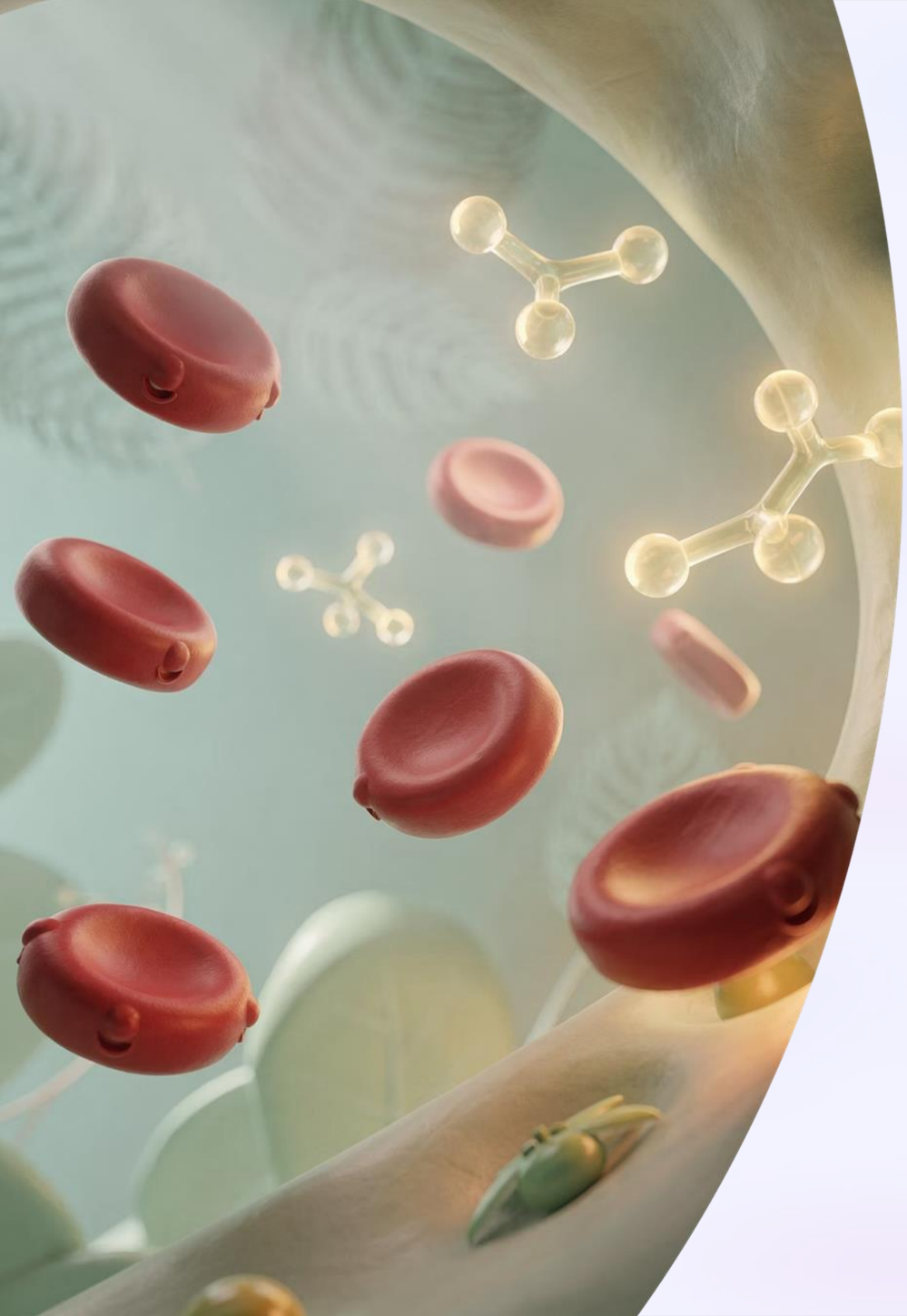

IN THE NAME OF GOD

Thrombophilias and Pregnancy Outcomes

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Classification of Thrombophilias

A. Inherited Thrombophilias

B. Acquired Thrombophilia

Inherited Thrombophilias in Pregnancy

Overview

Understanding Pregnancy-Related Hypercoagulability

A modest association with some adverse pregnancy outcomes (recurrent and nonrecurrent pregnancy loss) has been suggested, but this is controversial and the body of evidence suggests anticoagulation does not improve subsequent pregnancy outcome.

Most Common Inherited Thrombophilias

1

Factor V Leiden

Most prevalent variant in White populations; Activates Protein C resistance pathway

2

Prothrombin G20210A

Combined with FVL: 50-60% of primary hypercoagulable states; Increases prothrombin levels

3

Protein C Deficiency

Natural anticoagulant pathway disruption; Impairs thrombin inactivation

4

Protein S Deficiency

Cofactor for activated protein C; Essential for anticoagulant cascade

5

Antithrombin Deficiency

Highest risk variant; Impairs thrombin and Factor Xa inhibition

Why Pregnancy Increases VTE Risk

Physiologic Changes

Coagulation system alterations: increased fibrinogen, factors VII/VIII/X, decreased protein S

Physical Factors

Venous stasis from uterine compression of IVC and pelvic vessels

Delivery Process

Decreased mobility, vascular injury, placental separation triggers

Traditional Risk Factors

Age >35, obesity, smoking, immobilization, cesarean delivery

Baseline VTE Risk in Pregnancy

General Population

~0.1% overall absolute risk in obstetric patients without thrombophilia

Despite low baseline risk, thrombophilia significantly amplifies VTE probability—up to 50% of pregnancy-associated VTE attributed to inherited/acquired disorders

Two Major Risk Determinants

Type of Thrombophilia

- FVL or PGM homozygosity = high risk
- Concurrent FVL and PGM heterozygosity = high risk
- Antithrombin deficiency = high risk
- FVL or PGM heterozygosity = lower risk
- Protein C or S deficiency = lower risk

Personal/Family History

History of VTE or VTE in first-degree relative dramatically increases risk compared with negative history

Critical modifier: Prior unprovoked VTE confers substantially higher recurrence probability than provoked event

