Impact of Antiphospholipid Syndrome on Reproductive Outcomes: Current Insights and Management Approaches

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Abstract

Antiphospholipid syndrome (APS) is a disease characterized by the presence of antiphospholipid (aPL) antibodies, thrombosis, and obstetric complications. While patients with APS can have successful pregnancies, many important considerations exist. APS can also cooccur with other systemic autoimmune diseases which can affect pregnancy, particularly systemic lupus erythematosus. This article reviews specific considerations for pregnancy and reproductive health in patients with APS. Similar to other autoimmune diseases, stable or quiescent disease and planning with a rheumatologist and obstetrician prior to conception are vital components of a successful pregnancy. Pregnancy management for patients with aPL antibodies or diagnosis of APS with aspirin and/or anticoagulation depending on disease profile is discussed, as well as the effects of physiologic changes during pregnancy in maternal and fetal outcomes for this population. Given the reproductive span lasts beyond conception through delivery, we include discussions on safe contraception options, the use of assistive reproductive technology, pregnancy termination, menopause, and male fertility. While APS is a relatively rare condition, the effects this disease can have on maternal and fetal outcomes even with available therapies demonstrates the need for more high-quality, evidence-based research.

Keywords
- antiphospholipid syndrome
- pregnancy
- reproduction

Antiphospholipid syndrome (APS) is an autoimmune disease characterized by the presence of antibodies and recurrent thrombosis or fetal loss. While there is no diagnostic criterion for APS, the clinical diagnosis requires both laboratory evidence with the presence of an antiphospholipid (aPL) antibody (anticardiolipin, anti-B2-glycoprotein, or lupus anticoagulant [LAC]) which is positive on two consecutive occasions at least 12 weeks apart and clinical evidence of a thrombotic event or obstetric complication. These criteria are based on the Sydney Classification Criteria commonly used in clinical practice.[1] The ACR and EULAR have recently published updated classification criteria for APS, which have increased specificity for use in observational studies and clinical trials.[2]

A core component of the diagnosis of APS is the presence of at least one aPL antibody as well as clinical characteristics outlined in ►**Table 1**. There are three recognized antibodies widely used in current clinical practice: anticardiolipin (aCL), anti-beta-2-glycoprotein (anti-B2GP), and LAC.[1] There have been newer antibodies discovered recently which may also play pathogenic roles in APS, including phosphatidylserine/prothrombin (PS/PT); however, consensus regarding use in clinical diagnosis has not yet been reached.[3] The diagnosis of APS is further divided into two categories: thrombotic and

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Table 1 Sydney criteria for diagnosis of APS

Laboratory criteria: at least one of the following measured on two or more occasions at least 12 wk apart	Thrombotic APS: laboratory criteria + one of the following:	Obstetric APS: laboratory criteria + one of the following:
1. Lupus anticoagulant present 2. Anticardiolipin antibody (IgG and/or IgM) in medium or high titer (>99th percentile) 3. Anti-B2-glycoprotein I antibody IgG and/or IgM present in titer >99th percentile	1. Venous, arterial, or microvascular thrombosis 2. No evidence of inflammation in the vessel wall	1. ≥1 unexplained fetal death ≥10th week of gestation 2. ≥1 premature birth <34th week of gestation due to: - Severe preeclampsia or eclampsia - Features of placental insufficiency 3. ≥3 unexplained miscarriages <10th week of gestation

Abbreviation: APS, antiphospholipid syndrome.

obstetric. Obstetric APS is defined by laboratory criteria and prior pregnancy complications including three losses prior to 10 weeks of gestation, one fetal loss at or after 10 weeks of gestation, or delivery at <34 weeks (due to preeclampsia, fetal distress, or intrauterine growth restriction [IUGR]).[1] Thrombotic APS is defined by patients who meet laboratory criteria and have had at least one venous or arterial thrombotic event.[1]

The annual incidence of APS in adults is 2.1 per 100,000 people, with an estimated prevalence of 50 per 100,000 people.[4] These estimates are from one cohort study in the United States which was based on mostly white population, lacked standardized clinical criteria and titer cut-offs, and was not population based—flaws which are present in many studies on APS.[5] It is estimated that the incidence in females of childbearing age is 1.4 per 100,000 people, and that APS may be associated with up to 10% of cases of obstetric morbidity.[5] As discussed in this article, it can be difficult to determine the exact cause of obstetric morbidity given many patients have multiple comorbidities like advanced maternal age and other health conditions. However, APS is recognized as a known contributor to maternal and fetal morbidity and mortality.[5]

Reproductive health is not only pregnancy and delivery: this topic spans from contraception and family planning through the childbearing years of patients and beyond. In 2020, the American College of Rheumatology (ACR) created guidelines on reproductive health in patients with autoimmune disease and included recommendations for patients with APS.[6] These include specific contraception considerations, pregnancy planning and management, infertility options, recommendations regarding hormone therapy during menopause, and male fertility considerations. This article will outline these topics as well as other components of reproductive health including vaccines, cancer screenings, and pregnancy termination as it pertains to patients with APS.

