INTRODUCTION — Antiphospholipid syndrome (APS) is a systemic autoimmune disorder characterized by venous or arterial thrombosis and/or pregnancy loss in the presence of persistent antiphospholipid antibodies (aPL). It can occur as a primary condition, or it can occur with systemic lupus erythematosus (SLE) or another systemic autoimmune disease. Patients with SLE frequently have aPL, whereas the development of APS is much less common. aPL can also be found in healthy individuals. The main types of aPL of concern during pregnancy are lupus anticoagulant (LA), anticardiolipin antibodies (aCL), and anti-beta-2-glycoprotein-1 antibodies.

This topic will discuss the potential impact of APS and aPL alone during pregnancy, as well as the management of APS during pregnancy and postpartum. The medical management of women with non-obstetric APS and prenatal care of women with SLE with or without anti-Ro/SSA and anti-La/SSB antibodies are reviewed separately:

- (See "Treatment of antiphospholipid syndrome".)
- (See "Pregnancy in women with systemic lupus erythematosus".)
- (See "Neonatal lupus: Management and outcomes", section on 'In utero management'.)

IMPACT OF APS AND APL ON PREGNANCY

APS

Adverse pregnancy outcome — APS is characterized by both (1) arterial or venous thrombosis and/or specific pregnancy complications and (2) laboratory evidence of relevant antibodies conventionally called aPL. (See "Diagnosis of antiphospholipid syndrome", section on 'Definitions' and "Diagnosis of antiphospholipid syndrome", section on 'Diagnosis'.)

Updated Sapporo criteria (also called Sydney criteria) for defining pregnancy morbidity in the diagnosis of APS are [1] (see "Diagnosis of antiphospholipid syndrome", section on 'Classification criteria'):

- ≥1 unexplained fetal deaths ≥10 weeks of gestation with normal anatomy by prenatal ultrasound examination or direct postnatal examination.

- ≥1 preterm deliveries of a morphologically normal infant before 34 weeks of gestation due to severe preeclampsia, eclampsia, or features consistent with placental insufficiency. Generally accepted features of placental insufficiency include (1) abnormal or non-reassuring fetal surveillance test (eg, nonreactive nonstress test), (2) abnormal Doppler flow velocimetry waveform analysis (eg, absent end-diastolic flow in the umbilical artery), (3) oligohydramnios, or (4) birth weight less than the 10th percentile for the gestational age. (See "Overview of antepartum fetal surveillance".)
APS is not associated with placental abruption.

Poor prognostic factors — Poor prognostic factors for pregnant women with APS include the presence of lupus anticoagulant and the number of aPLs. In prospective studies, lupus anticoagulant appears to be the major predictor of poor pregnancy outcome in women with APS [2,3]. The number of different aPL specificities also appears to be a prognostic factor [4,5]. For example, in a multicenter retrospective cohort study of 750 singleton pregnancies with primary APS treated with low-dose aspirin and prophylactic low-molecular-weight heparin from the first trimester, the incidence of live birth was 80 percent in the 7 percent of women with lupus anticoagulant only, 56 percent in the 61 percent of women with anticardiolipin antibodies only, 48 percent in the 17 percent of women with anti-beta-2 glycoprotein-I only, 43 percent in the 12 percent of women with anticardiolipin and anti-beta-2 glycoprotein-I antibodies but lupus anticoagulant-negative, and 30 percent in the 3 percent of women with all three aPL [4]. Compared with women with only one antibody-positive result, women with multiple antibody-positive results had a 29 percent reduction in live-birth rate (41 versus 57 percent; adjusted odds ratio 0.71, 95% CI 0.51-0.90) and increased risks for disorders associated with placental insufficiency. A limitation of retrospective studies is that all tests were not routinely performed in all patients.

Pathogenesis — The pathogenesis of pregnancy morbidity in APS is incompletely understood, but is thought to involve platelet and endothelial cell activation as well as procoagulant effects of aPL [6]. Although uteroplacental thrombosis and vascular insufficiency may be one mechanism for adverse pregnancy outcome, not all affected placentas display signs of thrombosis or infarction. aPL also appears to have a direct effect on human placental trophoblast function [7], decreasing trophoblast viability, syncytialization, and capacity for invasion as measured by an in vitro assay [6]. In addition, aPL may affect the production of hormones and signaling molecules by cells in the trophoblast, and stimulate coagulation and complement activation [9-11]. Placental neutrophil extracellular traps are characteristic of APS dysfunctional placentas, though similar findings characterize placentas from preeclamptic patients [12]. Another hypothesis proposes that aPL induces factors that activate Toll-like receptor 8 [13].

