The Art and Science of Infusion Nursing

Mara Taraborelli, MD
Doruk Erkan, MD, MPH

Pregnancy-Related Challenges in Systemic Autoimmune Diseases

ABSTRACT

The awareness of pregnancy-related physiologic changes and complications is critical for the appropriate assessment and management of pregnant patients with systemic autoimmune diseases. The overlapping features of physiologic and pathological changes, selected autoantibodies, and the use of potentially teratogenic medications can complicate their management during pregnancy. While pregnancy in lupus patients presents an additional risk to an already complex situation, in patients with no disease activity, the risk of a future pregnancy-related complication is relatively low. Anti-Ro and anti-La antibodies increase the risk of neonatal lupus erythematosus, eg, photosensitive rash and irreversible congenital heart block. Antiphospholipid antibodies increase the risk of pregnancy morbidity, eg, fetal loss and early preeclampsia. Pregnancy usually has a positive effect on rheumatoid arthritis; however, a disease flare is common during the postpartum period. Both the rheumatologist and the obstetrician should partner throughout the pregnancy to manage patients for successful outcomes.

Key words: antiphospholipid syndrome, connective tissue diseases, pregnancy, rheumatic diseases, systemic lupus erythematosus

Systemic autoimmune diseases (SADs) are relatively common in women of childbearing age. Given the chronic relapsing nature of SADs, it is more likely that a woman with an established SAD will get pregnant than that a new SAD will be diagnosed in a previously healthy pregnant woman.

Author Affiliations: Spedali Civili di Brescia, Brescia, Italy (Dr Taraborelli); University of Brescia, Brescia, Italy (Dr Taraborelli); University of Pavia, Pavia, Italy (Dr Taraborelli); Barbara Volcker Center for Women and Rheumatic Diseases, Hospital for Special Surgery, New York, New York (Drs Erkan and Taraborelli); Weill Medical College, Cornell University, New York, New York (Dr Erkan).

Mara Taraborelli, MD, is a rheumatology fellow at the Spedali Civili di Brescia and the University of Brescia in Italy. She is also affiliated with the University of Pavia in Italy and the Hosptial for Special Surgery in New York City.

Doruk Erkan, MD, MPH, is an associate physician-scientist at the Barbara Volcker Center for Women and Rheumatic Diseases and an associate attending physician at the Hospital for Special Surgery in New York City, where he is also an associate professor of medicine at Weill Medical College of Cornell University.

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Corresponding Author: Mara Taraborelli, MD, Spedali Civili di Brescia, Piazzale Spedali Civili 1, 25100, Brescia, Italy (mara.taraborelli@gmail.com).

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Pregnancy and disease outcomes during and after pregnancy of SAD patients have improved significantly in the past decades, as the result of a better understanding of the diseases and the creation of multidisciplinary teams—including rheumatologists, high-risk obstetricians, and neonatologists—experienced in autoimmune diseases.[1] However, the overlapping features of physiologic and pathological changes during pregnancy, selected autoantibodies (eg, antiphospholipid [aPL] and anti-Ro/La antibodies), and the teratogenicity of commonly used immunosuppressive agents can complicate the management of patients with SADs during pregnancy.

The purpose of this review is to discuss the challenges health professionals may face while managing pregnant patients with established SADs, as well as optimal medication management, including counseling and safety.

PREGNANCY-RELATED PHYSIOLOGIC CHANGES

Pregnancy is an altered physiologic state characterized by particular signs, symptoms, and hormonal changes. Various changes can occur during a normal pregnancy

and create a challenge in the management of pregnant patients with SADs[2]:

- Hemodynamic (intravascular volume increase, generalized edema)
- Renal (glomerular filtration rate and urine protein increase)
- Cutaneous (palmar and facial erythema)
- Musculoskeletal (arthralgia, back pain)
- Hematologic (anemia, thrombocytopenia, leukocytosis, erythrocyte sedimentation rate increase, prothrombotic profile)
- Immunologic (variation in the function of B cells, T cells, and monocytes; elevated complement [C]3 and C4 levels)

PREGNANCY-RELATED PATHOLOGIC CHANGES

Some pregnancy-related complications are more common in patients with SADs compared with the general population. Complications health professionals always should include in pregnancy-related discussions are:

- Preeclampsia (PEC): Blood pressure higher than 140/90 mm Hg after 20 weeks of gestation on at least 2 occasions and proteinuria more than 300 mg/d
- HELLP (hemolysis, elevated liver enzymes, and low platelet count) syndrome
- Eclampsia: Seizures occurring in the setting of a PEC
- Preembryonic loss: Loss between conception through week 4 of gestation
- Embryonic loss: Loss between weeks 5 through 9
- Fetal loss: Loss between week 10 of gestation through delivery
- Intrauterine growth restriction (IUGR): Ultrasound-assessed fetal abdominal circumference < 5th percentile
- Preterm delivery: Delivery before week 37

PREGNANCY IN SELECTED SADs

Systemic Lupus Erythematosus

Systemic lupus erythematosus (SLE) is a multisystem autoimmune disease with a wide spectrum of clinical manifestations and a variable course characterized by exacerbations and remissions. The disease can affect any organ system, including cutaneous, musculoskeletal, cardiovascular, renal, and neurological systems. It is characterized by specific autoantibodies, eg, anti–double-stranded DNA (dsDNA) and anti-Smith antibodies.