Preventative Reproductive Health

When considering patients who are of reproductive age with APS, one core component of preventative care is vaccinations. Concerns regarding disease flare, the ability of the immune system to mount an appropriate response, and the risk of causing thrombosis can arise. Recommended vaccinations for females of childbearing age include the human papillomavirus (HPV), influenza, and coronavirus disease 2019 (COVID-19) vaccinations, among others.[7] ACR guidelines recommend that any patient with rheumatic disease between 26 and 45 years old who is on immunosuppressive medication should get the HPV vaccination (conditionally recommended) and high-dose influenza vaccination (conditionally recommended). COVID-19 vaccinations were not included in these recommendations given the rapidly changing landscape during the time of publication.[8] For those not on immunosuppressive medications, these vaccinations remain recommended in accordance with population guidelines. Despite some literature exploring a possible relationship between COVID-19 vaccination and the development of inflammatory disease and thrombosis, there is no evidence that patients with APS are at higher risk of thrombotic complications from vaccinations including COVID-19.[9,10] Immunosuppression including high-dose glucocorticoids, rituximab, mycophenolate mofetil, and abatacept have been associated with lower post-vaccination antibody titers. In patients with rheumatic disease on other or no medications, antibody response to vaccinations is similar to the normal healthy population.[11,12] To improve vaccination response, the ACR conditionally recommends holding some immunosuppressive medications for a period of time after the vaccine is given: for example, holding methotrexate for 2 weeks following the influenza vaccine.[8] However, these guidelines are dependent on the type of medication and vaccination and should be referred to prior to patient counseling.

Contraception

Contraception is an important part of planning a safe and successful pregnancy with the goal of a healthy mother and healthy baby. Currently used methods of contraception and comparable efficacies are shown in ►**Table 2**.[13] Notably, there are no contraindications for the three most effective birth control options based on rheumatic disease profile or thrombotic risk, which are tubal ligation/vasectomy, implant, or intrauterine device (IUD). One specific consideration for the copper IUD is the tendency for increased menstrual bleeding with this form of contraception, which should be considered for a patient who is on anticoagulation and possibly already at higher bleeding risk.

Table 2 Contraception methods with associated efficacy and contraindications

Contraception method	Efficacy	Contraindications
Tubal ligation/or vasectomy	Very effective[a]	
Implant (etonogestrel-releasing)	Very effective	
Intrauterine device (copper or levonorgestrel-containing)	Very effective	
Depot-medroxyprogesterone acetate (DMPA)	Effective[b]	Prior thromboembolism and/or +aPL antibody
Combined oral contraception pill	Effective	Prior thromboembolism and/or +aPL antibody
Progestin-only pill	Effective	
Vaginal ring (estrogen ring)	Effective	Prior thromboembolism and/or +aPL antibody
Patch (estrogen and progestin releasing)	Effective	Prior thromboembolism and/or +aPL antibody
Condom or diaphragm	Ineffective[c]	
Fertility awareness	Ineffective	

[a]Very effective: <1% incidence of pregnancy per year.
[b]Effective: 6–9% incidence of pregnancy per year.
[c]Ineffective: 10–25% incidence of pregnancy per year.

Any contraception with estrogen is contraindicated for patients with a history of thrombotic disease and/or the presence of aPL antibody due to increased risk of thrombosis.[14] The risk of VTE in healthy females taking oral contraception pills (OCPs) containing estrogen is 36-fold higher than those not on OCPs.[15] Therefore, females with APS who are already at increased risk of VTE should not use contraception containing estrogen. Even in the absence of a clinical diagnosis of APS, those with previous blood clots or +aPL antibody testing should not use these methods due to the risk of thrombosis. Depot-medroxyprogesterone acetate (DMPA) is similarly recommended against use in patients with APS or the presence of aPL antibody given the concern of thrombogenicity. This recommendation is based largely on a study conducted by the World Health Organization (WHO) in 1998 which reported a small increase in the risk of venous thrombosis for those using injectable progesterone-only contraceptives (odds ratio [OR]: 2.2, confidence interval [CI]: 0.7–7.3), which has been supported by more recent smaller scale studies.[16,17] The WHO Medical Eligibility Criteria for Contraception now specifies that females with systemic lupus erythematosus (SLE) and positive or unknown aPL status should not use estrogen-containing contraceptives, and should use an alternative to DMPA if available.

IUDs and the progestin-only pill remain the most recommended forms of contraception in patients with APS based on published guidelines due to their efficacy and safety profile.[6] While there is some debate regarding the thrombogenicity of progestin-containing contraception in females with rheumatic disease, there is no evidence of increased thrombosis frequency in those with increased thrombotic risk due to factors other than the presence of aPL antibodies or APS.[18] Recommendations supporting the use of progestin-only-containing contraception are therefore extrapolated from these data given the paucity of controlled studies in females with rheumatic diseases. Although there is a lack of data in the specific APS population, the theoretical risk of progestin-related thrombosis must be weighed against the risk of thrombosis in a pregnant APS patient: as discussed later, this is estimated to be about 1 in 10 to 1 in 50 APS pregnancies.[19] In the case of unprotected sex or failure of birth control, patients with APS can consider the use of emergency contraception. Emergency contraception, defined as methods used to prevent pregnancy after unprotected intercourse, includes the copper IUD, oral selective progesterone modulators, and oral levonorgestrel. These are all safe to use in those with positive aPL antibodies or a history of thrombosis with or without a diagnosis of APS.[20]

