer >99th percentile), present on 2 or more occasions, at least 12 weeks apart, measured by a standardized ELISA, according to recommended procedures.

* Added by majority, not consensus.

than ASRM definition. Of note, the laboratory criteria for APA syndrome now requires an elevation on 2 or more occasions at least 12 weeks apart (prior was 6 weeks) and higher-level anticardiolipin antibodies (>40 GPL or MPL).

Low-dose aspirin (ASA) and/or prophylactic heparin have been used to treat patients with first trimester recurrent miscarriage (RM), either empirically or in those associated with APA. Despite an association of APA and first trimester miscarriage, the medical evidence is contradictory for definitive treatment of APA syndrome or thrombophilia patients.

Two large trials examined ASA versus ASA with prophylactic heparin in RM.^{5,6} The type of heparin used and the trimester

of pregnancy in treating APA in RM patients may be an implicating factor in pregnancy outcome.

The Ziakis meta-analysis showed a benefit of unfractionated heparin and ASA but not low-molecular-weight heparin (LMWH) when compared to ASA alone; specifically, the benefit was seen only in the first trimester.⁷ Additionally, though combination treatment seemed to have reduced miscarriage in the first trimester, there were significant limitations. They included a limited number of studies (only 3 qualified for meta-analysis) and a low patient population (less than 50 patients in each group); dissimilar definitions for APA syndrome; and inconsistent timing in regard to when to begin taking heparin and/or ASA.

TABLE 2. Risk of Venous Thromboembolism With Different Thrombophilias

	Prevalence in General Population (%)	VTE Risk per Pregnancy (no history) (%)	VTE Risk per Pregnancy (previous VTE) (%)	Percentage of All VTE (%)
FVL heterozygote	1–15	<0.3	10	40
FVL homozygote	<1	1.5	17	2
Prothrombin gene heterozygote	2–5	<0.5	>10	17
Prothrombin gene homozygote	<1	2.8	>17	0.5
FVL/prothrombin double heterozygote	0.01	4.7	>20	1–3
Antithrombin III activity (<60%)	0.02	3–7	40	1
Protein C activity (<50%)	0.2–0.4	0.1–0.8	4–17	14
Protein S free antigen (<50%)	0.03–0.13	0.1	0–22	3

Abbreviations: FVL, factor V Leiden; VTE, venous thromboembolism.

The HepASA trial, which also included select thrombophilias, exclusively used LMWH and demonstrated no effect on live birth when compared with ASA.⁶

The Cochrane Database presented data that prophylactic heparin and ASA may reduce recurrent pregnancy loss by 50% and is superior to ASA or prednisone. Most experts recommend 6 to 8 weeks postpartum thromboprophylaxis in APA, because 75% to 80% of fatal pulmonary emboli occur postpartum.⁷⁻⁹

Thrombophilias

Inherited thrombophilias comprise hyperhomocysteinemia (C677T mutation), FVL (A506G mutation), mutation in PG, protein S deficiency, and protein C deficiency. A summary of their prevalence in the general population and risk of VTE in pregnancy is shown in Table 2. Case-control studies have suggested a link between FVL, and perhaps other thrombophilias, and stillbirth; the absolute magnitude of the association was modest.¹⁰⁻¹⁶

Although a meta-analysis of small case-control studies suggested a link between fetal growth restriction and both FVL and PG mutation, cohort studies failed to support an association. Any statistical correla-

tion may be a result of low patient numbers and/or poor-quality studies that demonstrated aberrant associations.

Prospective studies have not shown an association between inherited thrombophilias and adverse pregnancy outcomes. The majority of asymptomatic women who carry an inherited thrombophilia polymorphism have a successful pregnancy outcome.¹⁷⁻²²

SUMMARY OF ACOG PRACTICE BULLETIN #113

The ACOG recommendations allow for expectant management in defined low-risk patients, as well as advising discontinuation of thrombophilia testing for first trimester RM patients.

First Trimester Management

1. A definitive association with reproductive loss less than 10 weeks' gestation and thrombophilias has not been identified.
2. Testing for inherited thrombophilias in women with recurrent fetal loss is *not* recommended. Despite a possible association, currently there is insufficient evidence that prophylactic anticoagulation prevents recurrence.
3. Screening for specific APA is appropriate

in patients with recurrent fetal loss.

4. Due to a lack of association between MTHFR mutations and recurrent fetal loss, screening with fasting homocysteine levels or MTHFR mutation analysis is *not* recommended.
5. Low-risk thrombophilias (ie, FVL heterozygous; PG mutation heterozygous; protein C or protein S deficiency) without previous VTE or with a single previous VTE (not receiving long-term anticoagulation) may be managed in the antepartum with or without prophylactic anticoagulation.
6. A patient without thrombophilia and a previous single episode of VTE associated with transient risk factors that were pregnancy- or estrogen-related (eg, combined oral contraception) or without an associated risk factor (idiopathic and not receiving long-term anticoagulation) may be managed in the antepartum with or without prophylactic anticoagulation.