Thromboembolic disease — Pregnancy and the puerperium are normally associated with an increased risk of thromboembolic disease, and this risk is particularly high in pregnant women with APS. In prospective studies, the risk of thromboembolic disease during pregnancy or postpartum was 5 to 12 percent among women with known APS (compared with 0.025 to 0.10 percent in the general obstetric population) [14,15]. Venous thromboses are more common than arterial thromboses. The risk of both venous and arterial thrombosis and/or thromboembolism is increased in individuals with positive tests for lupus anticoagulant activity, medium or high levels of anticardiolipin antibodies, and in those with positivity to three aPLs. (See "Clinical manifestations of antiphospholipid syndrome", section on 'Thrombotic events'.)

Women with thrombosis-associated APS may have higher rates of pregnancy complications than those with only obstetric-associated APS [16].

Neonatal APS — Neonatal APS is defined by the same criteria as APS in other populations: presence of at least one type of aPL in serum and the occurrence of at least one clinical feature, such as venous or arterial thromboses or thrombocytopenia [17]. A confounding factor, however, is that aPL in the neonate almost always results from placent al transfer of maternal antibody, and thus may not have the same significance as endogenously-produced antibody. Passively-acquired aPL completely disappears by 6 to 12 months of age [18].

Neonatal APS is rare. Studies reporting the neonatal outcome of maternal APS have not described any cases of neonatal APS among 277 neonates [18-23]; a registry that collects outcome data on pregnancies complicated by APS also has not recorded any cases of neonatal APS during follow-up of 134 children [24].
However, a literature review found 16 case reports of thrombosis in infants born to women with aPL, and 12 of these infants met criteria for neonatal APS (for the other four infants, aPL was detected only in the mother) [25]. Causality related to aPL has not been established. Some authors attribute morbidity to local vascular injury, others to the antibody itself [24,26-29].

**aPL without APS** — Indications for aPL testing are reviewed separately. (See "Diagnosis of antiphospholipid syndrome", section on 'When to suspect the diagnosis'.)

It is unclear whether women with aPL who do not meet criteria for APS are at increased risk of pregnancy morbidity. The body of evidence suggests little or no increase in risk in this group [30-32]. The risk of first-time thrombosis in pregnant women with aPL and no personal history of thrombosis is also uncertain [33,34]. Furthermore, there is no strong evidence for an association between aPL and primary infertility, in vitro fertilization failure, or mild or near-term/term preeclampsia [35-39].

Most patients without APS who are aPL positive in the first trimester (defined as aCL or anti-beta2-GPI ≥40 units or lupus anticoagulant positive) remain in the high-positive range throughout pregnancy [40]. Modest decreases in aPL have been observed during the course of pregnancy, but have not been associated with changes in pregnancy outcomes. Conversion from negative to positive occurs infrequently and is not associated with adverse pregnancy outcomes. Therefore, repeat measurement of aPL during pregnancy is unnecessary.

Although associations between aPL and pregnancy morbidity have been reported in women without APS, the association is weak. The reported prevalence of aCL in women with uncomplicated pregnancies ranges from 0 to 11 percent, with a median value of about 2 percent [30,31,41-47]. Since aPL can be found in normal asymptomatic individuals, a causal relationship between these antibodies and a clinical event in any individual is difficult to prove, particularly when the adverse obstetrical outcome is relatively common (eg, spontaneous abortion before 10 weeks). Additional explanations for the poor predictive value of positive aPL results include the following:

- Reliance upon nonstandardized assays for aPL and failure to use internationally-recognized standards.
- Failure to control for the severity of coexisting disorders known to cause adverse obstetrical outcomes.
- Failure to perform repeat confirmatory aPL testing (repeat aPL testing should be performed >12 weeks after the first positive aPL test).
- Inclusion of patients with low positive aPL levels among patients considered positive.
- Broad criteria/definitions for case selection in series involving pregnancy loss.
- Variable thrombogenic potential of a given patient's aPL.