Preconception Counseling

One of the most important considerations in helping a patient with APS achieve a successful and healthy pregnancy is preconception counseling and planning. For females with rheumatic disease including APS, it is recommended to have quiescent or low disease activity for at least 6 months prior to conception.[6] This recommendation is based on data extrapolated mostly from trials including patients with SLE, as patients with higher disease activity around the time of conception had higher rates of stillbirth, preeclampsia, preterm delivery, IUGR, and emergency cesarean section.[21] In contrast, 81% of patients with well-controlled SLE had uncomplicated pregnancies.[22]

Given the inherent difficulty in defining quiescent or stable disease in a patient with APS, there has been a recent movement to determine the best strategy for risk stratifying these patients.[23] Risk stratification is determined by a high-risk or low-risk aPL antibody profile (►**Table 3**). A high-risk aPL profile is defined as persistent moderate to high aPL antibody titers, the presence of LAC, or multiple aPL antibody positivity which corresponded to increased maternal thrombotic events (OR: 12.1), preeclampsia (OR: 2.3), APS-related morbidity (OR: 9.2), IUGR (OR: 4.7), and preterm birth.[24] The presence of aPL antibody in the setting of SLE is also associated with increased pregnancy morbidity, putting these patients in a higher risk category.[24] The aPL antibody

Table 3 Risk stratification based on aPL profile

High-risk aPL profile	One or more of the following: 1. Presence of LAC 2. Presence of more than one aPL in any combination 3. Presence of persistently high aPL titers (see below)	Low-risk aPL	Isolated aCL or B2GP antibodies at low-medium titers
		High aPL titers	One or both of the following: 1. aCL IgG or IgM >40 (IgG phospholipid units or IgM phospholipid units) *or* >99th percentile by standard ELISA 2. B2GP antibody IgG or IgM isotype titer >99th percentile measures by standard ELISA

Abbreviations: aCL, anticardiolipin; aPL, antiphospholipid; B2GP, beta-2-glycoprotein.
Note: All aPL antibody criteria require measurements on two or more occasions at least 12 wk apart.

profile along with previous vascular and pregnancy morbidity, hypertension, and the use of recommended medications during pregnancy are all taken into consideration when risk stratifying a pregnant patient with APS.[23]

The most common obstetric complication from APS is recurrent miscarriage, thought to be secondary to the activation of endothelial cells, monocytes, and platelets by the aPL antibodies leading to an increased synthesis of tissue factor and thromboxane A2 leading to a procoagulant state, provoking thrombosis and fetal loss.[25] Approximately 10 to 15% of women with recurrent miscarriage are diagnosed with APS.[25] In patients with a diagnosis of APS, those with both high-titer IgG aCL and previous fetal loss are at the highest risk for recurrent fetal loss (approximately 80%).[25] In patients without a clinical diagnosis of APS but with the presence of aPL, those with elevated IgG aCL antibody had significantly more frequent fetal losses (RR: 3.5) (26 lynch).[25] It is estimated that half of aPL-associated miscarriages occur prior to 10 weeks of gestation: half of miscarriages therefore occur after 10 weeks of gestation, indicating there is not a point at which this risk is mitigated.[25] Other risks including arterial and venous thromboembolism, preeclampsia, IUGR, premature birth, and stillbirth should be discussed prior to conception to ensure the patient can make an informed decision about becoming pregnant.[26,27] If the patient wishes to proceed with becoming pregnant after counseling, further discussions should include optimal timing of pregnancy based on disease activity and expectations based on disease profile.

Impact of Pregnancy on APS

Women experience physiologic changes during pregnancy including fluctuations in estrogen and progesterone.[28] These hormonal shifts result in increased clotting factors (e.g., factor VII, factor VIII, factor X), increased fibrinolytic pathway inhibitors, and decreased activity of proteins C and S, all of which contribute to a prothrombotic state.[29] It is theorized that this prothrombotic state evolved to protect women from hemorrhage during miscarriage and delivery.[30] However, this has resulted in an increased risk for thromboembolic events, which are a cause of morbidity and mortality in pregnant women.[31] This transient prothrombotic state during pregnancy is a concern for patients with APS who are already predisposed to thromboembolic events. Prior studies have demonstrated that pregnant women with primary APS are up to 15 times more likely to experience an acute cardiovascular event compared to the general population.[32] In women with primary APS, more than 80% of their cardiovascular events were found to be venous thromboembolisms, but also included ischemic and hemorrhagic strokes and heart failure.[32] Notably, additive risks for these events were observed in women with APS and concomitant SLE (18.1-fold) and lupus nephritis (12.7-fold).[32] While pregnant patients with APS are certainly at higher risk for cardiovascular events compared to the general population, less than 10% of women with APS experienced these complications in a population-based study.[32] Patients who experience these complications during pregnancy are at higher risk for maternal mortality and long-term complications including recurrence of thrombosis, decreased quality of life, leg ulcerations, and postthrombotic syndrome.[33]

Pregnancy may serve as a risk factor for the development of catastrophic APS (CAPS) characterized by fulminant multiorgan damage (e.g., brain, kidney, lung) resulting from extensive small vessel thrombosis usually associated with thrombocytopenia and mechanical hemolytic anemia.[34] CAPS is a rare complication (< 1%) of APS and results in multiorgan thrombosis and subsequent damage over a 1-week period.[35] The majority of patients with CAPS are female (70%) with pregnancy serving as a precipitating factor in 8% of cases.[36] While immune system activation appears to be a common thread among triggers for CAPS, it is unclear how pregnancy elicits the onset of CAPS. It is theorized to be due to hormonal changes throughout pregnancy, but this has yet to be well characterized.