While pregnancy in SLE patients presents an additional risk to an already complex situation, the risk of a pregnancy-related complication in stable patients with no disease activity is relatively low. Many SLE patients can undergo successful pregnancies without significant deterioration in their clinical status and with good fetal outcome.

Case-control studies support little or no increased risk for disease flare during pregnancy[3]; however, SLE patients may flare any time during pregnancy, most often in the latter half, and in the postpartum period.[4,5] Inactive disease for the 6 months preceding pregnancy is associated with a lower risk of disease flare[6]; the longer a patient is in remission, the better are her chances for completing a pregnancy without exacerbation. Hypertension and active kidney disease preceding pregnancy increase the risk of lupus renal flare and PEC[7]; renal insufficiency, in particular prepregnancy serum creatinine greater than 1.6 mg/dL, is an important risk factor for serious renal deterioration during pregnancy.[8] Pregnancy is inadvisable in the setting of uncontrolled hypertension, progressive renal failure (serum creatinine > 2.5 mg/dL or glomerular filtration rate < 35 mL/min), severe neurologic and cardiopulmonary involvement (pulmonary hypertension or severe cardiomyopathy with ejection fraction < 30%-40% or severe restrictive lung disease with forced vital capacity < 50% of predicted), severe thrombocytopenia (< 30,000/mm^3), and teratogenic medications.[9]

Proteinuria during pregnancy requires careful evaluation. The differential diagnosis includes new onset or worsening lupus nephritis, PEC, or both. Differentiating lupus flare from PEC can be challenging: rapid worsening of proteinuria over days; microscopic hematuria with erythrocyte casts; an increase in anti-dsDNA level, and extrarenal lupus activity, eg, lymphadenopathy, rash, inflammatory arthritis, fever, or leukopenia support lupus activity.[10] Pregnancy-related rash may mimic a lupus rash as a result of palmar and facial erythema from increased blood flow to the skin. Bland joint effusion and diffuse arthralgias, common in pregnancy, may be confused with lupus arthritis.

The most common risks to the fetus in a lupus pregnancy are fetal loss, prematurity, or IUGR.[11] Fetal outcome is related more to renal involvement, anti-Ro/La antibodies, and aPL, which is discussed below, than the occurrence of lupus flare. Proteinuria higher than 0.5 g per 24 hours is an independent predictor of poor fetal outcome: fetal loss occurs in almost 60% of patients with proteinuria as opposed to 10% of patients who do not have proteinuria.[7] Hypertension and thrombocytopenia are additional risk factors for pregnancy loss in SLE patients.[12]

Anti-Ro (SS-A) and anti-La (SS-B) antibodies increase the risk of neonatal lupus erythematosus (NLE) consisting of photosensitive rash, thrombocytopenia, abnormal liver function tests, and rarely irreversible congenital heart block (CHB).[13] With the exception of CHB, all manifestations disappear with the clearance of maternal

antibodies at about 4 to 6 months. During pregnancy, maternal IgG anti-Ro/La are transferred through the placenta to the fetus, where they bind cross-reactive epitopes on calcium-regulating molecules in the fetal cardiac cells, such as ion channels, which lead to calcium overload and cellular apoptosis.[14] Antibodies then may bind their antigen on the surface of apoptotic cells, inducing first-degree atrioventricular block. Depending on the fetal susceptibility, the local inflammation may be resolved or propagated, leading to permanent third-degree atrioventricular block. The first-time risk of NLE for the newborn of an anti-Ro positive woman is about 25%, and the risk of CHB is 1% to 2%.[15] The CHB risk in mothers with a previous history of NLE of any type is approximately 20%.[16,17]

Antiphospholipid Syndrome

Antiphospholipid syndrome (APS) is defined as vascular thromboses and/or pregnancy morbidity occurring in patients with a clinically significant aPL profile (positive lupus-anticoagulant test, anticardiolipin [aCL] IgG/M > 40 GPL/MPL, and/or anti-β_2Glycoprotein I [aβ_2GPI] IgG/M > 99th percentile on 2 or more occasions at least 12 weeks apart). Positive aPL without characteristic clinical complications does not indicate APS, and asymptomatic (no history of vascular or pregnancy events) aPL-positive patients exist. APS can occur in otherwise healthy individuals (primary APS) or in patients with other SADs, particularly SLE. Approximately 30% to 40% of SLE, 10% to 20% of rheumatoid arthritis (RA), and as many as 25% of systemic sclerosis patients are positive for aPL.[18-20]

Murine models demonstrate that aPL is a risk factor for pregnancy morbidities; purified IgG from women with aPL, when injected into pregnant mice, results in fetal loss and decidual necrosis.[21]

A positive LA test is the primary predictor of an adverse pregnancy outcome after 12 weeks of gestation in aPL-associated pregnancies.[22] APS should be considered in clinically significantly aPL-positive patients with late fetal loss, which is more strongly associated with aPL, and with recurrent consecutive early embryonic losses.[23] Other pregnancy morbidities associated with aPL include IUGR, premature delivery, early PEC, and HELLP syndrome.[24] Other causes of pregnancy loss, such as anatomical, chromosomal, or hormonal abnormalities, always should be investigated in aPL-positive patients.