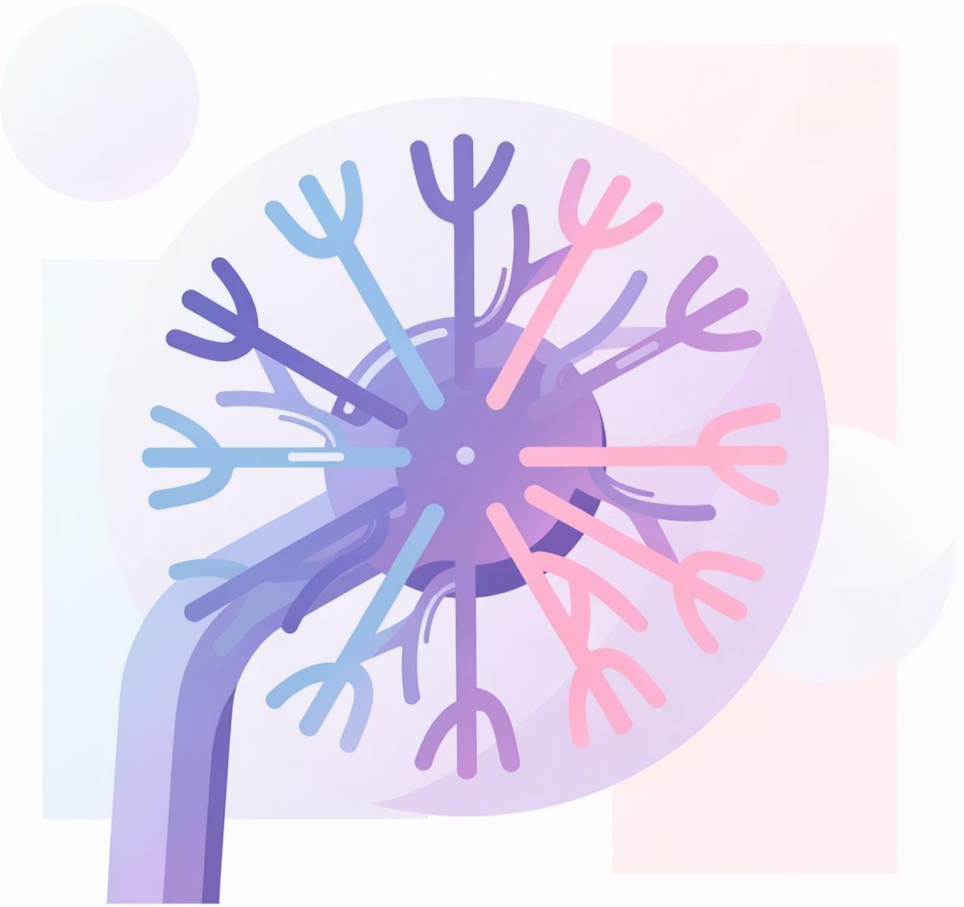
Inherited thrombophilias grouped by higher versus lower risk for VTE

Higher VTE-risk inherited thrombophilias
Antithrombin (AT) deficiency
Factor V Leiden (FVL) variant homozygote
Prothrombin G20210A variant homozygote*
Concurrent heterozygosity for both FVL and prothrombin G20210A variants
Rare combined thrombophilias (eg, AT deficiency and FVL)
Lower VTE-risk inherited thrombophilias
FVL variant heterozygote
Prothrombin G20210A variant heterozygote
Protein C deficiency
Protein S deficiency

Adverse Pregnancy Outcomes

Controversy and Current Evidence

It has been hypothesized that inherited thrombophilias increase the risk of thrombosis at the low-flow maternal-placental interface, resulting in placenta-mediated complications, such as pregnancy loss, fetal demise, preeclampsia, fetal growth impairment, and placental abruption; however, data do not clearly support an increase in these adverse pregnancy outcomes. If an association between inherited thrombophilia and these adverse pregnancy outcomes exists, it is likely modest and limited to populations with high-risk thrombophilias.



Testing Strategy

Routinely testing for inherited thrombophilias in unselected populations is not recommended because of the low frequency of the condition becoming symptomatic and the lack of a safe, cost-effective, long-term method of prophylaxis against thromboembolism . Furthermore, there is no strong evidence on which to base recommendations regarding whom to test or the optimal panel of tests.

Our Approach: When to Test

Principle: Test only when results will affect management decisions

01

High-Risk VTE History

Unprovoked VTE, recurrent VTE, or VTE with hormonal contraception/pregnancy—indicates need for prophylactic anticoagulation assessment

02

VTE with Transient Nonhormonal Provocation

Femoral fracture, surgery, prolonged immobilization—testing determines intensity/duration of prophylaxis

03

Positive Family History

First-degree relative with known high-risk thrombophilia—identifies asymptomatic carriers requiring intervention

When NOT to Test

Pregnancy Loss/Complications

❌ **Recurrent or nonrecurrent pregnancy loss**

❌ **Placental abruption**

❌ **Fetal growth restriction**

❌ **Preeclampsia**

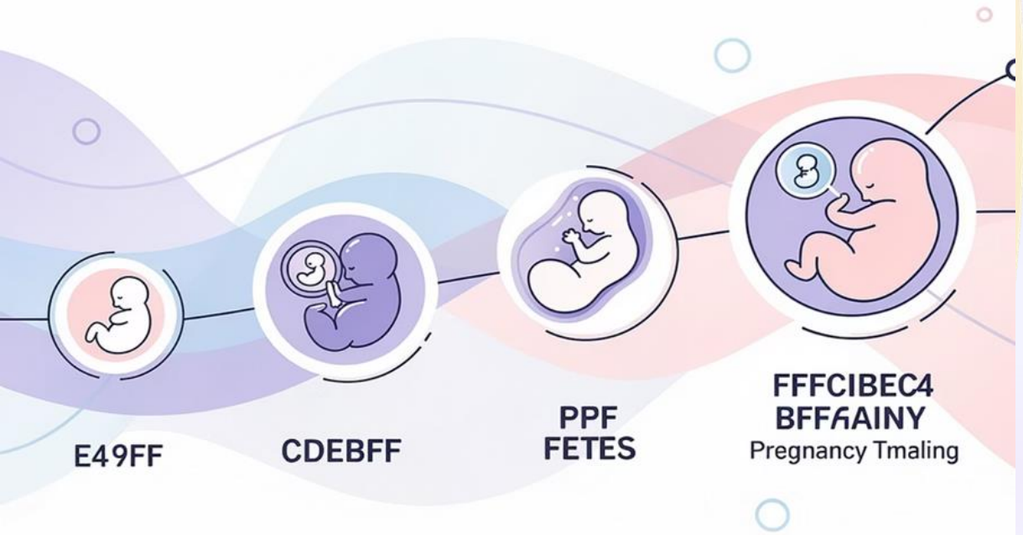
Rationale: No causal association proven; anticoagulation doesn't improve outcomes