**MANAGEMENT OF APS DURING PREGNANCY**

**Antithrombotic therapy** — Our approach to antithrombotic treatment of pregnant women with APS varies depending on whether they have APS based on a prior thrombosis versus an APS-associated pregnancy morbidity. A suggested approach is summarized in the tables and clinical scenarios discussed below (table 1). When selecting anticoagulation regimens during pregnancy, we prefer low-molecular-weight heparin (LMWH) to unfractionated heparin, and avoid oral anticoagulants (eg, warfarin, fondaparinux) (see "Use of anticoagulants during pregnancy and postpartum", section on 'Choice of anticoagulant'). If heparin is contraindicated because of heparin-induced thrombocytopenia (HIT), which occurs rarely in pregnancy, then danaparoid or fondaparinux are reasonable options [48]. (See "Use of anticoagulants during pregnancy and postpartum", section on 'HIT during or immediately preceding pregnancy'.)

The optimum low dose of aspirin (ASA), which may be used either alone or in combination with anticoagulation depending on the clinical scenario, is unclear. Although one meta-analysis reported the
optimum dose may be 100 to 150 mg [49], 81 mg is a more practical dose as 100 to 150 mg doses are not readily available in the United States. Taking one and one-half 81 mg tablets is an option. (See "Preeclampsia: Prevention", section on 'Candidates'.)

APS based on aPL and prior thrombosis — Nonpregnant women with a definite diagnosis of APS based on laboratory criteria for aPL and a history of arterial or venous thrombosis are at high risk of recurrent thrombosis and are generally treated with warfarin for an indefinite period that may be lifelong. (See "Treatment of antiphospholipid syndrome".)

During pregnancy, we agree with American College of Chest Physicians (ACCP) Evidence-Based Clinical Practice Guidelines suggesting use of LMWH for anticoagulation in these women [33]. We prefer LMWH because of its potentially greater safety and efficacy compared with unfractionated heparin, but unfractionated heparin is an acceptable alternative.

We administer a therapeutic dose of LMWH (table 2). The ACCP also suggests using therapeutic rather than prophylactic LMWH dosing in this setting. Management of anticoagulation (eg, advantages and disadvantage of LMWH versus unfractionated heparin, switching from warfarin to LMWH, dosing and monitoring) is discussed in detail separately. (See "Use of anticoagulants during pregnancy and postpartum".)

We also administer low-dose ASA during pregnancy, as APS is one of the risk criteria the United States Preventive Services Task Force and the American College of Obstetricians and Gynecologists consider sufficient for using this therapy to reduce the risk of preeclampsia. (See "Preeclampsia: Prevention", section on 'Candidates'.)

APS based on aPL and pregnancy morbidity — We offer pharmacologic treatment (as described below) to pregnant women with APS based on laboratory criteria for aPL and pregnancy-related morbidity, but no history of venous or arterial thrombosis. Some experts consider close clinical surveillance with or without the addition of hydroxychloroquine to be a reasonable alternative approach in this population [50]. (See 'Treatment failure' below.)

Early or late loss — For women with APS based on laboratory criteria for aPL and ≥1 fetal losses ≥10 weeks of gestation or ≥3 unexplained consecutive spontaneous pregnancy losses <10 weeks of gestation, we suggest combined therapy with low-dose ASA (50 to 100 mg per day), beginning when conception is attempted, and prophylactic-dose LMWH upon confirmation of intrauterine pregnancy; low-dose ASA and unfractionated heparin is a reasonable alternative [33,50-54].

In three meta-analyses of randomized trials in women with APS, compared with ASA alone, the combination of heparin and ASA significantly reduced pregnancy loss (relative risk [RR] 0.46, 95% CI 0.29-0.71) [51] or first-trimester pregnancy loss (odds ratio [OR] 0.39, 95% CI 24-0.65) [59] and increased live births (RR 1.3, 95% CI 1.04-1.63) [56]. However, there are several limitations to these analyses, including the small number of trials, the small sample size in each trial, and the low quality of the trials themselves. For example, information about patient dropout and some adverse outcomes was not always available, and patients/providers were not blinded to the treatment. Both therapies were associated with relatively high live-birth rates, ranging from 71 to 84 percent for combined therapy and 42 to 80 percent for ASA alone. Therefore, the improvement in outcome with combined therapy versus ASA alone appears to be modest at best.