Although the risk of pregnancy morbidity is unknown in asymptomatic aPL-positive patients and in APS patients with only vascular events, untreated patients with high-titer aPL and a history of previous pregnancy loss have a 50% to 75% chance of subsequent fetal loss. With current therapy, discussed below, APS patients have almost an 80% rate of live births. However, 20% of pregnancies continue to experience pregnancy morbidities other than miscarriages, despite conventional treatment.

In the general population, the risk of venous thromboembolism increases during a physiologic pregnancy by a factor of 5, as a result of a prothrombotic state, eg, increased fibrinogen levels, venous stasis due to compression by the gravid uterus, and bed rest.[25] Patients with aPL have an even higher risk of thrombotic events during pregnancy and the postpartum period.

Rheumatoid Arthritis

RA is a systemic, immune-mediated inflammatory disease, which results in chronic inflammation of the joints and symmetrical arthritis. Pregnancy usually has a positive effect on RA symptoms: as many as three-quarters of patients experience some degree of clinical remission during pregnancy, even in the absence of medications.[26] The disease flare is common (40%) in the postpartum period.[27] A slightly increased rate of fetal complications of prematurity and low birth weight, in particular in association with prednisone use and a higher disease activity during pregnancy, respectively, has been reported.[28,29]

Other SADs

The most relevant pregnancy-related issues associated with other selected SADs are summarized in Table 1.

MANAGEMENT OF SADs DURING PREGNANCY

Preconception Counseling

Preconception counseling to assess risks, strict follow-up during pregnancy to recognize complications early, and an experienced neonatal unit to assist newborns are essential for successful pregnancies in patients with SADs.[9] Physicians should tell their patients about how pregnancy can affect their disease and how the disease could influence the gestational outcome. Patients should be reassured that a successful pregnancy is generally achieved, if conception occurs in a stable disease remission state and if teratogenic medications are managed properly. Patients must be informed about medications that must be withdrawn before conception—those that can be maintained, and those that could be added in the event of disease flare. The main message to patients should be to plan the pregnancy according to their doctors' advice.[30] A close collaboration between the physician who follows the autoimmune disease and the obstetrician who will follow the pregnancy should begin as soon as possible.

TABLE 1

Classic Presentation of and Major Pregnancy-Related Considerations in Systemic Autoimmune Diseases, Other Than Lupus, Antiphospholipid Syndrome, and Rheumatoid Arthritis

Disease	Classic Presentation	Major Pregnancy-Related Considerations
Polymyositis and dermatomyositis[48,49]	Muscle weakness Rash Raynaud's disease Dysphagia Pulmonary fibrosis	Mild risk of flare if in remission Favorable fetal outcome if in remission Risk of fetal loss, preterm delivery, and IUGR if active
Sjögren's syndrome[13]	Dry eyes Dry mouth Arthritis	No risk of flare Risk of NLE as a result of anti-Ro/La
Systemic sclerosis[50,51]	Raynaud's disease Skin thickening Esophageal reflux Calcinosis Telangiectasia Pulmonary fibrosis Pulmonary arterial hypertension	Favorable maternal outcomes if no severe cardiac, pulmonary, or renal involvement Renal crisis rare, but potentially indistinguishable from PEC Increased risk of preterm delivery, IUGR, and cesarean section
Ankylosing spondylitis[52]	Low-back pain and stiffness Arthritis Enthesitis Uveitis	Moderate to high risk of flare No increased risk of obstetrical complications
Wegener granulomatosis[53,54]	Upper and lower respiratory tract symptoms Necrotizing glomerulonephritis Cutaneous purpura Peripheral neuropathy	Mild risk of flare if in remission Increased risk of fetal death and preterm delivery if active
Churg-Strauss syndrome[55]	Asthma Pulmonary infiltrates Cutaneous purpura Peripheral neuropathy Eosinophilia	Moderate risk of flare if in remission Increased risk of preterm delivery and low birth weight
Takayasu's arteritis[56,57]	Claudication Visual disturbances Hypertension	Mild risk of disease flare; pregnancy contraindicated if severe aortic valvular disease or aortic aneurysms Increased risk of IUGR and PEC
Polyarteritis nodosa[58]	Purpura Livedo reticularis Abdominal pain Hypertension Peripheral neuropathy	Mild risk of flare if in remission Increased risk of preterm delivery and low birth weight
Behçet disease[59-61]	Oral and genital aphthosis ulceration Uveitis Erythema nodosum Pathergy Pseudofolliculitis	Mild risk of flare Favorable fetal outcome

Because of the heterogeneous reporting of flare risk in the literature, the authors defined risk of flare as mild, moderate, or high when it affected 1% to 24%, 25% to 50%, or > 50% of pregnancies, respectively.