IVF Failure

❌ Couples with *in vitro* fertilization failure

Evidence: FVL heterozygosity associated with **shorter** time to conception (11 vs 23 weeks)

Insight: Suggests improved, not impaired, implantation



ACOG Recommendations

Test when results will affect pregnancy/postpartum management

1. Personal history of VTE

   With or without recurrent risk factor, no prior testing—guides prophylaxis strategy

2. First-degree relative

   With high-risk inherited thrombophilia—identifies asymptomatic high-risk carriers

Important: ACOG recommends not testing mothers of stillborns for inherited thrombophilias (but does recommend testing for antiphospholipid syndrome)

ASH 2023 Conditional Recommendations

The American Society of Hematology 2023 guidelines for thrombophilia testing made conditional recommendations for thrombophilia testing, which included the scenarios described below .

- **Pregnant individuals with a family history of high-risk thrombophilia.**

- **Patients with VTE associated with nonsurgical major transient or hormonal risk factors**

- **Patients with cerebral or splanchnic venous thrombosis, in settings where anticoagulation would otherwise be discontinued**

- **Patients with a family history of antithrombin, protein C or protein S deficiency when considering thromboprophylaxis for minor provoking risk factors, and for guidance to avoid hormonal contraceptives or menopausal hormone therapy**

- **Patients with cancer at low or inter mediate risk of thrombosis and with a family history of VTE**

Laboratory Testing

Comprehensive panel and timing considerations

Recommended Test Panel

- **Antithrombin Deficiency**

  Functional assay—measures anticoagulant activity

- **Factor V Leiden**

  Genetic testing—identifies G1691A mutation

- **Prothrombin G20210A**

  Genetic testing—identifies G20210A mutation

- **Protein S Deficiency**

  Free antigen assay—measures active fraction

- **Protein C Deficiency**

  Functional assay—measures anticoagulant activity

- **Antiphospholipid Syndrome**

  Acquired thrombophilia—lupus anticoagulant, anticardiolipin, anti-β2 glycoprotein I antibodies

Optimal Testing Timing

Molecular Analysis

Can be performed anytime—genetic variants don't change with pregnancy or anticoagulation status

1

2

Non-Molecular Testing

Ideal: ⩾3 months post-delivery, after breastfeeding cessation—allows normalization of coagulation factors

Coagulation Factor Normalization

Returns to baseline by 6-8 weeks postpartum—protein S remains low during lactation

3

4

Anticoagulation Status

Preferably test when patient has stopped anticoagulant—heparin affects antithrombin, warfarin affects protein C/S

Tests to Avoid

Homocysteine Level

Why skip:

- Decreased since folic acid fortification
- Pregnant patients take folic acid
- No evidence for management changes
- No reduction in events with B vitamin supplementation

MTHFR Polymorphisms

Why skip:

- C677T, A1298C very common in population
- No significant VTE risk in quality studies
- No evidence linking to pregnancy complications

PAI-1 & Factor VIII

Why skip:

- PAI-1: 50% prevalence, limited evidence
- Factor VIII: Assays not standardized, no pregnancy interpretation
- Weaker VTE risk factor than initially reported

Homocysteine level – We do not check homocysteine levels for several reasons.
In the United States population, homocysteine levels have decreased since folic acid fortification of flour and enriched grain products was mandated; thus, fewer patients with venous thromboembolism (VTE) are found to have high homocysteine levels.

Pregnant patients are routinely prescribed multivitamins containing folic acid to reduce the risk of neural tube defects.

High homocysteine levels are a weaker risk factor for VTE or arterial thrombosis than reported in early studies (odds ratio 1.2-1.6 versus 2.0) and may not be an independent risk factor at all . Furthermore, intervention studies with B vitamin supplementation, albeit in nonpregnant patients, do not show a reduction in arterial or venous thrombotic events.

Factor VIII level – Increased levels of some procoagulant factors other than prothrombin are risk factors for VTE. For example, elevated factor VIII coagulant activity is a prothrombotic risk factor for a first unprovoked VTE; however, elevated levels should not be viewed as an inherited thrombophilia. Furthermore, assays for factor VIII levels have not been standardized, and there is no information on the interpretation of factor VIII levels in pregnancy with respect to prothrombotic risk.

MTHFR and PAI-1 polymorphisms – the available studies linking MTHFR and PAI-1 polymorphisms with preeclampsia and other adverse pregnancy outcomes have many limitations and do not provide any evidence for testing patients with an adverse pregnancy outcome or using the results of prior testing to influence patient management.

VTE Prevention

In pregnant patients with inherited thrombophilias, the treatment goal is prevention of maternal venous thromboembolism (VTE).

Approach to anticoagulation for pregnant individuals with inherited thrombophilia

Clinical setting		Antepartum management	Postpartum management
Lower-risk thrombophilia*	With personal history of previous VTE	Unprovoked VTE or VTE associated with a hormonal risk factor: Anticoagulation (low-dose heparin)	Anticoagulation (low-dose heparin)
		VTE associated with a nonhormonal temporary provoking risk factor and no other risk factors for VTE: No antepartum anticoagulation	Anticoagulation (low-dose heparin)
	No personal history of VTE	Surveillance for VTE without anticoagulation. Anticoagulation may be warranted for individual patients with additional factors that place them at greater risk of thrombosis (eg, prolonged immobility, first-degree relative with unprovoked VTE under age 50 years).	Anticoagulation (low-dose heparin) for patients who have a cesarean birth
Higher-risk thrombophilia¶	With previous VTE and on long-term anticoagulation	Anticoagulation (therapeutic-dose heparin)	Anticoagulation (therapeutic-dose heparin)
	With previous VTE not on long-term anticoagulation	Anticoagulation (intermediate- or therapeutic-dose heparin)	Anticoagulation (intermediate- or therapeutic-dose heparin)
	No personal history of previous VTE and not on chronic anticoagulation	Anticoagulation (low- or intermediate-dose heparin)	Anticoagulation (intermediate-dose heparin)