In women with a prior history of two or more fetal losses, a live-birth rate of 70 to 80 percent has been reported for patients treated with medication (eg, heparin, low-dose ASA, and/or prednisone) [15,57-62]. However, even among patients with live births, there is an increased risk of complications relating to the pregnancy (preterm birth, preeclampsia, growth restriction) [14].

Preterm delivery related to uteroplacental insufficiency — For women with APS based on aPL and ≥1 preterm deliveries of a morphologically normal infant before 34 weeks of gestation due to preeclampsia with severe features, eclampsia, or other findings consistent with placental insufficiency, we suggest low-dose
ASA therapy (50 to 100 mg per day), beginning at the end of the first trimester and continuing through delivery [33,50]. Although some clinicians prescribe LMWH as well, available evidence does not support this approach [63]. (See "Preeclampsia: Prevention", section on 'Low-dose aspirin'.)

However, we do prescribe LMWH with low-dose ASA selectively in cases of ASA failure or when placental examination shows extensive decidual inflammation and vasculopathy and/or thrombosis, although this approach has not been validated by a randomized trial. In a systematic review, the most common histopathological features of the placenta in women with APS were infarction, impaired spiral artery remodeling, decidual inflammation, increased syncytial knots, decreased vasculosyncytial membranes, and deposition of complement split product C4d [64].

**aPL alone** — There is a paucity of information to guide management of pregnant women with the incidental finding of persistent aPL, without meeting any of the clinical criteria for APS. Over 50 percent of such women will have a successful pregnancy without drug treatment [43,65,66].

Therapeutic options in pregnancy include no therapy, low-dose ASA (50 to 150 mg per day) alone, or low-dose ASA and prophylactic-dose heparin [53]. Given the uncertainty about pregnancy morbidity in these women, treatment decisions should be made on an individual basis. We agree with the majority of the Advisory Board of the 10th International Congress on aPL, who favored prescribing low-dose ASA alone during pregnancy for these patients [52].

The rationale for using low-dose ASA is that, in addition to its antiplatelet effects, low-dose ASA enhances leukocyte-derived interleukin-3 production, which stimulates normal trophoblast growth and hormone expression [67]. However, it should be noted that a 2015 systematic review of trials of primary prophylaxis to prevent obstetric complications in asymptomatic women with aCL did not find a benefit from ASA therapy, but included only 154 pregnancies [68].

If prophylactic-dose LMWH (table 2) is given to selected women, it should begin in the first trimester after confirmation of intrauterine pregnancy.

### Additional management considerations

**Antepartum monitoring** — There are no high-quality data on which to base recommendations for maternal and fetal monitoring. As in all pregnancies at increased risk of complications, the frequency and content of prenatal care in APS are tailored to allow timely intervention in the event of maternal or pregnancy complications, such as preeclampsia. In addition to routine prenatal care, this includes:

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

- Screening for anti-Ro/SSA and anti-La/SSB antibodies. If one lupus-related autoantibody is present, another may be as well, and these antibodies have implications for the fetus/neonate. Monitoring for and evaluation and management of fetal heart block are reviewed separately. (See "Neonatal lupus: Epidemiology, pathogenesis, clinical manifestations, and diagnosis", section on 'Fetal surveillance for heart block'.)

- Ultrasound examination before 20 weeks of gestation (ideally in the first trimester) to establish the estimated date of delivery (see "Prenatal assessment of gestational age, date of delivery, and fetal weight"). We also perform serial sonograms about every four weeks beginning in the late second or early third trimester to evaluate fetal growth and amniotic fluid volume. (See "Fetal growth restriction: Diagnosis" and "Assessment of amniotic fluid volume".)

- Weekly or twice per week nonstress tests and/or biophysical profile scoring beginning at 32 weeks of gestation because of the increased risk of antepartum fetal death. (See "Overview of antepartum fetal surveillance".)
If fetal growth restriction, oligohydramnios, and/or preeclampsia are diagnosed, management is the same as in pregnancies without APS. (See "Fetal growth restriction: Evaluation and management" and "Preeclampsia: Management and prognosis" and "Oligohydramnios".)