Abbreviations: IUGR, intrauterine growth restriction; NLE, neonatal lupus erythematosus; PEC, preeclampsia.

Disease Assessment

Initial disease evaluation should include an assessment of the disease activity and organ damage, a review of medications, a laboratory evaluation, and a discussion of specific risks. The suggested initial laboratory tests for lupus patients who are planning pregnancy or who are already pregnant include a complete blood count, urinalysis, creatinine clearance, 24-hour urine protein (or protein-to-creatinine ratio), lupus anticoagulant

test, aCL IgG-IgM, aβ_2GPI IgG-IgM, anti-dsDNA, anti-Ro, and anti-La, C3, and C4.[31] These recommendations could be followed with modifications for pregnant patients who have other SADs, eg, the assessment of baseline kidney function and aPL profiles. Further laboratory tests—depending on patient characteristics, the underlying SAD, and the laboratory profile—are recommended during each trimester or monthly, as needed.

Disease Management

Patients taking potentially teratogenic drugs should be removed from them or transitioned to safer ones. Conception should be delayed at least 3 months to monitor disease activity and adverse reactions.[32]

In general, the treatment of a disease flare in pregnant patients with an SAD does not differ from the treatment of patients who are not pregnant. Corticosteroids are the first-line choice, with the dose adjusted according to severity. Depending on the disease as well as the disease activity in steroid-resistant cases, certain immunosuppressive medications, plasma exchange, and/or intravenous (IV) immunoglobulin (IVIG) can be started after a disease flare during pregnancy.

Fetal echocardiography, generally at weeks 16 through 34, should be performed for the evaluation of fetal heart rhythm, pericardial effusion, or myocarditis in mothers positive for anti-Ro and anti-La antibodies.[33] Treatment of incomplete CHB is betamethasone or dexamethasone, which easily crosses the placenta. Rarely, plasmapheresis may be helpful.[34,35] Complete CHB in a newborn usually requires a permanent pacemaker. Fetal outcomes in anti-Ro/SS-A antibody-positive patients are significantly improved with screening fetal echocardiographies. A neonatal electrocardiogram to identify clinically silent first-degree block should be performed on all infants born to mothers with anti-Ro/La antibodies. A recent study suggested that hydroxychloroquine (HCQ) may lower the risk of CHB in mothers positive for anti-Ro/La antibodies.[36] IVIG[37,38] and plasmapheresis[39] both failed to prevent CHB based on small-scale studies.

Although controversial because of a limited number of well-designed controlled studies, the current standard of care for pregnant aPL-positive patients during pregnancy includes low-dose aspirin (LDA) and prophylactic-dose heparin for patients meeting the APS classification criteria based on a history of pregnancy morbidity only; LDA and therapeutic-dose heparin for patients meeting the APS classification criteria based on a thrombotic vascular event, regardless of pregnancy history; and no treatment or LDA for asymptomatic (ie, no history of vascular or pregnancy events) medium- to high-titer aPL-positive patients.[40]

If patients fail the LDA and heparin combination, common next steps are increasing the heparin dose with antifactor Xa level monitoring with or without adding HCQ, corticosteroids, and/or IVIG, although a small placebo-controlled study showed no benefit.[41] All patients with aPL require at least 8 to 12 weeks of anticoagulation postpartum (prophylactic-dose heparin) to prevent thrombotic events.[42]

Some obstetricians frequently use LDA to prevent PEC in women identified as being at high risk, usually because of preexisting hypertension, renal insufficiency, or a history of previous PEC. However, a recent meta-analysis concluded that early administration of LDA reduces the risk of preterm, but not term, PEC[43] and of severe, but not mild, PEC.[44] In high-risk pregnancies, uterine artery Doppler is recommended around 20 weeks of gestation, and if abnormal, it should be repeated around the 24th week. Abnormal waveforms are good predictors of PEC, while normal results are related to good obstetric outcomes.[45]

In patients with systemic sclerosis, careful monitoring of renal function and systemic arterial pressure is recommended during pregnancy. In general, angiotensin-converting enzyme inhibitors should be stopped because of the risk of fetal renal toxicity. However, they may be the only effective therapy for true scleroderma renal crisis—a life-threatening complication.[46] A previous episode of renal crisis is not a strict contraindication for future pregnancy, but it is recommended that a woman should have good renal function and wait several years until her disease is stable before trying to conceive.

All pregnant patients should take folic acid during the first trimester to prevent fetal neural tube defects. Concomitant prophylactic calcium and vitamin D supplements should be prescribed to women who take corticosteroids and/or heparin, and/or are at high risk for osteoporosis.

Delivery

Patients with aPL who are receiving prophylactic-dose heparin should discontinue heparin once labor is established. Patients on a therapeutic dose should discontinue or decrease it to a prophylactic dose 24 hours before a planned delivery. Graduated elastic compression stockings should be recommended for thromboembolism prophylaxis in patients who are admitted for labor or delivery or who require prolonged bed rest.

Stress doses of hydrocortisone at delivery are recommended in patients on long-term corticosteroid therapy, especially more than 20 mg/d of prednisone or the equivalent for more than 3 weeks, to avoid hemodynamic instability.