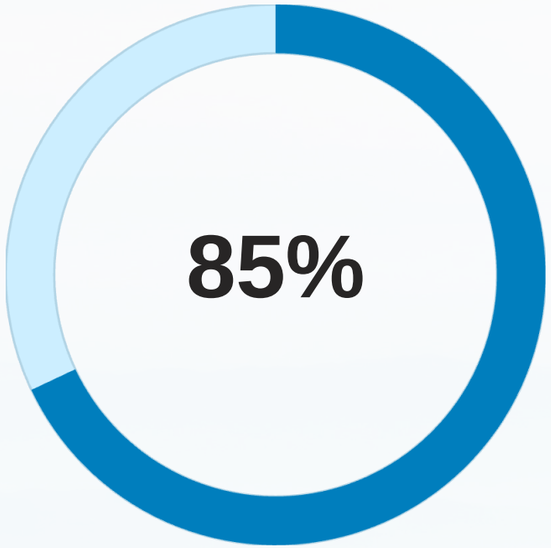
Pregnancy Complications

Evidence against anticoagulation for non-VTE outcomes

No Role for Anticoagulation in Pregnancy Loss

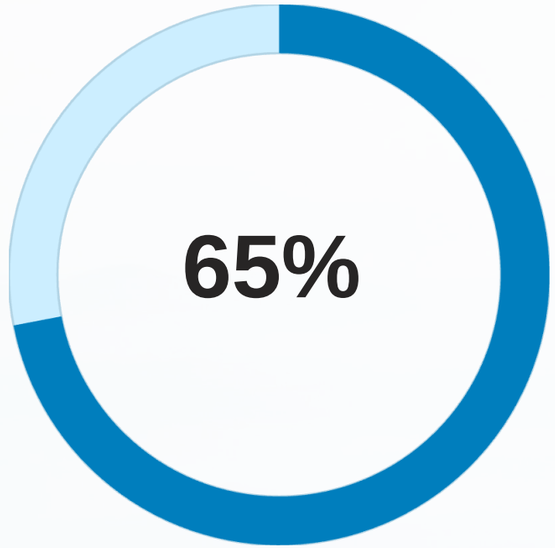
2016 Meta-Analysis: 8 trials, 483 patients with thrombophilia + prior late loss or recurrent early loss

Compared with no treatment or aspirin alone



Live Birth with LMWH

Treatment group



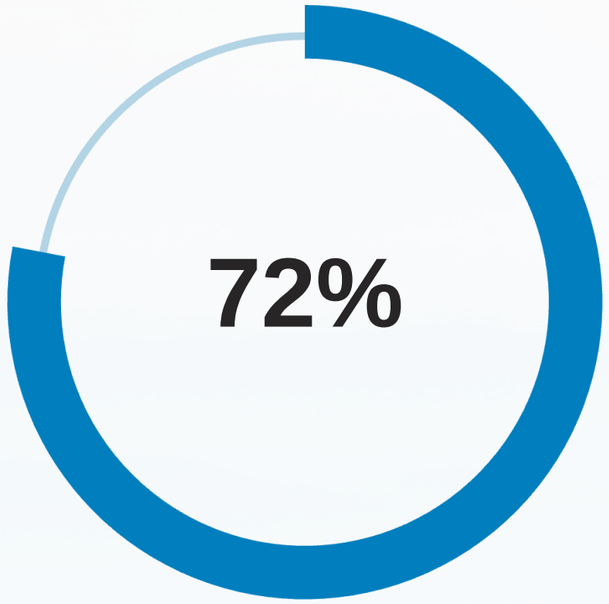
Live Birth without LMWH

Control group

Result: Pregnancy loss **not significantly reduced** (RR 0.81, 95% CI 0.55-1.19)

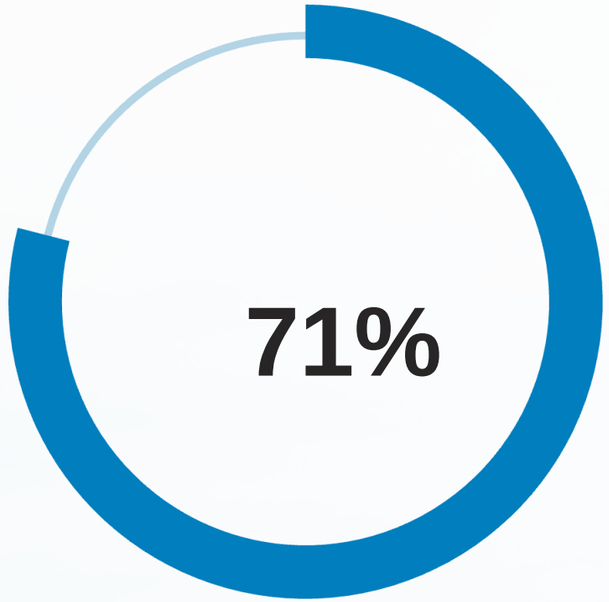
Confirmatory Randomized Trial

326 participants with recurrent loss and inherited thrombophilia



LMWH Group

Livebirth rate with treatment



Standard Care

Livebirth rate without treatment

No difference in miscarriage, preterm birth, or small for gestational age

FRUIT Trial: Hypertensive Disorders

Population: Inherited thrombophilia + history of uteroplacental insufficiency with delivery <34 weeks

Comparison: LMWH + aspirin vs. aspirin alone

- **Recurrent hypertensive disorder <34 weeks:** 0/70 vs 6/69 (reduced)
- **All recurrent hypertensive disorders:** No difference
- **Fetal growth/Doppler:** No difference

Mixed results—benefit limited to severe early-onset disease subgroup

TIPPS Trial: Placenta-Mediated Complications

292 pregnant patients with thrombophilia or previous placenta-mediated complications

Intervention: Dalteparin 5,000 IU once daily up to 20 weeks, then twice daily vs. no dalteparin

Composite Outcome with Dalteparin

Pregnancy loss, preeclampsia, SGA, major VTE

Composite Outcome without Dalteparin

Same composite endpoint measured

No significant difference (risk difference -1.8%) — largest trial to date shows no benefit for pregnancy outcomes

Low-Dose Aspirin: Not Indicated

We do not prescribe low-dose aspirin for preeclampsia prevention in patients with inherited thrombophilias who lack standard preeclampsia risk criteria

Candidates for aspirin prophylaxis determined by standard preeclampsia risk factors, not thrombophilia status alone