**Labor and delivery** — In the absence of standard medical or obstetric indications for early delivery, we schedule delivery (induction or cesarean) at 39 weeks of gestation to control the timing of discontinuation of antithrombotic drugs.

**Anticoagulation** — Patients receiving therapeutic LMWH should be switched to therapeutic doses of unfractionated heparin at 36 to 37 weeks to exploit the latter agent's shorter half-life and thus allow administration of neuraxial anesthesia and minimize delivery-related bleeding if spontaneous labor occurs in the late preterm or early term period. Therapeutic unfractionated heparin therapy is then discontinued 24 hours before labor and delivery, also to allow administration of neuraxial anesthesia and minimize delivery-related bleeding. This approach generally ensures that patients with prior thromboses are not off anticoagulants for more than 48 hours. Management of peripartum LMWH is described in detail separately. (See "Use of anticoagulants during pregnancy and postpartum", section on 'Labor and delivery'.)

**Low-dose ASA** — Low-dose ASA can be stopped any time after 36 weeks of gestation in women with no history of thrombosis. Stopping ASA 7 to 10 days before delivery avoids the slight increase in mostly minor perioperative bleeding observed with continuation of the drug [69]. However, in women with a past history of serious arterial thrombotic complications, such as stroke or myocardial infarction, we continue ASA through labor and delivery because the potential benefit of reducing the risk of these serious complications outweighs the small risk of incisional bleeding.

**Postpartum** — Women with APS by laboratory criteria for aPL and a prior history of arterial or venous thrombosis are at high risk of recurrence and are generally on an indefinite period of anticoagulation with warfarin, which should be resumed postpartum. Anticoagulation can generally be resumed four to six hours after vaginal delivery or 6 to 12 hours after cesarean delivery, unless there is significant bleeding or risk for significant bleeding. Heparin and warfarin are not contraindicated in breastfeeding mothers. (See "Treatment of antiphospholipid syndrome").

There are no high-quality data to guide postpartum management of women with APS based on obstetric morbidity and no history of prior thrombosis or women with aPL alone. Our approach is described in the table, and takes into account past medical and obstetric history, antepartum therapy, and route of delivery (table 1).

The Nimes Obstetricians and Hematologists Antiphospholipid Syndrome study followed women with APS based on obstetric history and no history of thrombosis for a median of 9.3 years [70]. Compared with women with no thrombophilia, these women were at increased lifetime risk of deep vein thrombosis (adjusted hazard ratio [aHR] 1.85, 95% CI 1.50-2.28; annualized rate 1.46 percent) and stroke (aHR 2.10, 95% CI 1.08-4.08; annualized rate 0.17 percent). Although postpartum risk was not specifically studied, these women would likely be at particularly high risk postpartum, given that the postpartum state is a risk factor for thromboembolic events. (See "Deep vein thrombosis in pregnancy: Epidemiology, pathogenesis, and diagnosis" and "Deep vein thrombosis and pulmonary embolism in pregnancy: Prevention").

The ACCP Evidence-Based Clinical Practice Guidelines concluded that women with aPL and no personal or family history of thrombosis are probably not at increased risk of developing pregnancy-related venous thrombosis, but suggested postpartum anticoagulation for those with a family history of thrombosis [33].

**TREATMENT FAILURE** — Patients with obstetric APS treated with low-dose aspirin/LMWH may require additional treatment measures as conventional treatment fails to prevent obstetric morbidity in 20 percent of...
cases [5]. For women who have adverse pregnancy outcomes despite antithrombotic therapy, there is no second line therapy with proven efficacy.

The antimalarial drug hydroxychloroquine appears to depress aPL levels in humans [71]. This effect might be beneficial in women with APS-related recurrent pregnancy loss. No high-quality data are available, but retrospective human and experimental animal data suggest that hydroxychloroquine may benefit patients with APS [72,73]. However, it takes about three months for hydroxychloroquine to have an effect, thus it should be started prior to pregnancy. Case series have not described teratogenicity with use of hydroxychloroquine in pregnant women with systemic lupus erythematosus, and miscarriage rates have been similar in treated and untreated women. (See "Antimalarial drugs in the treatment of rheumatic disease" and "Safety of antinflammatory and immunosuppressive drugs in rheumatic diseases during pregnancy and lactation", section on 'Hydroxychloroquine'.)