Cervical spine arthritis with atlanto-axial instability dictates careful management of RA patients undergoing

TABLE 2
Medication Safety During Pregnancy and Breastfeeding

Drug	FDA[a]	Potential Fetal and Maternal Effects	P[b]	BF[c]	Comments
Acetaminophen	B	Not reported	Yes	Yes	
Nonsteroidal anti-inflammatory drugs	B/D	Premature closure of ductus arteriosus Impaired renal function Maternal bleeding	Yes	Yes	P: Until 32 weeks' gestation (lowest effective dose, shortest duration, shortest half-life drug) BF: If possible, breastfeed just before ingestion
Prednisone	B	Small increase of oral cleft during first trimester Prematurity IUGR Maternal diabetes/hypertension/osteopenia, especially for high dose	Yes	Yes	P: Keep dose ≤ 15 mg/d during first trimester for maintenance BF: If possible, breastfeed just before ingestion. At doses > 40 mg, consider breastfeeding 4 hours after the dose.
Dexamethasone	C	Neurodevelopmental abnormalities	Yes	No	P: Only for antenatal treatment
Betamethasone	C	Neurodevelopmental abnormalities suspected	Yes	No	P: Only for antenatal treatment
Bisphosphonate	C	Transient hypocalcemia	No	No	P: Withdraw at least 6 months before conception
Heparin, unfractionated or low molecular weight	C	Maternal bleeding Osteopenia Thrombocytopenia	Yes	Yes	
Warfarin	D	Congenital malformations before 10 weeks' gestation Maternal and fetal bleeding	Yes	Yes	P: Only consider after 10 weeks' gestation in high-risk patients
Hydroxycloroquine	C	Not reported	Yes	Yes	P: Keep dose ≤ 400 mg/d
Thalidomide	X	Congenital malformations	No	No	P: Withdraw 4 weeks before conception
Sulphasalazine	B	Case reports of aplastic anemia and neutropenia at dose > 2 g/d	Yes	Yes	P: Keep dose ≤ 2 g/d, folate supplementation throughout pregnancy BF: Only in healthy full-term infants
Azathioprine	D	Sporadic congenital anomalies Transient immune alterations in newborns	Yes	NC	P: Keep dose ≤ 2 mg/kg/d BF: Weigh risk/benefit
Methotrexate	X	Teratogenicity Cytopenia	No	No	P: Withdraw 3 months before conception Folate supplementation throughout pregnancy
Cyclosporine	C	Transient immune alteration Maternal hypertension	Yes	NC	BF: Weigh risk/benefit
Tacrolimus	C	Hyperkalemia and renal dysfunction in newborns	Yes	NC	P: Use lowest effective dose BF: Weigh risk/benefit
Cyclophosphamide	D	Teratogenicity Cytopenia	No	No	P: Withdraw 3 months before conception
Leflunomide	X	Possible teratogenicity	No	No	P: Withdraw 2 years before conception or use washout procedure (see package insert)
Mycophenolate mofetil	D	Possible teratogenicity	No	No	P: Withdraw 3 months before conception
Intravenous immunoglobulin	C	Not reported	Yes	Yes	

(*continues*)

TABLE 2

Medication Safety During Pregnancy and Breastfeeding (*Continued*)

Drug	FDA[a]	Potential Fetal and Maternal Effects	P[b]	BF[c]	Comments
Antitumor necrosis α agents (adalimumab, certolizumab, etanercept, golimumab, infliximab)	B	Increased susceptibility to infections in newborns suspected	NC[d]	No	P: Consider withdrawal at conception Weigh risk/benefit for reintroduction, if severe disease activity
Tocilizumab	C	Not reported (insufficient data)	No	No	P: Withdraw 3 months before conception
Abatacept	C	Not reported (insufficient data)	No	No	P: Withdraw 10 weeks before conception
Rituximab	C	Transient hematologic abnormalities (insufficient data)	No	No	P: Withdraw 12 months before conception
Belimumab	C	Unknown	No	No	P: Withdraw 4 months before conception

Data from Østensen M, et al.[32]

[a] *Food and Drug Administration pregnancy risk categories: A, no risk in controlled clinical studies in humans; B, human data reassuring or, when absent, animal studies show no risk; C, human data are lacking; animal studies show risk or are not done; D, positive evidence of risk benefit may outweigh; NC, ; X, contraindicated during pregnancy.*

[b] *Allowed during pregnancy, if needed.*

[c] *Allowed during breastfeeding, if needed.*

[d] *See text for details. Recent positive safety experience based on limited data, long-term effects unknown.*

Abbreviations: FDA, Food and Drug Administration; P, pregnancy; BF, breastfeeding; IUGR, intrauterine growth restriction; NC, no consensus.

general anesthesia, since manipulation of the unstable spine may produce spinal cord compression. Severe cricoarytenoid involvement may also be a relative contraindication to intubation with general anesthesia. Assessment for adequate hip range of motion should be carried out before vaginal delivery, especially if epidural anesthesia is planned.