Rationale: Prospective studies have not confirmed increased preeclampsia risk in thrombophilia carriers

Fetal Surveillance

Monitoring and delivery timing considerations

Peripartum Anticoagulation Management

01

Before Delivery

Discontinue heparin 12-24 hours before scheduled delivery

Timing based on thrombotic risk, dose, and delivery plan

02

~36 Weeks

Consider transition from LMWH to UFH to facilitate neuraxial anesthesia

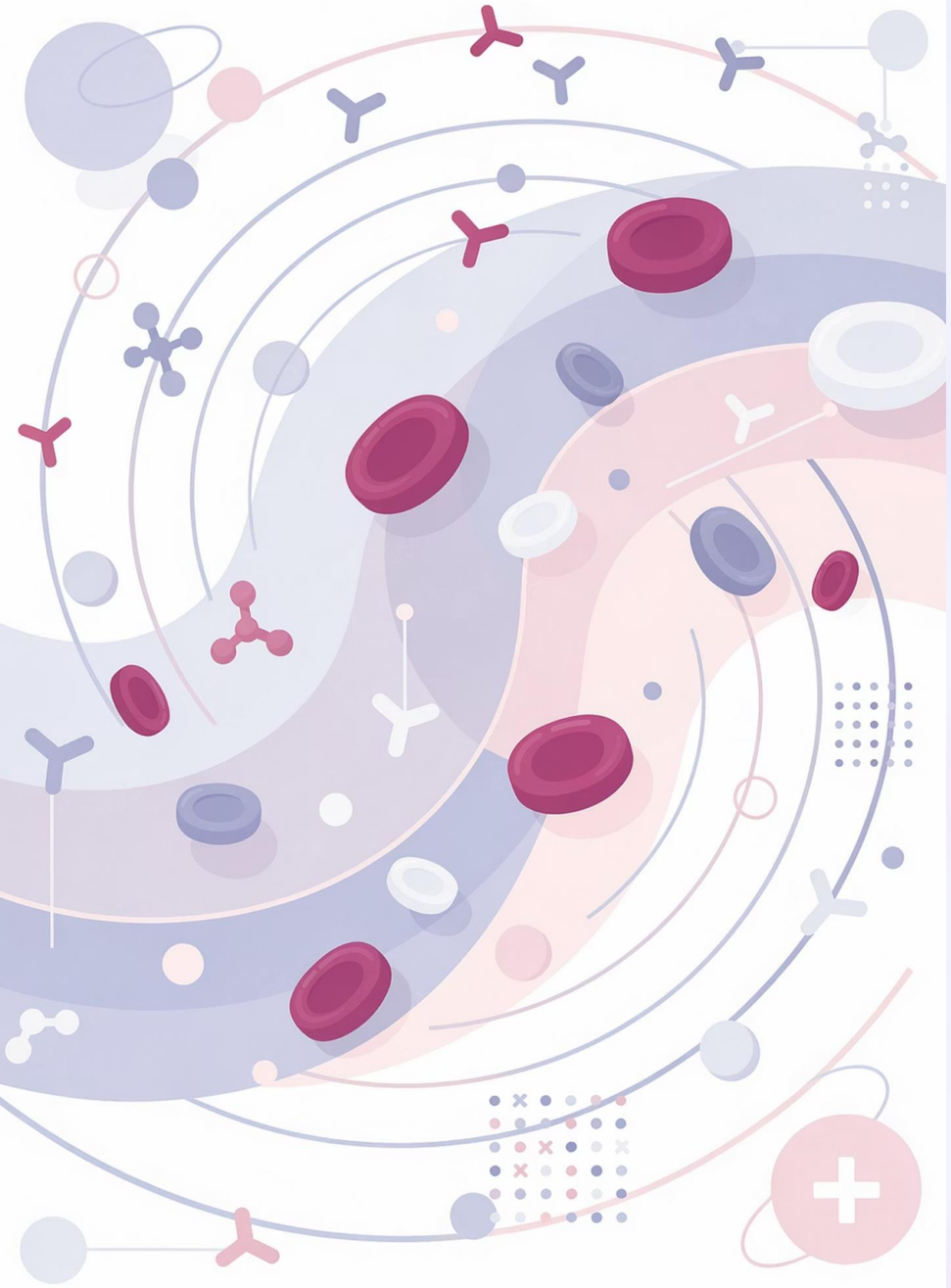
UFH shorter half-life allows more flexible timing

03

Postpartum

Resume as soon as safe: 4-6 hours vaginal, 6-12 hours cesarean (with normal bleeding)

Balance thrombotic vs. hemorrhagic risk



Antiphospholipid Syndrome

Overview

What is Antiphospholipid Syndrome?

Clinical Definition: Autoimmune syndrome characterized by:

- **Thrombotic events (venous/arterial)**
- **Pregnancy complications**
- **Persistent antiphospholipid antibodies**

What is APS?

Clinical Syndrome

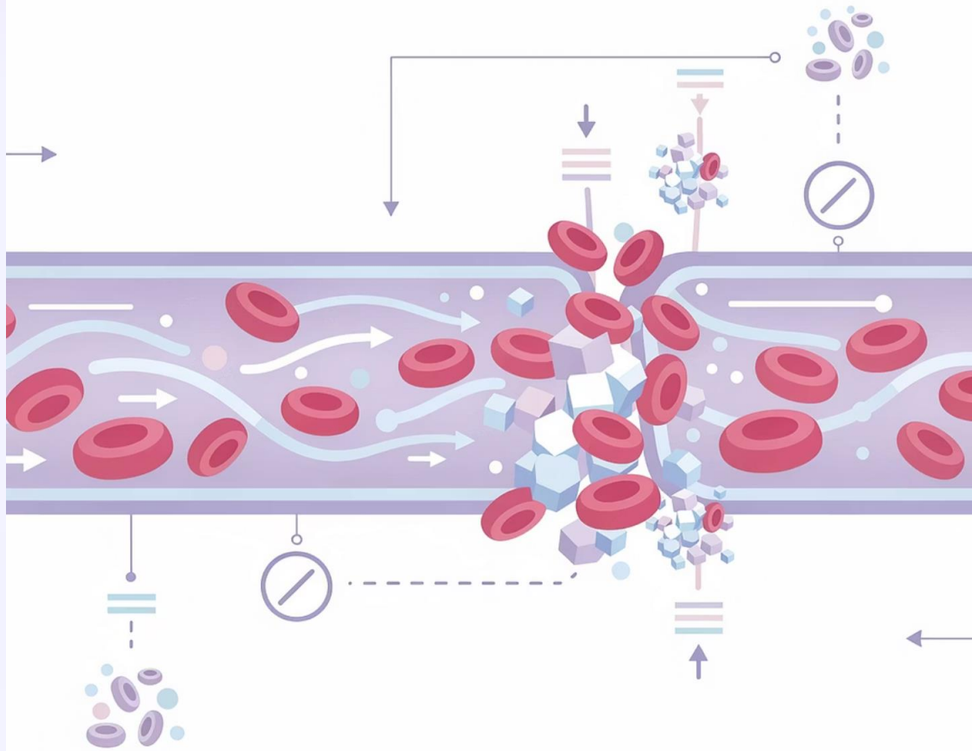
Autoimmune condition with thrombosis, pregnancy complications, or other manifestations

