Antiphospholipid syndrome (APS) & pregnancy

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Antiphospholipid syndrome (APS)

- autoimmune disorder
- venous or arterial thrombosis
- and/or
- pregnancy loss in the presence of **persistent** antiphospholipid antibodies (aPL).
- lupus anticoagulant (LA),
- anticardiolipin antibodies (aCL),
- anti-beta-2-glycoprotein-1 antibodies.
- **Of note, aPL can also be found in healthy individuals.**
Treatment of APS during pregnancy

• **reduces** the frequency of thrombosis

• **reduces** the risk of an adverse pregnancy outcome
Sapporo (or Sydney) criteria

- defining pregnancy morbidity in the diagnosis of APS
- ≥1 unexplained fetal deaths ≥10 w with normal anatomy
- ≥1 preterm deliveries of a normal infant before 34 due to preeclampsia, or placental insufficiency
- placental insufficiency include:
  - Abnormal or nonreassuring fetal surveillance tests (eg, lack of fetal heart rate acc. low score on BPP)
  - Abnormal Doppler
  - Oligohydramnios
  - Birth weight <10th percentile
- ≥3 unexplained, consecutive, spontaneous pregnancy losses <10 w after exclusion of maternal anatomic and hormonal abnormalities and paternal and maternal chromosomal abnormalities.
placental abruption

- Although placental abruption has been associated with placental insufficiency,
- APS is not associated with abruption,
- placental abruption is not a defining morbidity for APS.
higher risk of adverse outcome

<table>
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<tr>
<th>LA major predictor</th>
<th>39 % of patients with LA poor</th>
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<td>13 % for IgM anti-beta-2-glycoprotein-1.</td>
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"Triple positivity" only 30 percent had a live birth with tx ASA & CELEXAN

| 8 % for (IgG) aCL, | 0 % for IgM aCL, | 0 % for IgG anti-beta-2-glycoprotein-1, |
mechanism for adverse pregnancy outcome

Uteroplacental thrombosis

vascular insufficiency may be one
Thromboses are the hallmark of APS,

**venous thromboses** are more common than arterial.

The **deep veins of the lower extremities** are the most common sites of venous thrombosis.

**the cerebral vasculature** (stroke and transient ischemic attack) is the most common site for arterial thrombosis.
risk of thromboembolic disease

- during pregnancy or postpartum
- among APS 5 to 12 percent
- the general obstetric population 0.025 to 0.10 percent
Anticoagulation

- prefer LMWH to UFH
- avoid oral anticoagulants, warfarin
- factor Xa inhibitors fondaparinux

- **Direct oral anticoagulants:**
  rivaroxaban, dabigatran may be ineffective in APS
- should not be used
- they cross the placenta
- lack of safety data
(prophylactic versus therapeutic)

- depends on the indication for anticoagulation,
- If heparin is contraindicated because of heparin-induced thrombocytopenia (HIT), danaparoid or fondaparinux are reasonable options
The optimum low dose of aspirin (ASA),

•, is unclear.

• optimum dose to reduce the risk of preeclampsia may be 100 to 150 mg,

• 81 mg is a more practical dose as 100 to 150 mg

• Taking one and one-half 81 mg tablets is an option.
Selection of patients for antithrombotic therapy varies depending on whether they have APS based on a prior thrombosis versus an APS-associated pregnancy morbidity.
APS based on aPL and prior thrombosis, with/without APS-defining pregnancy morbidity

- lab. criteria for aPL
- history of arterial or venous thrombosis
  - high risk of recurrent thrombosis
- treated with warfarin for an indefinite period that may be lifelong
APS based on aPL and prior thrombosis, with/without APS-defining pregnancy morbidity

- American College of Chest Physicians (ACCP)
  - use of LMWH anticoagulation

- Risk of thrombosis
  - in untreated patients 10%
  - in treated patients, less than 1%
We prefer LMWH for its greater safety and efficacy compared with UFH, but UFH is an acceptable alternative.
APS based on aPL and prior thrombosis, with/without APS-defining pregnancy morbidity