OTHER ISSUES

In vitro fertilization

In vitro fertilization in women with aPL — We do not prescribe prophylactic antithrombotic therapy during in vitro fertilization (IVF) for women with aPL who have no clinical criteria for APS. The presence of aPL alone does not appear to adversely affect pregnancy rates or outcome in patients who are undergoing IVF [74-77]. A meta-analysis by the American Society for Reproductive Medicine (ASRM) Practice Committee concluded that assessment of aPL was not indicated among couples undergoing IVF, and treatment was not justified in this population based upon existing data [37,78]. However, this issue remains controversial because of the heterogeneity of these studies and the different aPL assay methodologies used [36,79]. As an example, the American Society for Reproductive Immunology Antiphospholipid Antibody Committee strongly disagreed with the ASRM recommendation and called for studies to determine whether there are circumstances when evaluation and treatment of women with aPL undergoing fertility therapy are important [79].

In vitro fertilization in women with APS — Experience with IVF in women with APS is extremely limited. IVF is potentially dangerous since ovulation induction regimens trigger an estrogen-induced hypercoagulable state. The authors extensively counsel and caution women with APS who are considering IVF, given the significant risk of thrombosis, which is particularly high 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 unfractionated heparin, which should be maintained after oocyte retrieval. If the patient conceives, she should be switched to LMWH, as described above (see 'APS based on aPL and prior thrombosis' above). If she does not conceive, she should be maintained on unfractionated heparin through repeated IVF cycles or switched back to her usual anticoagulant if further cycles are not planned.

A series including four women with APS plus systemic lupus erythematosus and 10 women with APS reported three patients had a total of four thromboembolic events (one lumbo-ovarian thrombosis, two distal deep venous thrombosis, one distal pulmonary embolism) associated with IVF [77]. In two of these patients, thrombosis was attributed to discontinuing anticoagulant treatment after the oocyte retrieval (LMWH, prophylactic for one, therapeutic for the other); thus, adherence to treatment may have prevented these complications. All complications occurred in cycles that included gonadotropin-releasing hormone (GnRH) agonists for ovulation induction. Using a GnRH antagonist protocol or natural cycles may minimize risk of thrombosis.

SOCIETY GUIDELINE LINKS — Links to society and government-sponsored guidelines from selected countries and regions around the world are provided separately. (See "Society guideline links: Antiphospholipid syndrome".)

SUMMARY AND RECOMMENDATIONS
Pregnancy morbidity in antiphospholipid syndrome (APS) is defined by (see 'Adverse pregnancy outcome' above):

- ≥1 unexplained fetal deaths ≥10 weeks of gestation with normal morphology by prenatal ultrasound examination or direct postnatal examination
- ≥1 preterm deliveries of a morphologically-normal infant before 34 weeks of gestation due to severe preeclampsia, eclampsia, or features consistent with placental insufficiency
- ≥3 unexplained, consecutive, spontaneous pregnancy losses <10 weeks of gestation, after exclusion of maternal anatomic and hormonal abnormalities and paternal and maternal chromosomal abnormalities

The pathogenesis of pregnancy morbidity in APS is incompletely understood. Antiphospholipid antibodies (aPL) are thought to affect platelet and endothelial cell activation, promote coagulation, activate complement, and have direct effects on the human placental trophoblast. (See 'Adverse pregnancy outcome' above.)

It is unclear whether asymptomatic healthy women with aPL who do not meet criteria for APS are at increased risk of pregnancy morbidity. The body of evidence suggests little or no increase in risk in this group. (See 'aPL without APS' above.)

Nonpregnant women with a definite diagnosis of APS, based on laboratory criteria for aPL and a history of arterial or venous thrombosis, are at high risk of recurrent thrombosis and are generally treated with warfarin for an indefinite period that may be lifelong. We agree with American College of Chest Physicians Evidence-Based Clinical Practice Guidelines for use of low-molecular-weight heparin (LMWH) for anticoagulation of these women during pregnancy, with resumption of warfarin postpartum. We suggest a therapeutic dose of LMWH (table 2) throughout pregnancy rather than prophylactic-dose LMWH (Grade 2C). We also prescribe low-dose aspirin (ASA) to reduce the risk of preeclampsia. (See 'APS based on aPL and prior thrombosis' above.)