Laboratory Evidence

Persistent antiphospholipid antibodies detected on multiple occasions

Primary or Secondary

Occurs alone or with systemic lupus erythematosus (SLE)



Types of APS

Thrombotic APS

Venous or arterial thrombosis with persistent aPL

Obstetric APS

adverse pregnancy outcomes

Microvascular APS

Small vessel involvement without large-vessel thrombosis

Catastrophic APS

Rare, life-threatening multi-organ thrombotic complications

Obstetric APS – Obstetric APS describes APS based on certain adverse pregnancy outcomes (fetal death after 10 weeks gestation, premature birth due to severe preeclampsia or placental insufficiency, or multiple embryonic losses [before 10 weeks gestation]).

Microvascular APS – Microvascular APS describes small vessel involvement, such as diffuse alveolar hemorrhage or aPL nephropathy, without moderate- to large-vessel thrombosis.

Catastrophic APS – Catastrophic APS (CAPS) is a rare, life-threatening form of APS characterized by thrombotic complications (macrovascular and microvascular) affecting multiple organsthat develop simultaneously or over a short period of time.

When to Suspect APS

Thrombotic Events

- Unexplained venous or arterial thrombosis
- Especially in young patients
- Microvascular disease

Pregnancy Complications

- Multiple embryonic losses <10 weeks
- Fetal death after 10 weeks
- Severe preeclampsia or placental insufficiency

Clinical Red Flags

Livedo Reticularis/Racemosa

Distinctive skin pattern suggesting vascular involvement

Valvular Heart Disease

Heart valve thickening or abnormalities

Neurologic Findings

Cognitive deficits, white matter lesions

Systemic Lupus

Presence of SLE increases suspicion significantly

Laboratory Clues

Thrombocytopenia

Unexplained low platelet count

Prolonged aPTT

Increased activated partial thromboplastin time

False-Positive Syphilis Test

VDRL or RPR tests use cardiolipin

Diagnostic Evaluation

Comprehensive assessment combining clinical and laboratory findings

Medical History Focus

01

Thrombotic Events

Nature, frequency, and timing of events

02

Pregnancy Outcomes

Complete obstetric history

03

Risk Factors

Immobility, estrogen use, family history

04

Medication History

Anticoagulants affect lupus anticoagulant testing

05

SLE Symptoms

Arthritis, photosensitivity, oral ulcers, Raynaud

Physical Examination Findings

Skin Manifestations

- Livedo reticularis or racemosa
- Digital ischemia or gangrene
- Sequelae of deep vein thrombosis

Other Findings

- Heart murmur
- Neurologic abnormalities
- Signs of prior stroke

Routine Laboratory Testing

Complete Blood Count

Assess for thrombocytopenia

Coagulation Tests

PT and aPTT baseline before anticoagulation

Kidney Function

Creatinine and urinalysis with sediment

SLE Testing

If clinical features suggest lupus

The Three Essential aPL Tests

Anticardiolipin (aCL)

IgG and IgM by ELISA

Anti-beta2GPI

IgG and IgM by ELISA

Lupus Anticoagulant

Functional clotting assay

These three tests are included in APS classification criteria

Lupus Anticoagulant Testing

Step 1: Screening

Prolonged phospholipid-dependent test (dRVVT or optimized aPTT)