In patients with significant Raynaud's phenomenon, measures that could prevent vasospasm during delivery—such as warming the delivery room and providing warm (IV) fluids, thermal socks, and warm external compresses—should be used routinely. Epidural anesthesia is preferred because it provides peripheral vasodilatation and increased skin perfusion of lower extremities. In systemic sclerosis, general anesthesia should be avoided because of the difficulty in intubation in patients with small mouths and concerns about aspiration.

MEDICATION SAFETY DURING PREGNANCY AND BREASTFEEDING

Knowledge of the drug pharmacology relevant to the SAD is essential to the management of pregnant patients. Most of the information regarding the safety of drugs during pregnancy is extracted from retrospective case series, case reports, and experts' consensus,[32] which is summarized in Table 2.

Hydroxycloroquine can be safely continued during pregnancy and may even improve pregnancy outcomes in lupus patients.[47] In RA patients receiving biologic therapies, manufacturers' guidelines recommend discontinuation of the medication before conception for different periods of time. Nevertheless, data from uncontrolled case reports show that exposure to antitumor necrosis factor-α (anti-TNF) therapies at the time of conception does not result in an increased risk of adverse pregnancy and fetal outcomes.[48] Exposure to anti-TNF therapies in later pregnancy, particularly to monoclonal antibodies, is associated with high drug levels in the newborn. Live vaccines should be avoided for at least the first 6 months of life in children with in utero exposure to biologics. The long-term effects of this exposure remain unknown. In clinical practice, the goal is to continue the least possible number of medications during pregnancy. Thus, the current practice is to allow RA patients to conceive on these medications and to discontinue them when pregnancy is confirmed. If a pregnant patient has a severe flare of arthritis, restarting the anti-TNF therapy should be considered after a careful risk/benefit assessment.[30] Pregnancy data for non–anti-TNF biologics are insufficient, and their use during pregnancy cannot be recommended.

CONCLUSIONS

Managing a pregnancy in patients with SADs still represents a challenge. The overlapping features of physiologic and pathological changes and selected autoantibodies, and the use of potentially teratogenic medications, can complicate the management of patients with SADs during pregnancy.

A planned pregnancy in a patient with disease remission or low disease activity control before conception has a better chance of success. Preconception counseling, expert monitoring by a multidisciplinary team with experience in the field, and neonatal intensive care units remain the best ways to manage these high-risk pregnancies and obtain favorable maternal and neonatal outcomes.