For women with laboratory criteria for aPL and ≥1 fetal losses ≥10 weeks of gestation or ≥3 unexplained, consecutive, spontaneous pregnancy losses <10 weeks of gestation, we suggest combined therapy with low-dose ASA (50 to 100 mg per day) and prophylactic-dose LMWH rather than low-dose ASA alone (Grade 2B). (See 'Early or late loss' above.)

For women with laboratory criteria for aPL and ≥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, we suggest low-dose ASA therapy rather than no therapy or heparin (Grade 2C). We prescribe prophylactic-dose LMWH with low-dose ASA in cases of ASA failure or when placental examination shows extensive decidual inflammation and vasculopathy and/or thrombosis, although this approach has not been validated by a randomized trial. (See 'Preterm delivery related to uteroplacental insufficiency' above.)

For pregnant women with the incidental finding of persistent aPL without meeting any of the clinical criteria for APS, we suggest low-dose ASA alone rather than no therapy (Grade 2C). (See 'aPL alone' above.)

Our approach to postpartum venous thromboembolism prophylaxis depends on past medical and obstetric history, antepartum therapy, and route of delivery, and is illustrated in the table (table 1). (See 'Postpartum' above.)

ACKNOWLEDGMENT — The editorial staff at UpToDate would like to acknowledge Peter Schur, MD, who contributed to an earlier version of this topic review.
REFERENCES


Perinatol 2006; 23:247.


38. Chighizola CB, de Jesus GR. Antiphospholipid antibodies and infertility. Lupus 2014; 23:1232.


45. Parke AL, Wilson D, Maier D. The prevalence of antiphospholipid antibodies in women with recurrent spontaneous abortion, women with successful pregnancies, and women who have never been pregnant. Arthritis Rheum 1991; 34:1231.


Topic 6813 Version 41.0
### Approach to treatment of pregnant and postpartum women with APS or aPL

<table>
<thead>
<tr>
<th>APS with prior arterial or venous thrombosis</th>
<th>Antepartum</th>
<th>Postpartum</th>
</tr>
</thead>
<tbody>
<tr>
<td>Therapeutic-dose LMWH</td>
<td>Warfarin for an indefinite period of time</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>APS with prior arterial or venous thrombosis and APS-defining pregnancy morbidity</th>
<th>Antepartum</th>
<th>Postpartum</th>
</tr>
</thead>
<tbody>
<tr>
<td>Therapeutic-dose LMWH and low-dose ASA</td>
<td>Warfarin for an indefinite period of time</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>APS based on laboratory criteria for APS and APS-defining pregnancy morbidity of ≥1 fetal losses ≥10 weeks of gestation or ≥3 unexplained consecutive spontaneous pregnancy losses &lt;10 weeks of gestation and NO history of arterial or venous thrombosis</th>
<th>Antepartum</th>
<th>Postpartum</th>
</tr>
</thead>
<tbody>
<tr>
<td>Prophylactic-dose LMWH and low-dose ASA</td>
<td>Prophylactic-dose LMWH and low-dose ASA for six weeks regardless of route of delivery</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>APS based on laboratory criteria for APS 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</th>
<th>Antepartum</th>
<th>Postpartum</th>
</tr>
</thead>
</table>

<table>
<thead>
<tr>
<th>APS based on laboratory criteria for APS (ie, NO history of venous or arterial thrombosis and NO history of APS defining obstetric morbidity)</th>
<th>Antepartum</th>
<th>Postpartum</th>
</tr>
</thead>
</table>

Examples of therapeutic LMWH (also referred to as weight-adjusted, full-treatment dose): enoxaparin 1 mg/kg every 12 hours, dalteparin 200 units/kg once daily, tinzaparin 175 units/kg once daily, dalteparin 100 units/kg every 12 hours.
Examples of prophylactic LMWH: enoxaparin 40 mg SC once daily, dalteparin 5000 units SC once daily, tinzaparin, 4500 units SC once daily. These doses may need to be modified at extremes of body weight. Anticoagulation can generally be resumed four to six hours after vaginal delivery or 6 to 12 hours after cesarean delivery, unless there is significant bleeding or risk for significant bleeding.

NOTE: Tinzaparin is not available in the United States. The role and frequency of anti-Xa testing for management of therapeutic dosing of LMWH in pregnancy are reviewed in the UpToDate topic on anticoagulation in pregnancy.