Early recognition and timely interventions are necessary to optimize clinical outcomes for pregnant patients with CAPS. It is critical to distinguish CAPS from other thrombotic microangiopathies during pregnancy that can present with similar lab values and clinical manifestations including preeclampsia, thrombotic thrombocytopenic purpura, and hemolysis, elevated liver enzymes, and low platelets (HELLP) syndrome. While some women have a clinical history of APS, half of patients experience CAPS as a presenting feature of APS, highlighting the importance of including this on the differential in all patients.[36] Medical factors to consider when differentiating these diseases include time of disease onset (trimester, puerperium), unique clinical manifestations (hypertension, central nervous system involvement), histopathology, and lab values (LAC, ADAMTS13 activity). ►**Table 4** summarizes the differences among these distinct clinical states.[35–46] Patients with CAPS typically present in

Table 4 Distinguishing between catastrophic antiphospholipid syndrome and mimics during pregnancy

	CAPS	Preeclampsia	TTP	HELLP
Traditional clinical features	Fulminant multiorgan damage (e.g., brain, kidney, lung) resulting from extensive small vessel thrombosis	Headache, elevated blood pressure, vision changes, and abdominal pain	Neurologic abnormalities, nausea, vomiting	Nausea, abdominal pain, and elevated blood pressure
Prevalence	< 1% in patients with APS; pregnancy is a precipitating factor in 8% of cases	2–8% pregnancies	7–11.5% of cases in women of childbearing age	0.5–9% of pregnancies; 10–20% of cases with preeclampsia
Timing	Second, third trimesters and puerperium	After 20 weeks of gestation and postpartum	Any time, but most commonly in third trimester	Third trimester and postpartum
Platelets	<100,000/μL	<100,000/μL in severe cases	< 50,000/μL	Class 1: < 50,000/μL Class 2: 50,000–100,000/μL Class 3: 100,000–150,000/μL
Proteinuria	Not traditionally present	Yes; ≥0.3 mg/mg (urine protein to creatinine ratio) or ≥300 mg/24 h (24-h urine protein test) or ≥1+ (dipstick)	Present with hematuria	Can be present, but not necessary for diagnosis
Transaminases	May be elevated in cases of Budd-Chiari syndrome or small hepatic vein thrombosis	2× the upper limit of normal	Not traditionally present	Class 1: ≥ 70 IU/L Class 2: ≥ 70 IU/L Class 3: ≥ 40 IU/L
ADAMTS13 activity	Normal to moderately reduced	Normal to moderately reduced	Severely deficient (<10%)	Normal to moderately reduced
Intervention	Glucocorticoids, anticoagulation, plasma exchange; immunosuppression in cases overlapping with connective tissue disease	Blood pressure control, magnesium, betamethasone <36 wk and timely delivery	Plasma exchange, corticosteroids, plasma infusion, low-dose aspirin	Blood pressure control, glucocorticoids, and timely delivery

Abbreviations: ALT, alanine aminotransferase; AST, aspartate transaminase; CAPS, catastrophic antiphospholipid syndrome; HELLP, hemolysis, elevated liver enzymes, low platelets; puerperium, period of 6 weeks after delivery; TTP, thrombotic thrombocytopenic purpura.

the second or third trimester of pregnancy or in the puerperium period. In addition to mechanical hemolysis and thrombocytopenia, they also traditionally exhibit coagulopathy, renal disease, and persistently positive aPL serologies. Treatment of CAPS during pregnancy includes therapeutic anticoagulation with unfractionated heparin, as this is rapidly reversible in preparation for procedures, glucocorticoids, intravenous immunoglobulin, and plasma exchange.[34] In patients with overlapping autoimmune conditions, such as SLE, additional immunosuppression may be initiated.[34]

Impact of APS on Pregnancy

As previously described, there are several pregnancy outcomes that serve as diagnostic features of obstetric APS including recurrent pregnancy loss, early fetal death, IUGR, preeclampsia, and placental dysfunction.[2] In a study assessing women with recurrent pregnancy loss ($n = 500$), more than a quarter of cases (26%) were associated with the presence of aPL antibodies.[47] The presence of LAC, triple positivity of aPL antibodies, APS overlap with SLE, and history of thrombosis have been identified as strong predictors for these poor pregnancy outcomes.[48,49]

Pregnancy complications associated with APS are thought to originate from placental dysfunction secondary to uteroplacental thrombosis and decidual vasculopathy. Uteroplacental thrombosis is hypothesized to result from aPL antibodies binding to gestational tissues or endothelium resulting in a cascade of prothrombotic agents (e.g., tissue factor, platelet-activating factor, thrombin).[50] This thrombosis leads to poor uteroplacental circulation and subsequent infarction and necrosis. Additional studies have discovered pathologic changes in the placenta including acute atherosis, intimal thickening, fibrinoid necrosis, and an absence of the normal physiologic changes in the spiral arteries consistent with a decidual vasculopathy. The subsequent decrease in

uteroplacental circulation and placental dysfunction resulting from APS is thought to contribute to the increased risk for stillbirth, intrauterine death, preeclampsia, premature birth, and IUGR.[27,50]