REFERENCES

1. Clark CA, Spitzer KA, Laskin CA. Decrease in pregnancy loss rates in patients with systemic lupus erythematosus over a 40-year period. *J Rheumatol*. 2005;2(9):1709-1712.
2. Gordon MC. Maternal physiology. In: Gabbe SG, Niebyl JR, Simpson JL, eds. *Obstetrics: Normal and Problem Pregnancies*. 5th ed. Philadelphia, PA: Churchill Livingstone Elsevier; 2007: 56-84.
3. Lockshin MD, Reinitz E, Druzin ML, Murrman M, Estes D. Lupus pregnancy: case-control prospective study demonstrating absence of lupus exacerbation during or after pregnancy. *Am J Med*. 1984;77(5):893-898.
4. Ruiz-Irastorza G, Lima F, Alves J, et al. Increased rate of lupus flare during pregnancy and the puerperium: a prospective study of 78 pregnancies. *Br J Rheumatol*. 1996;35(2):133-138.
5. Urowitz MB, Gladman DD, Farewell VT, Stewart J, McDonald J. Lupus and pregnancy studies. *Arthritis Rheum*. 1993;36(10): 1392-1397.
6. Petri M, Howard D, Repke J. Frequency of lupus flare in pregnancy. The Hopkins Lupus Pregnancy Center experience. *Arthritis Rheum*. 1991;34(12):1538-1545.
7. Moroni G, Quaglini S, Banfi G, et al. Pregnancy in lupus nephritis. *Am J Kidney Dis*. 2002;40(4):713-720.
8. Nossent HC, Swaak TJ. Systemic lupus erythematosus. VI. Analysis of the interrelationship with pregnancy. *J Rheumatol*. 1990;17(6):771-776.
9. Ateka-Barrutia O, Khamashta MA. The challenge of pregnancy for patients with SLE. *Lupus*. 2013;22(12):1295-1308.
10. Ruiz-Irastorza G, Khamashta MA. Lupus and pregnancy: integrating clues from the bench and bedside. *Eur J Clin Invest*. 2011;41(6):672-678.
11. Clowse ME, Jamison M, Myers E, James AH. A national study of the complications of lupus in pregnancy. *Am J Obstet Gynecol*. 2008;199(2):127.
12. Clowse ME, Magder LS, Witter F, Petri M. Early risk factors for pregnancy loss in lupus. *Obstet Gynecol*. 2006;107(2 pt 1): 293-299.
13. Brucato A, Cimaz R, Stramba-Badiale M. Neonatal lupus. *Clin Rev Allergy Immunol*. 2002;23(3):279-299.
14. Ambrosi A, Sonesson SE, Wahren-Herlenius M. Molecular mechanisms of congenital heart block. *Exp Cell Res*. 2014; 325(1):2-9.
15. Cimaz R, Spence DL, Hornberger L, Silverman ED. Incidence and spectrum of neonatal lupus erythematosus: a prospective study of infants born to mothers with anti-Ro autoantibodies. *J Pediatr*. 2003;142(6):678-683.
16. Julkunen H, Eronen M. The rate of recurrence of isolated congenital heart block: a population-based study. *Arthritis Rheum*. 2001;44(2):487-488.
17. Buyon JP, Hiebert R, Copel J, et al. Autoimmune-associated congenital heart block: demographics, mortality, morbidity and recurrence rates obtained from a national neonatal lupus registry. *J Am Coll Cardiol*. 1998;31(7):1658-1666.
18. Cervera R, Piette JC, Font J, et al. Antiphospholipid syndrome: clinical and immunologic manifestations and patterns of disease expression in a cohort of 1,000 patients. *Arthritis Rheum*. 2002; 46(4):1019-1027.
19. Palomo I, Pinochet C, Alarcón M, et al. Prevalence of antiphospholipid antibodies in Chilean patients with rheumatoid arthritis. *J Clin Lab Anal*. 2006;20(5):190-194.
20. Chung L, Utz PJ. Antibodies in scleroderma: direct pathogenicity and phenotypic associations. *Curr Rheumatol Rep*. 2004;6(2): 156-163.
21. Branch DW, Dudley DJ, Mitchell MD, et al. Immunoglobulin G fractions from patients with antiphospholipid antibodies cause fetal death in BALB/c mice: a model for autoimmune fetal loss. *Am J Obstet Gynecol*. 1990;163(1 pt 1):210-216.
22. Lockshin MD, Kim M, Laskin CM, et al. Lupus anticoagulant, but not anticardiolipin antibody, predicts adverse pregnancy outcome in patients with antiphospholipid antibodies. *Arthritis Rheum*. 2012;64(7):2311-2318.
23. Miyakis S, Lockshin MD, Atsumi T, et al. International consensus statement on an update of the classification criteria for definite antiphospholipid syndrome (APS). *J Thromb Haemost*. 2006;4(2):295-306.
24. Ruffatti A, Calligaro A, Hoxha A, et al. Laboratory and clinical features of pregnant women with antiphospholipid syndrome and neonatal outcome. *Arthritis Care Res*. 2010;62(3): 302-307.
25. Toglia MR, Weg JG. Venous thromboembolism during pregnancy. *N Engl J Med*. 1996;335(2):108-114.
26. Barrett JH, Brennan P, Fiddler M, Silman AJ. Does rheumatoid arthritis remit during pregnancy and relapse postpartum? Results from a nationwide study in the United Kingdom performed prospectively from late pregnancy. *Arthritis Rheum*. 1999;42(6): 1219-1227.
27. de Man YA, Dolhain RJ, van de Geijn FE, Willemsen SP, Hazes JM. Disease activity of rheumatoid arthritis during pregnancy: results from a nationwide prospective study. *Arthritis Rheum*. 2008;59(9):1241-1248.
28. Bowden AP, Barrett JH, Fallow W, Silman AJ. Women with inflammatory polyarthritis have babies of lower birth weight. *J Rheumatol*. 2001;28(2):355-359.
29. de Man YA, Hazes JM, van der Heide H, et al. Association of higher rheumatoid arthritis disease activity during pregnancy with lower birth weight: results of a national prospective study. *Arthritis Rheum*. 2009;60(11):3196-3206.
30. Andreoli L, Bazzani C, Taraborelli M, et al. Pregnancy in autoimmune rheumatic diseases: the importance of counselling for old and new challenges. *Autoimmun Rev*. 2010;10(1): 51-54.
31. Lockshin MD, Sammaritano LR, Schwartzman S. Lupus pregnancy. In: Lahita RG, ed. *Systemic Lupus Erythematosus*. 3rd ed. New York, NY: Academic Press; 1999:507-536.