- **therapeutic dose of LMWH**, as suggested by the American College of Rheumatology (ACR)
- **low-dose ASA**, reducing the risk criteria for preclampsia
- **Aspirin** reduces the risk of arterial thrombosis.
APS based on aPL and APS-defining pregnancy morbidity alone, no prior thrombosis

We offer pharmacologic treatment

experts consider close clinical surveillance

with or without the addition of hydroxychloroquine to be a reasonable alternative approach
Early or late loss

combined therapy with

low-dose ASA beginning when conception is attempted,

prophylactic-dose LMWH upon confirmation of intrauterine pregnancy;

improvement in outcome with combined therapy.
Preterm delivery related to uteroplacental insufficiency

- Low-dose ASA therapy beginning at the end of the first trimester and continuing through delivery
- Some clinicians prescribe LMWH, available evidence does not support this approach
cases of ASA failure

- in cases of ASA failure
- or when placental examination shows extensive decidual inflammation and vasculopathy and/or thrombosis
- prophylactic-dose LMWH with low-dose ASA selectively
common histopathologic features of the placenta

- infarction,
- impaired spiral artery remodeling,
- decidual inflammation,
- increased syncytial knots,
- decreased vasculosyncytial membranes,
- and deposition of complement split product C4d
Antepartum maternal and fetal monitoring

**intervention in the event** of maternal or pregnancy complications, such as preeclampsia.

**Baseline** platelet count, creatinine, urine protein-to-creatinine ratio, (ALT), (AST) for comparison in the event of active APS or other complications later in pregnancy.

**anti-Ro/SSA and anti-La/SSB antibodies**

serial sonograms approximately **every four weeks** beginning in the late second or early third trimester
fetal well-being (nonstress tests and/or BPP)

because of the increased risk of antepartum fetal death

beginning at 32 weeks

Weekly

or twice per week
Labor and delivery

In the absence of standard medical or obstetric indications for early delivery, TO control the timing of discontinuation of antithrombotic drugs, schedule delivery (induction or cesarean) at 39 weeks.
Anticoagulation

therapeutic LMWH **switch to** therapeutic doses of UFH at 36 to 37 week

**24-h interval** between therapeutic LMWH and placement of an **epidural catheter**

(at least **12 h** for prophylactic dose).

Therapeutic UFH DC 24 h before labor and delivery,

**patients with prior thromboses are not off anticoagulants for more than 48 hours**
Low-dose ASA

Stopped after 36 weeks in women with no history of thrombosis.

Stopping ASA 7 to 10 days before delivery minor perioperative bleeding

Past history of serious arterial thrombotic complications, such as stroke or myocardial infarction, we continue ASA through labor and delivery.
Postpartum care

— APS by lab. criteria and a prior history of arterial or venous thrombosis

high risk of recurrence

4 to 6 hours after NVD or 6 to 12 hours after CS,

indefinite period of anticoagulation with warfarin
Postpartum care

APS based only on obstetric morbidity (no venous or arterial thrombotic events)

who have an early pregnancy loss

not administer anticoagulation after expulsion of the products of conception.
PATIENTS WITH POOR PREGNANCY OUTCOME DESPITE ANTITHROMBOTIC THERAPY

- no second line therapy with proven efficacy.

- hydroxychloroquine appears to depress aPL levels

- might be beneficial in women with APS-related recurrent pregnancy loss

- three months for HQ to have an effect, thus it should be started prior to pregnancy.
Pregnancy outcomes of women with aPL without APS

- It is unclear whether women with aPL who do not meet criteria for APS are
  increased risk of pregnancy morbidity.
- risk of first-time thrombosis in pregnant women with aPL and no personal history of thrombosis
- aPL and primary infertility
- (IVF) failure
- near-term/term preeclampsia
measurement of aPL during pregnancy is unnecessary

Most patients without APS who are aPL positive in the first trimester (defined as aCL or anti-beta-2-glycoprotein-1 ≥40 units or LA-positive) remain in the high-positive range throughout pregnancy.