Uteroplacental thrombosis develops due to increased activity of procoagulant factors but occurs in tandem with decreased activity of potent anticoagulants, such as annexin-V.[51] This phospholipid-binding protein is present on syncytiotrophoblasts along placental villi to sustain placental blood flow. Pathologic evaluation of placentas from women with APS has demonstrated decreased activity of annexin-V, which may reduce uteroplacental perfusion and result in pregnancy loss.[51] Placental pathology in animal models with APS show complement deposition, neutrophil infiltration, and local tumor necrosis factor secretion, which contribute to placental inflammation, fetal resorption, and growth restriction.[52]

Prior studies of pregnant women with APS, which included other high-risk clinical features such as overlapping SLE and prior thrombosis, have demonstrated an increased risk of preeclampsia in 20 to 50% of pregnancies.[50] Half of the pregnancies impacted by preeclampsia were complicated by severe features, which can include systolic blood pressure $\geq$ 160, low urine output ($<$ 500 mL/24 hours), and proteinuria $\geq$ 5 g in 24 hours. Preeclampsia poses several risks to maternal health, including the immediate risk for progression to eclampsia and lifelong risk of developing hypertensive disorders, and requires preterm delivery in 30% of APS cases.[50] Unfortunately, treatment of APS with standard of care does not appear to mitigate the risk of developing preeclampsia.[50] However, therapy with aspirin and anticoagulation (e.g., low-molecular-weight heparin [LMWH]) can improve some pregnancy outcomes, including live births, demonstrating the critical nature of appropriate therapies during pregnancy.

Pregnancy Management

Given maternal and fetal risk factors associated with pregnancy in APS, there are special considerations for the management of these patients including obstetric monitoring, treatment strategies, and assessment of complications that may arise. Patients with APS are considered at high risk for hypertensive disorders and placental insufficiency which guides many screening recommendations.[23] Given the elevated risk of hypertensive disorders of pregnancy in this population, close physician monitoring with frequent appointments is recommended.[53] There is no recommendation for routine remote blood pressure monitoring due to a lack of high-quality studies; however, this can be considered on a case-by-case basis.[53] It is recommended that patients receive routine ultrasound (US) at 11 to 14 weeks, 20 to 24 weeks (with Doppler), and monthly US during the third trimester.[23] Third trimester US should include Doppler sonography of umbilical artery, uterine artery, ductus venosus, and middle cerebral artery to screen for the risk of placental-associated pregnancy disorders including IUGR and preeclampsia.[23] In women with positive anti-Ro/SSA or anti-La/SSB and a child previously affected by a congenital heart block, weekly fetal echocardiograms are recommended after 16 weeks of gestation given the elevated risk of autoimmune congenital heart block of the fetus (16%).[54] In those without a previously affected child, there is conflicting opinion on fetal monitoring with echocardiogram given the low rate of fetal congenital heart block: the ACR conditionally recommends serial fetal echocardiograms starting between weeks 16 and 18.[6,54]

All women with APS should be treated with aspirin and anticoagulation during pregnancy depending on their serologic profile and clinical diagnosis (►**Table 5**).[23] All patients with either positive aPL antibody or APS should be started on

Table 5 Medical management of females with APS during pregnancy

Clinical scenario	Stratification	Treatment	Timing
+aPL without obstetric or thrombotic APS	Non–high-risk profile[a]	ASA 81–162 mg	Start ASA +/− anticoagulation early in pregnancy (before 16 wk) and continue through delivery
	High-risk profile	ASA 81–162 mg + prophylactic anticoagulation	
	High-risk profile + high risk of first thrombotic event	ASA 81–162 mg + therapeutic anticoagulation	
	Concurrent SLE	ASA 81–162 mg + prophylactic anticoagulation	
Obstetric APS		ASA 81–162 mg + prophylactic anticoagulation Hydroxychloroquine 200–400 mg daily	Start ASA and therapeutic anticoagulation at the time of conception and continue for 6–12 wk postpartum Start hydroxychloroquine in the first trimester and continue through delivery
Thrombotic APS		ASA 81–162 mg + therapeutic anticoagulation Hydroxychloroquine 200–400 mg daily	Start ASA and therapeutic anticoagulation at the time of conception and continue for 6–12 wk postpartum Start hydroxychloroquine in the first trimester and continue through delivery

Abbreviations: aPL, antiphospholipid; APS, antiphospholipid syndrome; ASA, aspirin; SLE, systemic lupus erythematosus.
[a]See Table 3 for aPL antibody risk profiling.

low-dose aspirin at or before conception.[6,23] Low-dose aspirin is typically defined as 60 to 150 mg/day. Using a dose of 150 mg/day (or 162 mg/day in the United States) has been shown to decrease the risk of preeclampsia by 28% (vs. 0–10% with lower doses).[55,56] The choice of anticoagulation is made in conjunction with obstetrics and sometimes hematology consultation. The most widely used agent is LMWH due to ease of administration as an outpatient; however, unfractionated heparin has been the most studied in randomized controlled trials.[57] Anticoagulation should be started at the time of the positive pregnancy test and continue through 12 weeks postpartum, with interruption at the time of delivery if indicated.[57] Warfarin is contraindicated in pregnancy due to its vitamin K antagonism and decreased vitamin K–dependent protein synthesis early in embryogenesis, leading to nasal and limb hypoplasia and stippling of cartilage in the fetus.[58] Among patients with mechanical heart valves who require warfarin therapy, there is support for heparin to be substituted at least one half-life (up to 60 hours) prior to 6 weeks of gestation; however, this can be realistically challenging given many females do not know they are pregnant until after 6 weeks of gestation.[58]