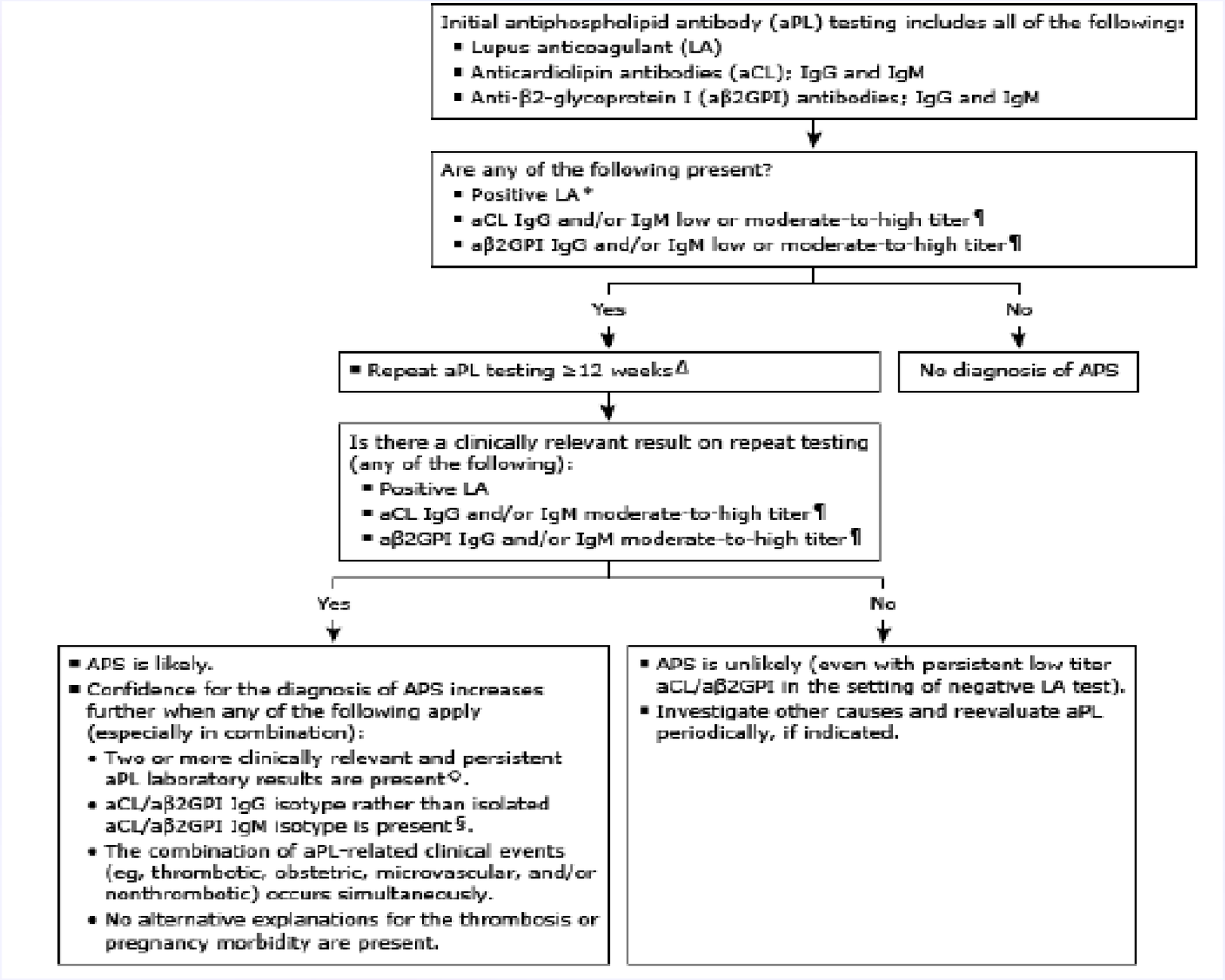
Step 2: Mixing Study

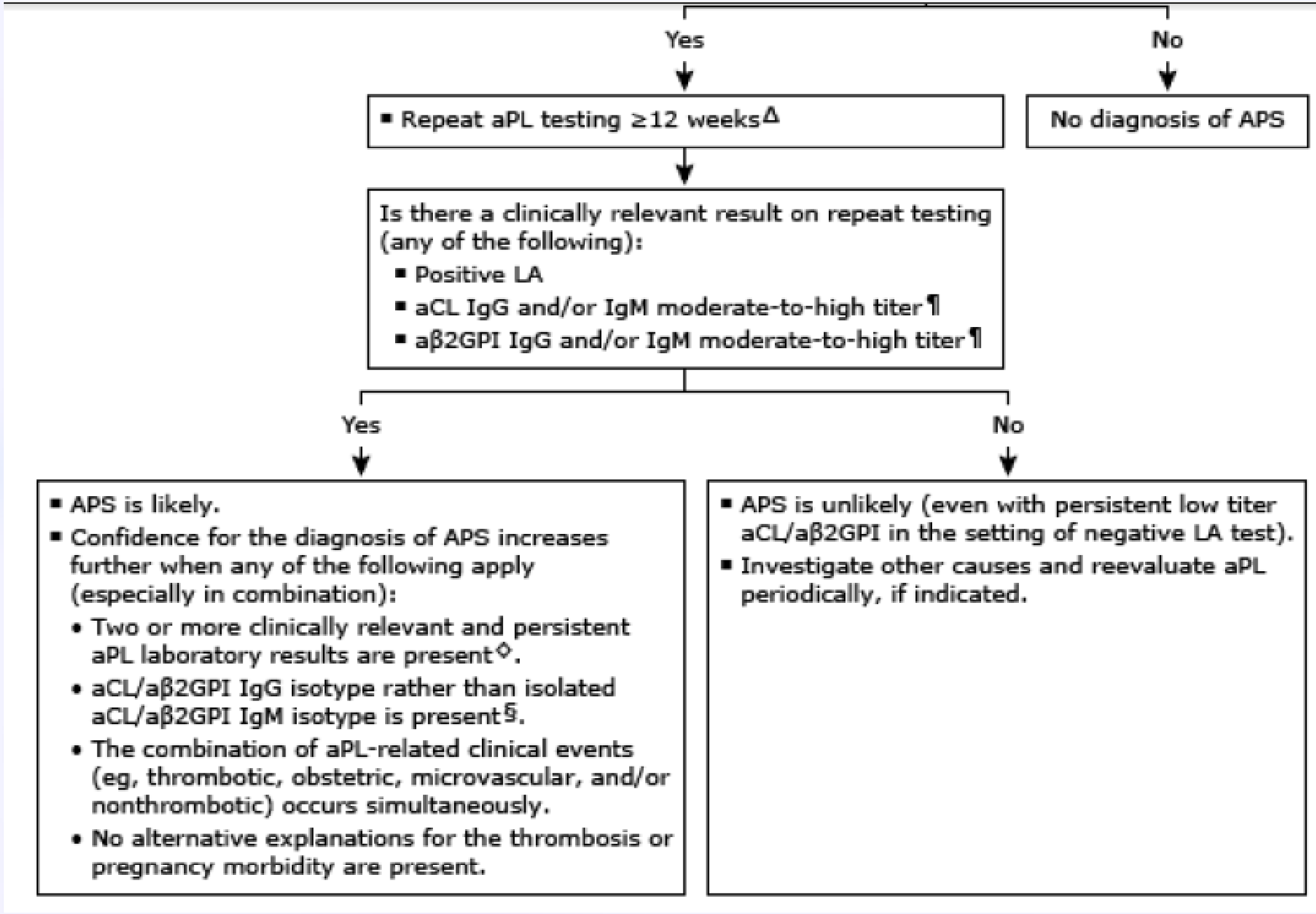
Mixing with normal plasma fails to correct prolongation

Step 3: Confirmation

Excess phospholipid corrects the prolonged clotting time

Antiphospholipid antibody (aPL) testing and interpretation




Yes
No
■ Repeat aPL testing ≥12 weeks△
No diagnosis of APS
Is there a clinically relevant result on repeat testing (any of the following):
■ Positive LA
■ aCL IgG and/or IgM moderate-to-high titer¶
■ aβ2GPI IgG and/or IgM moderate-to-high titer¶
Yes
No
■ APS is likely.
■ Confidence for the diagnosis of APS increases further when any of the following apply (especially in combination):
• Two or more clinically relevant and persistent aPL laboratory results are present◇.
• aCL/aβ2GPI IgG isotype rather than isolated aCL/aβ2GPI IgM isotype is present§.
• The combination of aPL-related clinical events (eg, thrombotic, obstetric, microvascular, and/or nonthrombotic) occurs simultaneously.
• No alternative explanations for the thrombosis or pregnancy morbidity are present.
■ APS is unlikely (even with persistent low titer aCL/aβ2GPI in the setting of negative LA test).
■ Investigate other causes and reevaluate aPL periodically, if indicated.