Second and Third Trimester Management

The following points support a discontinuation of thrombophilia testing for patients with pregnancy complications such as preeclampsia and IUGR.

1. A definitive association between thrombophilias and preeclampsia has not been identified. Treating patients with a known thrombophilia to decrease the incidence or severity of preeclampsia is not supported by the literature.
2. A definitive association between thrombophilias and IUGR has not been identified. Treating patients with a known thrombophilia to decrease the incidence or severity of IUGR is not supported by the literature.
3. There is insufficient evidence to support anticoagulation in thrombophilia patients with a history of previous abruption.
4. Screening for specific APA is appropriate in patients with a history of one or more unexplained deaths of a morphologically normal fetus beyond 10 weeks, or one or more preterm births of a morphologically normal neonate at or before 34 weeks' gestation from preeclampsia, eclampsia, or placental insufficiency.²³
5. Treating patients with APA and a previous thrombotic event with anticoagulation through pregnancy and for up to 6

weeks postpartum is supported. Treating patients with APA and no previous thrombotic event with anticoagulation is controversial but supported by consensus and expert opinion.^{23,24}

6. Low-risk thrombophilia patients without previous VTE or with a single previous VTE (not receiving long-term anticoagulation) may be managed in the antepartum with or without prophylactic anticoagulation.
7. A patient without thrombophilia and a previous single episode of VTE associated with transient risk factors that were pregnancy- or estrogen-related (eg, combined oral contraception) or without an associated risk factor (idiopathic and not receiving long-term anticoagulation) may be managed in the antepartum with or without prophylactic anticoagulation.

Intrapartum Management

1. The use of pneumatic compression devices or elastic stockings should be considered for patients with a known thrombophilia presenting to the hospital, until they are ambulatory.
2. Consideration to switching a patient on LMWH to unfractionated heparin at 36

TAKE-HOME POINTS

- Most positive associations between thrombophilias and adverse pregnancy outcomes come from small case-control studies.
- Large prospective cohort studies fail to show consistent association between thrombophilias and adverse outcomes.
- There is a possible association between thrombophilias and fetal loss after 10 weeks in retrospective, not prospective, studies.
- There is no evidence to support thrombophilia screening in patients with recurrent pregnancy loss.
- A definitive association with reproductive loss at less than 10 weeks' gestation and thrombophilias has not been identified.
- Testing for inherited thrombophilias in women with recurrent fetal loss is not recommended. Despite a possible association, currently there is insufficient evidence that prophylactic anticoagulation prevents recurrence.
- Screening for specific APA is appropriate in patients with recurrent fetal loss.
- Due to a lack of association between MTHFR mutations and recurrent fetal loss, screening with fasting homocysteine levels or MTHFR mutation analysis is not recommended.

FOCUS POINT

While consensus for APA screening exists, no definitive cause and effect has been established between thrombophilias and first trimester pregnancy outcome.

- weeks can be given. This may increase the patient's candidacy for neuroaxial anesthesia when she enters labor.
3. Discontinuation of anticoagulation 24 to 36 hours prior to delivery is suggested to limit the risk of bleeding.
 4. Patients with delivery 4 or more hours after prophylactic dose of unfractionated heparin are not at significant risk for bleeding and can be treated with protamine sulfate to reverse the anticoagulant effect, if indicated.
 5. The risk for bleeding is limited to 12 hours after prophylactic dose or 24 hours after a therapeutic dose of LMWH, and spinal anesthesia should not be withheld in these patients.

Postpartum Management

1. Either unfractionated heparin or LMWH can be restarted 4 to 6 hours following a vaginal delivery or 6 to 12 hours following a cesarean delivery.
2. Patients who will be treated with warfarin may begin 5 mg daily for 2 days immediately after delivery. Subsequent doses then are determined by the international normalized ratio (INR).
3. For patients being treated with warfarin, therapeutic doses of unfractionated heparin or LMWH should continue until the INR is therapeutic for 2 days, to decrease the risk for paradoxical thrombosis and skin necrosis.
4. Warfarin, LMWH, and unfractionated heparin are compatible with breastfeeding.
5. Estrogen-containing oral contraceptives should be avoided in women heterozygous or homozygous for FVL and the PG mutations.
6. Screening all women for thrombophilias before initiating estrogen containing oral contraceptives is not recommended by ACOG.

CONCLUSION

While consensus for APA screening exists, no definitive cause and effect has been established between thrombophilias and first trimester pregnancy outcome. Patients should be considered candidates for thrombophilia screening if they have a personal history of VTE, or a first-degree relative with a known high-risk thrombophilia or

VTE prior to age 50. Nevertheless, the use of heparin has not been shown to improve pregnancy outcome in thrombophilia patients but may be of benefit in the first trimester, particularly with the use of unfractionated heparin. The authors concur with Lockwood's urging of "a moratorium on screening and treating patients for inherited thrombophilias when they suffer from recurrent pregnancy loss and prior stillbirth, preeclampsia, abruptio, and IUGR, unless it is part an [institutional review board]-approved study."

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