Women should transition to a pregnancy-compatible medication and have stable disease on this medication for at least 6 months prior to conception.[6] Medications that are contraindicated in pregnancy include methotrexate, leflunomide, mycophenolate mofetil, and oral small molecules.[6] These medications can be used in other autoimmune conditions that can be associated with APS, including SLE, making this an important consideration. The decision to hold or continue immunosuppression during pregnancy should be made between the patient and provider depending on patient-centered risk factors. It is important to emphasize that there are many immunosuppressive options safe to use during pregnancy. This is particularly true for hydroxychloroquine, which has been used safely in women with SLE during pregnancy and has shown beneficial effects for both the mother and the baby.[59] In one observational cohort study, women with APS who took hydroxychloroquine during pregnancy had higher rate of live births (67 vs. 57%) and lower prevalence of APS-related pregnancy morbidity (47 vs. 63%) than women with APS who did not take hydroxychloroquine.[60] While there is a need for randomized controlled trials assessing maternal and fetal outcomes for patients with APS with and without hydroxychloroquine, its current use is supported based on available data.[6] For patients with positive aPL antibodies without APS diagnosis, hydroxychloroquine is not recommended due to insufficient data.[6]

Among other maternal and fetal risks during pregnancy with APS described previously, patients with aPL antibodies are at a risk of venous thrombosis. Those with "triple positive" disease defined as the presence of LAC, aCL, and B2GP have the highest risk of thromboembolic events at 30% in a 1-year follow-up study.[61] The increased risk of thrombosis in normal pregnancy is heightened in APS pregnancies: despite treatment, about 1 in 10 to 1 in 50 APS pregnancies are complicated by thrombosis.[19] If there is a concern for thrombosis during pregnancy, laboratory data and imaging can be used for diagnostic clarity especially if the information would change management. Plasma D-dimer increases in normal pregnancy with time, and there have been non-validated studies seeking to identify a cut-off value used to clinically rule out VTE in pregnancy. One prospective cohort study found that D-D-dimer of 3.24 mg/L had a negative predictive value of 96.1% in excluding VTE in an otherwise healthy pregnant population.[62] There is some evidence that using D-dimer to guide anticoagulation treatment in APS and pregnancy may be useful; however, this is not commonly used in practice at this time.[63,64] Imaging studies that do not use ionizing radiation are preferred during pregnancy for fetal safety.[65] Therefore, US and magnetic resonance imaging (MRI) are typically recommended. There have been no controlled studies in pregnant patients regarding the effects of ionizing radiation used in conventional computed tomography (CT); however, the benefit of accurate diagnosis in each clinical situation must be weighed against risks. The general consensus is that radiation doses lower than 50 mGy are not related to fetal adverse events, the threshold of which most CT scans do not approach.[65]

Postpartum Care in Women with APS

After delivery, women with APS continue to require specialized medical care to prevent thrombosis. The immediate postpartum state, defined as 6 weeks after delivery, is a particularly high-risk time in all patients for thrombosis including stroke, myocardial infarction, and venous thromboembolism.[66] The risk for thrombosis has been demonstrated up to 12 weeks postpartum, but the absolute increase in risk beyond 6 weeks after delivery is low.[66] Due to the even higher risk of thrombosis in women with APS during the postpartum period, the ACR strongly recommends anticoagulation for 6 to 12 weeks following delivery. As with pregnancy, combined anticoagulation and aspirin therapy is recommended for those with thrombotic APS, and prophylactic anticoagulation is recommended in obstetric APS.[6]

In addition to anticoagulation, some patients may require immunosuppression in the postpartum. It is important to consider breastfeeding and wound healing following delivery when deciding to initiate immunosuppression. A risks and benefits discussion should be held with the patient to decide about continuing or restarting immunosuppression during breastfeeding. The majority of medications are conditionally or strongly compatible with breastfeeding, but the ACR has designated leflunomide, mycophenolate mofetil, methotrexate, cyclophosphamide, and thalidomide as not compatible.[6] While exclusive breastfeeding is recommended by the American Academy of Pediatrics for the first 6 months postpartum, some patients with APS may require medications for disease control that have an unknown safety profile or are contraindicated in breastfeeding.[67] Medical providers can use LactMed, which is a database from the National Institutes of Health that summarizes peer-reviewed data on levels of medications in breastmilk and nursing infant's blood, to navigate these conversations.[68] Having a postpartum plan for immunosuppression is important as some women can

experience postpartum disease flares. Both CAPS and thrombotic microangiopathy have been reported during the postpartum period in women with APS.[69] It is important for providers to consider postpartum preeclampsia in their differential as CAPS and thrombotic microangiopathy can have similar clinical features and presentations to preeclampsia (►**Table 4**). This demonstrates the importance of close rheumatology follow-up after delivery to assess for disease activity and ensure the patient's immunosuppressive medications are compatible with their plans for breastfeeding.

Follow-up with subspecialists in the postpartum is also an important opportunity to assess for mood disorders such as depression. Symptoms of postpartum depression include intense feelings of sadness, anxiety, or despair that prevent patients from being able to perform their daily tasks.[70] Postpartum depression is most likely to occur in the first 6 weeks following delivery and occurs in 7 to 20% of all women.[71] Women with chronic and complex illnesses are at higher risk for postpartum depression.[72] In addition to the stress of pregnancy, delivery, breastfeeding, and caring for a newborn, patients with APS may require additional medical care including multiple appointments, labs, imaging, medications, and hospitalizations. The stress of managing a chronic illness in addition to acclimating to a new personal role may contribute to mood dysregulation. Inquiring about mood disorders allows for early identification and multiple options for intervention including counseling, medications, and support groups.