Interpreting Results

Not every positive test is clinically relevant

Clinically Relevant aPL Profile

Positive LA Test

Based on ISTH guidelines

aCL IgG or IgM

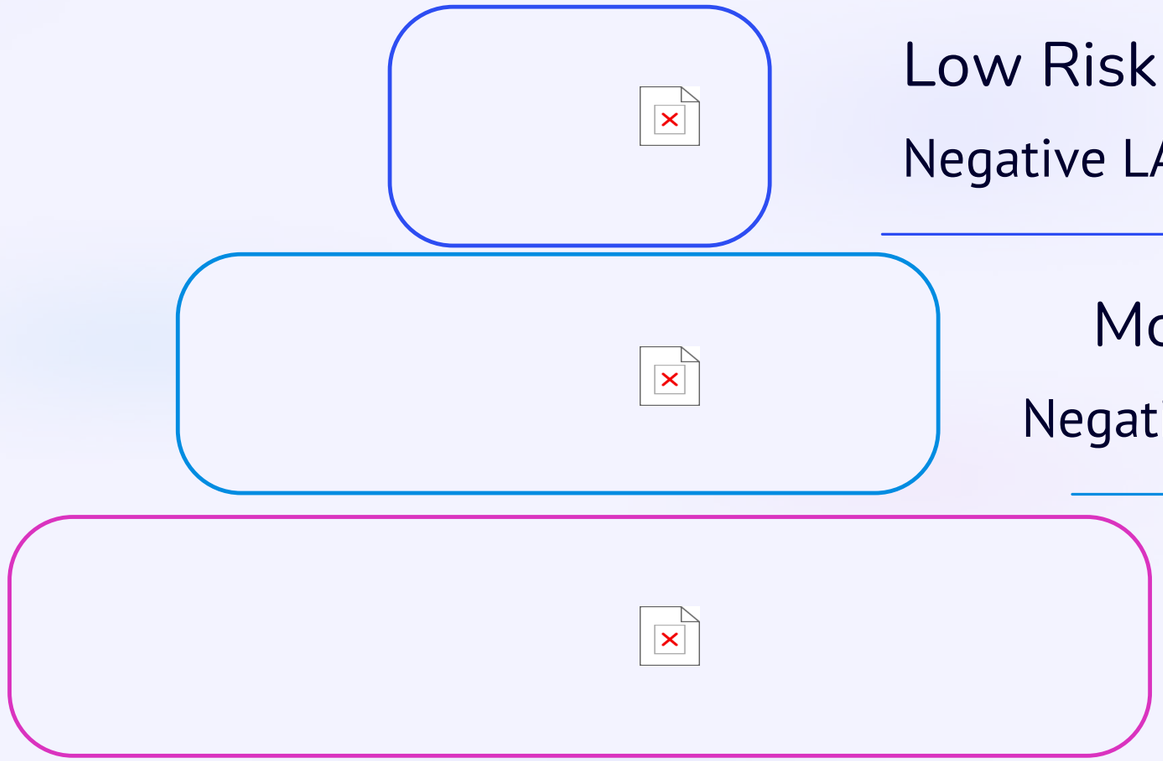
Titer ⩾40 units

Anti-beta2GPI IgG or IgM

Titer ⩾40 units

Essential: Must be persistent on two occasions ⩾12 weeks apart

Risk Stratification by aPL Profile



Low Risk

Negative LA, low-titer aCL/anti-beta2GPI (20-39 units)

Moderate Risk

Negative LA, moderate-high titer aCL/anti-beta2GPI (≥40 units)

High Risk

Positive LA with or without moderate-high titer antibodies

Triple-positive (LA + aCL + anti-beta2GPI) = highest risk

Diagnostic Confidence Increases With

Multiple Positive Tests

Two or more clinically relevant, persistent aPL results

IgG Predominance

IgG aCL/anti-beta2GPI stronger than isolated IgM

Additional Manifestations

Thrombocytopenia, valve disease, aPL nephropathy

No Alternative Explanation

Lack of other causes for thrombosis or pregnancy loss

Revised Sapporo antiphospholipid syndrome classification criteria

Antiphospholipid syndrome is present if at least 1 of the clinical criteria and 1 of the laboratory criteria that follow are met*

Clinical criteria

1. Vascular thrombosis¶
2. 1 or more clinical episodes$^{\Delta}$ of arterial, venous, or small vessel thrombosis$^{\Diamond}$, 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
    1. 1 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
    2. 1 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
    3. 3 or more unexplained consecutive spontaneous abortions before the 10th week of gestation, without maternal or hormonal abnormalities, and paternal and maternal chromosomal causes excluded.

    In studies of populations of patients who have more than 1 type of pregnancy morbidity, investigators are strongly encouraged to stratify groups of subjects according to a, b, or c above.

Laboratory criteria¥

1. 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. aCL of IgG and/or IgM isotype in serum or plasma, present in medium or high titer (ie, >40 GPL or MPL, or >the 99th percentile), on 2 or more occasions, at least 12 weeks apart, measured by a standardized ELISA.

3. Anti-beta2 glycoprotein I antibody of IgG and/or IgM isotype in serum or plasma (in titer >the 99th percentile), present on 2 or more occasions, at least 12 weeks apart, measured by a standardized ELISA, according to recommended procedures.

Approach to treatment of pregnant and postpartum patients with APS or aPL

Clinical setting	Antepartum	Postpartum
Thrombotic APS with or without obstetric APS *	Therapeutic-dose LMWH and LDA	Transition back to warfarin (safe for breastfeeding). Continue LDA if patient was taking it prepregnancy.
Obstetric APS ¶	Prophylactic-dose LMWH and LDA	Continue prophylactic-dose LMWH and LDA for six weeks postpartum
Persistent aPL with history of adverse pregnancy outcome but not meeting APS-defining criteria Δ	LDA	Vaginal birth: Continue LDA for six weeks postpartum Cesarean birth: Continue LDA and add prophylactic-dose LMWH for six weeks postpartum


Thank
you