APS: antiphospholipid syndrome; LMWH: low molecular weight heparin; ASA: aspirin; aPL: antiphospholipid antibodies; SC: subcutaneous.

Graphic 91501 Version 7.0
### Anticoagulation regimen definitions

<table>
<thead>
<tr>
<th>Management type</th>
<th>Dosage</th>
</tr>
</thead>
</table>
| **Prophylactic LMWH**<sup>*</sup> | Enoxaparin, 40 mg SC once daily  
Dalteparin, 5000 units SC once daily  
Tinzaparin, 4500 units SC once daily |
| **Therapeutic LMWH**<sup>¶</sup> (also referred to as weight-adjusted, full-treatment dose) | Enoxaparin, 1 mg/kg every 12 hours  
Dalteparin, 200 units/kg once daily  
Tinzaparin, 175 units/kg once daily  
Dalteparin, 100 units/kg every 12 hours |
| **Minidose prophylactic UFH** | UFH, 5000 units SC every 12 hours |
| **Prophylactic UFH** | UFH, 5000 to 10,000 units SC every 12 hours  
UFH, 5000 to 7500 units SC every 12 hours in first trimester  
UFH, 7500 to 10,000 units SC every 12 hours in the second trimester  
UFH, 10,000 units SC every 12 hours in the third trimester, unless the aPTT is elevated |
| **Therapeutic UFH** (also referred to as weight-adjusted, full-treatment dose) | UFH, 10,000 units or more SC every 12 hours in doses adjusted to target aPTT in the therapeutic range (1.5 to 2.5) six hours after injection |
| **Postpartum anticoagulation** | Prophylactic LMWH/UFH for four to six weeks  
**OR**  
Vitamin K antagonists for four to six weeks with a target INR of 2.0 to 3.0, with initial UFH or LMWH therapy overlap until the INR is 2.0 or more for two days |
| **Surveillance**<sup>Δ</sup> | |

In addition, the American College of Chest Physicians (ACCP) provides the option of intermediate dosing. Intermediate-dose UFH refers to doses adjusted to target a specific anti-Xa UFH level. Examples of intermediate-dose LMWH include dalteparin 5000 units subcutaneously every 12 hours or enoxaparin 40 mg subcutaneously every 12 hours. Antithrombotic Therapy and Prevention of Thrombosis, 9th ed: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines. February 2012.  
NOTE: Tinzaparin is not available in the United States.  
The role and frequency of anti-Xa level testing for management of therapeutic dosing of LMWH in pregnancy are reviewed in the UpToDate topic on anticoagulation in pregnancy.

LMWH: low molecular weight heparin; SC: subcutaneously; UFH: unfractionated heparin; aPTT: activated partial thromboplastin time; INR: international normalized ratio.

* Although at extremes of body weight, modification of dose may be required.

¶ May target an anti-Xa level in the therapeutic range of 0.6 to 1.0 units/mL for twice daily regimen; slightly higher doses may be needed for a once-daily regimen.

Δ Clinical vigilance and appropriate objective investigation of women with symptoms suspicious of deep vein thrombosis or pulmonary embolism may be needed.


Graphic 56377 Version 18.0
Contributor Disclosures

Charles J Lockwood, MD, MHCM Nothing to disclose Michael D Lockshin, MD, MACR Nothing to disclose Vincenzo Berghella, MD Nothing to disclose David S Pisetsky, MD, PhD Grant/Research/Clinical Trial Support: Pfizer [Rheumatoid arthritis, systemic lupus erythematosus]. Consultant/Advisory Boards: Celgene [Psoriatic arthritis (Apremilast); Lupus (Phase 2 study of CC-220)]; ImmunArray [Antinuclear antibodies (SLE molecular diagnostic test)]; Pfizer [Basic immunology, lupus (Tofacitinib, anti-IL6 trial)]. Vanessa A Barss, MD, FACOG Nothing to disclose Monica Ramirez Curtis, MD, MPH Nothing to disclose

Contributor disclosures are reviewed for conflicts of interest by the editorial group. When found, these are addressed by vetting through a multi-level review process, and through requirements for references to be provided to support the content. Appropriately referenced content is required of all authors and must conform to UpToDate standards of evidence.

Conflict of interest policy