Infertility

While a successful and healthy pregnancy is the goal of patients and providers, APS has been associated with infertility defined as failure to achieve viable pregnancy after 12 months or more of unprotected intercourse.[73,74] The prevalence of infertility among women with APS is unable to be estimated due to many methodological flaws in studies, including (1) measuring aPLs other than B2GP, aCL, and LAC; (2) variation in assay technique; and (3) different definitions of positive aPL cut-offs.[75] Additionally, defining a pregnancy loss due to the presence of aPL antibodies requires knowing if the embryo had no chromosome abnormalities leading to spontaneous termination, which cannot be done in real-life clinical scenarios.

Most women with APS who are experiencing infertility can safely undergo assisted reproductive technology (ART) in conjunction with a multidisciplinary team including a rheumatologist and maternal–fetal medicine specialists. Concerningly, some females with a history of autoimmune disease intentionally conceal their disease from their physicians in order to be allowed to undergo infertility treatment.[76] As before, special considerations exist for women with APS undergoing ART. Timing of infertility treatment after the patient has achieved stable or quiescent disease on pregnancy-compatible medications for at least 6 months is crucial.[6] Ovulation induction uses estrogen-lowering agents to stimulate natural FSH production or injectable gonadotropins which include recombinant FSH, human menopausal gonadotropin, and LH. These hormones stimulate follicular development leading to higher estrogen levels, which increases the risk of thrombosis particularly in patients with APS. It is therefore recommended to use anticoagulation in a similar fashion as during pregnancy (►**Table 6**).[6] These recommendations are based mostly on data from patients with thrombophilia given the lack of studies in females with APS. In a single-center retrospective study, ovulation induction therapy using gonadotropins led to a higher successful pregnancy rate but more flares in females with APS or SLE.[76] If undergoing in vitro fertilization, anticoagulation should be temporarily stopped 24 to 36 hours prior to oocyte retrieval and resumed afterward.[76] Giving prophylactic steroids prior to ART is currently not favored due to the lack of studies evaluating efficacy in preventing adverse events.[6] Overall, women with APS undergoing ART have similar pregnancy rates as those without APS, but studies using validated and consistent criteria are lacking.[75]

Pregnancy Termination

Elective termination of pregnancy or termination for medical reasons (TFMR) can be safe in women with rheumatic disease, including those with APS; however, there are no systematic data on termination specifically in this population. There is one descriptive database review that used the Barbara Volcker Center for Women and Rheumatic Disease (BVC) and the Predictors of Pregnancy Outcome: Biomarkers in Antiphospholipid Antibody Syndrome and Systemic Lupus Erythematosus (PROMISEE) cohorts which recorded prior elective termination of pregnancies.[77] Of this group, 60.6% of women (1,307 out of 2,156) had one or more prior pregnancies: of these, 21.7% (284) had undergone at least one elective termination.[77] Safety data was recorded only in the BVC database, which reported no complications from termination.[77] It is difficult to draw conclusions from this study given only a small portion of these patients had APS and the timing of the termination in relation to the diagnosis of autoimmune disease was not recorded.

Given the paucity of literature on rheumatic diseases and APS, recommendations can be extrapolated from studies including patients on anticoagulation or at risk of VTE for

Table 6 Recommendations for the use of anticoagulation during ART[a]

aPL profile	Anticoagulation
Asymptomatic aPL positive	Prophylactic with LMWH or heparin
Obstetric APS	Prophylactic with LMWH or heparin
Thrombotic APS	Therapeutic

Abbreviations: aPL, antiphospholipid; APS, antiphospholipid syndrome; ART, assisted reproductive technology; LMWH, low-molecular-weight heparin.

[a]Start with stimulation and hold for 24 to 36 hours prior to oocyte retrieval. Can then restart after retrieval is complete. If embryo transfer is successful, see Table 5 for pregnancy management recommendations.

reasons other than the presence of aPL antibodies. The Society of Family Planning recommends surgical management over medical management for first-trimester terminations in individuals who are at high risk of VTE or on anticoagulation given bleeding risk is generally higher with medical terminations.[78] Patients who are at high risk of VTE (including patients with obstetric or thrombotic APS) should be started on prophylactic anticoagulation if the termination procedure is not going to occur in the immediate future. This is typically done with prophylactic dose LMWH. There is not enough evidence to suggest delaying a procedure in order to start anticoagulation. Patients already on anticoagulation (and/or aspirin) who are undergoing a first-trimester procedural termination without other additional risk factors for bleeding can generally continue their anticoagulation uninterrupted.[78] For second-trimester terminations, there is not enough data to support any recommendations on preferred methods or management. One small case series reported no adverse events or bleeding in seven females on either prophylactic or therapeutic LMWH who underwent termination between weeks 16 and 22.[79] There is no current data on how long the increased risk of VTE persists after termination. Recommendations for the length of anticoagulation use are therefore based on recommendations after a full-term pregnancy, and patients are recommended to continue for 4 to 6 weeks.[78]