Modest decreases in aPL observed during pregnancy but not changes in pregnancy outcomes.

Conversion from negative to positive antibody tests occurs infrequently and is not associated with adverse pregnancy outcomes.

Repeat measurement of aPL during pregnancy is unnecessary.
aPL without APS

• Although associations between aPL and pregnancy morbidity have been reported in women without APS,

• the association is weak
management of pregnant women with the **incidental finding** of persistent aPL

- Over 50 percent successful pregnancy without drug treatment
no therapy,
low-dose aspirin (ASA; 50 to 150 mg per day) alone,
or low-dose ASA and prophylactic-dose heparin
treatment decisions should be made on an individual basis
favored prescribing low-dose ASA alone during pregnancy
???????????????????
IVF in women with aPL

- **not prescribe prophylactic antithrombotic** during IVF for women with aPL & no clinical criteria for APS
- not appear to adversely affect pregnancy rates or outcome
- (ASRM) concluded that **assessment of aPL was not indicated among** couples undergoing IVF
- American Society for Reproductive Immunology Antiphospholipid Antibody Committee **assessment of aPL indicated** among couples undergoing IVF
IVF in women with APS

IVF is potentially dangerous since ovulation induction regimens trigger an estrogen-induced hypercoagulable state

high R. for women with a prior venous thromboembolism and APS.

If performed, women with a history of thrombosis-associated APS should be switched from their usual oral anticoagulant to therapeutic dose UFH, which should be maintained after oocyte retrieval.
All complications occurred in cycles that included (GnRH) agonists for ovulation induction. Using a GnRH antagonist protocol or natural cycles may minimize risk of thrombosis.
Neonatal APS

aPL in the neonate almost always results from placental transfer of maternal antibody

thus may not have the same significance as endogenously produced antibody.

Passively acquired aPL completely disappears by 6 to 12 months of age
pregnant and postpartum women with APS or aPL

<table>
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<tr>
<th>APS with prior arterial or venous <strong>thrombosis</strong>, with or without APS-defining pregnancy morbidity</th>
<th><strong>Antepartum</strong></th>
<th><strong>Postpartum</strong></th>
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<tr>
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<td><strong>Therapeutic</strong>-dose LMWH and low-dose ASA</td>
<td>Warfarin for an indefinite period of time.</td>
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APS based on laboratory criteria for Apl+ and APS+ defining pregnancy morbidity of ≥1 fetal losses ≥10 weeks of gestation or ≥3 unexplained consecutive spontaneous pregnancy losses <10 weeks of gestation and NO history of arterial or venous thrombosis

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<td>Prophylactic-dose LMWH and low-dose ASA</td>
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<tr>
<td>APS based on laboratory criteria for aPL+ and APS+ defining pregnancy morbidity of ≥1 preterm deliveries of a morphologically normal infant before 34 weeks of gestation due to severe preeclampsia, eclampsia, or other findings consistent with placental insufficiency and NO history of arterial or venous thrombosis</td>
<td>Vaginal delivery: Intermittent pneumatic compression and low-dose ASA while in the hospital. Graduated compression stockings and low-dose ASA for six weeks. Cesarean delivery: Prophylactic-dose LMWH and low-dose ASA for six weeks.</td>
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<td><strong>Most cases: Low-dose ASA</strong></td>
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<td>In cases of <strong>ASA failure or when placental examination shows extensive decidual inflammation</strong> and vasculopathy and/or thrombosis, <strong>prophylactic-dose LMWH with low-dose ASA</strong></td>
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<td><strong>APL+ but NO clinical criteria for APS (ie, NO thrombosis and NO history of APS-defining obstetric morbidity)</strong></td>
<td><strong>Low-dose ASA</strong></td>
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**Vaginal delivery:**
Intermittent pneumatic compression and low-dose ASA while in the hospital.
Graduated compression stockings and low-dose ASA for six weeks.

**Cesarean delivery:**
Prophylactic-dose LMWH and low-dose ASA for six weeks.