Menopause

Similar to pregnancy, women with APS experiencing menopause require specialized care. There are conflicting data regarding ovarian reserve and the risk for premature menopause in women with APS. Some studies describe normal anti-Mullerian hormone (AMH) levels, a measure of ovarian reserve, in women with primary and secondary APS.[80] Alternatively, other studies have demonstrated a decrease in AMH with the presence of APS autoantibodies indicating concern for decreased ovarian reserve and risk of premature menopause.[81] It is theorized that antiovarian autoimmunity could be contributing to decreased ovarian reserve in patients with autoimmune diseases as 10 to 30% of women with premature loss of ovarian reserve have a concomitant autoimmune disease.[82] Premature menopause has multiple long-term clinical implications including increased risk for osteoporosis, sexual dysfunction, cardiovascular mortality, and decreased quality of life.[82] This is significant as women with autoimmune disease are already at increased risk for all of these long-term health complications independent of menopausal status.[83–86]

Patients with autoimmune diseases may experience an overlap in symptoms related to their disease and signs of menopause including insomnia, fatigue, headaches, and brain fog.[86] As women transition to menopause, serum levels of estradiol decrease resulting in changes in immune function. This includes increased production of proinflammatory cytokines (IL-1, IL-6, TNF-α) and decreased levels of anti-inflammatory cytokines.[87] In patients with autoimmune disease transitioning to menopause, this shift in immune cell activity resulting in a proinflammatory state could impact disease activity.[88] Women with APS may require the assessment of disease activity by their rheumatologist to distinguish symptoms related to APS and any overlapping autoimmune disease versus those related to menopause.

In patients with APS who are experiencing vasomotor symptoms (i.e., hot flushes, night sweats) related to menopause, consideration of the risks and benefits of interventions may be discussed with their rheumatologist and gynecologist. The American College of Obstetrics and Gynecology (ACOG) recommends hormone therapy, either estrogen alone or in combination with progestin, as the most effective therapy for vasomotor symptoms related to menopause.[89] ACOG does not recommend progestin-only or testosterone for the treatment of these symptoms.[89] Estrogen use in patients with APS should be avoided due to increased risk for thrombosis.[6] The ACR recommends against hormone therapy for women with a positive aPL antibody, obstetric APS, thrombotic APS, APS receiving anticoagulation, or history of obstetric or thrombotic APS currently testing negative for aPL antibodies. Hormone therapy can be considered in patients with a prior history of a positive aPL, no prior or current clinical APS, and who are now testing negative for any aPL.[6] In APS patients with contraindications to hormone therapy, alternative interventions, such as selective serotonin reuptake inhibitors and serotonin and norepinephrine reuptake inhibitors, can be considered to treat vasomotor menopausal symptoms.[90]

Impact of APS on Male Reproductive Health

Primary APS is more common in women than in men with a ratio of approximately 3:1.[35,91] However, studies assessing sex-based differences in clinical outcomes of patients with APS have discovered that arterial thrombotic events including myocardial infarction and limb thrombosis are experienced more frequently in men.[35,91] In male patients initiating treatment for APS, discussions regarding therapy are an opportunity to incorporate family planning and personal goals. All immunosuppressive medications are compatible with fathering a child except for cyclophosphamide and thalidomide, which should be stopped prior to attempts at conception.[6] In the event that a male patient with APS requires cyclophosphamide, the ACR strongly recommends sperm cryopreservation prior to the initiation of therapy to preserve their ability to conceive following therapy.[6] Cyclophosphamide can damage the spermatogonial stem cells of the testes impacting sperm development and can lead to permanent azoospermia.[92] Unfortunately, sperm development during cyclophosphamide therapy results in a high degree of genetic damage making sperm collected within 3 months of cyclophosphamide treatment the most likely to be abnormal.[93] Sperm collection should occur before treatment if possible. In critically ill patients with APS, urologists may be able to assist with acquiring sperm quickly prior to cyclophosphamide administration. In patients who cannot undergo sperm collection prior to cyclophosphamide therapy, it is important to discuss the risk for infertility after

treatment.[6] The ACR strongly recommends against testosterone cotherapy for men receiving cyclophosphamide, as evidence suggests that this approach does not help with the preservation of fertility.[6,94] Providing this information to patients allows for shared decision-making with providers to ensure therapeutic decisions are aligned with the patient's personal goals.

Conclusion

Special reproductive considerations exist for patients with APS from pregnancy planning through the reproductive years and beyond. This is a population within rheumatology with an increased risk of thrombosis, and assisting patients in achieving a successful and healthy pregnancy includes an understanding of the risks and current management practices in an attempt to decrease these risks. APS is a heterogeneous disease which includes a wide spectrum of manifestations, associated comorbidities, and risk profiles, all of which need to be taken into consideration when counseling a patient from preconception through the postpartum, lactation, and beyond. All patients with positive aPL antibodies should be placed on low-dose aspirin; however, further anticoagulation is determined by disease and aPL profile. Other than the use of aspirin and anticoagulation in pregnancy management, clear answers regarding more nuanced aspects of individual cases are lacking due to systematic flaws in how research involving APS populations has been conducted. The 2023 ACR/EULAR APS classification criteria sets the stage for future research on remaining questions, including randomized controlled trials assessing hydroxychloroquine use, safety and recommendations for pregnancy termination, and using ART in this population, among others.[2]

Conflict of Interest
None declared.

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