32. Østensen M, Khamashta MA, Lockshin M, et al. Anti-inflammatory and immunosuppressive drugs and reproduction. *Arthritis Res Ther*. 2006;8(3):209.
33. Buyon JP, Clancy RM. Neonatal lupus: review of proposed pathogenesis and clinical data from the US-based Research Registry for Neonatal Lupus. *Autoimmunity*. 2003;36(1):41-50.
34. Sonesson SE, Salomonsson S, Jacobsson LA, Bremme K, Wahren-Herlenius M. Signs of first-degree heart block occur in one-third of fetuses of pregnant women with anti-SSA/Ro 52-kd antibodies. *Arthritis Rheum*. 2004;50(4):1253-1261.
35. Ruffatti A, Marson P, Svaluto-Moreolo G, et al. A combination therapy protocol of plasmapheresis, intravenous immunoglobulins and betamethasone to treat anti-Ro/La-related congenital atrioventricular block: case series and review of the literature. *Autoimmun Rev*. 2013;12(7):768-773.
36. Izmirly PM, Costedoat-Chalumeau N, Pisoni CN, et al. Maternal use of hydroxychloroquine is associated with a reduced risk of recurrent anti-SSA/Ro-antibody-associated cardiac manifestations of neonatal lupus. *Circulation*. 2012;126(1):76-82.
37. Friedman DM, Llanos C, Izmirly PM, et al. Evaluation of fetuses in a study of intravenous immunoglobulin as preventive therapy for congenital heart block: results of a multicenter, prospective, open-label clinical trial. *Arthritis Rheum*. 2010;62(4):1138-1146.
38. Pisoni CN, Brucato A, Ruffatti A, et al. Failure of intravenous immunoglobulin to prevent congenital heart block: findings of a multicenter, prospective, observational study. *Arthritis Rheum*. 2010;62(4):1147-1152.
39. Makino S, Yonemoto H, Itoh S, Takeda S. Effect of steroid administration and plasmapheresis to prevent fetal congenital heart block in patients with systemiclupus erythematosus and/or Sjögren's syndrome. *Acta Obstet Gynecol Scand*. 2007;86(9):1145-1146.
40. de Jesus GR, Agmon-Levin N, Andrade CA, et al. 14th International Congress on Antiphospholipid Antibodies Task Force report on obstetric antiphospholipid syndrome. *Autoimmun Rev*. 2014;13(8):795-813.
41. Branch DW, Peaceman AM, Druzin M, et al. A multicenter, placebo-controlled pilot study of intravenous immune globulin treatment of antiphospholipid syndrome during pregnancy. *The Pregnancy Loss Study Group*. *Am J Obstet Gynecol*. 2000;182(1 pt 1):122-127.
42. Kamel H, Navi BB, Sriram N, Hovsepian DA, Devereux RB, Elkind MS. Risk of a thrombotic event after the 6-week postpartum period. *N Engl J Med*. 2014;370(14):1307-1315.
43. Roberge S, Villa P, Nicolaides K, et al. Early administration of low-dose aspirin for the prevention of preterm and term preeclampsia: a systematic review and meta-analysis. *Fetal Diagn Ther*. 2012;31(3):141-146.
44. Roberge S, Giguère Y, Villa P, et al. Early administration of low-dose aspirin for the prevention of severe and mild preeclampsia: a systematic review and meta-analysis. *Am J Perinatol*. 2012; 29(7):551-556.
45. Cnossen JS, Morris RK, ter Riet G, et al. Use of uterine artery Doppler ultrasonography to predict pre-eclampsia and intrauterine growth restriction: a systematic review and bivariable meta-analysis. *CMAJ*. 2008;178(6):701-711.
46. Teixeira L, Mahr A, Berezn A, Noël LH, Guillevin L, Mouthon L. Scleroderma renal crisis, still a life-threatening complication. *Ann NY Acad Sci*. 2007;1108:249-258.
47. Clowse ME, Magder L, Witter F, Petri M. Hydroxychloroquine in lupus pregnancy. *Arthritis Rheum*. 2006;54(11):3640-3647.
48. Hyrich KL, Verstappen SM. Biologic therapies and pregnancy: the story so far. *Rheumatology (Oxford)*. 2014;53(8):1377-1385.
49. Váncsa A, Ponyi A, Constantin T, Zeher M, Dank K. Pregnancy outcome in idiopathic inflammatory myopathy. *Rheumatol Int*. 2007;27(5):435-439.
50. Doria A, Iaccarino L, Ghirardello A, et al. Pregnancy in rare autoimmune rheumatic diseases: UCTD, MCTD, myositis, systemic vasculitis and Beçhet disease. *Lupus*. 2004;13(9):690-695.
51. Steen VD. Pregnancy in women with systemic sclerosis. *Obstet Gynecol*. 1999;94(1):15-20.
52. Taraborelli M, Ramoni V, Brucato A, et al. Brief report: successful pregnancies but a higher risk of preterm births in patients with systemic sclerosis—an Italian multicenter study. *Arthritis Rheum*. 2012;64(6):1970-1977.
53. Østensen M. The effect of pregnancy on ankylosing spondylitis, psoriatic arthritis, and juvenile rheumatoid arthritis. *Am J Reprod Immunol*. 1992;28(3-4):235-237.
54. Harber MA, Tso A, Taheri S, Tuck SM, Burns A. Wegener's granulomatosis in pregnancy: the therapeutic dilemma. *Nephrol Dial Transplant*. 1999;14(7):1789-1791.
55. Tuin J, Sanders JS, de Joode AA, Stegeman CA. Pregnancy in women diagnosed with antineutrophil cytoplasmic antibody-associated vasculitis: outcome for the mother and the child. *Arthritis Care Res*. 2012;64(4):539-545.
56. Hiyama J, Shiota Y, Marukawa M, et al. Churg-Strauss syndrome associated with pregnancy. *Intern Med*. 2000;39(11):985-990.
57. Sharma BK, Jain S, Vasishta K. Outcome of pregnancy in Takayasu arteritis. *Int J Cardiol*. 2000;75(suppl 1):S159-S162.
58. Hidaka N, Yamanaka Y, Fujita Y, Fukushima K, Wake N. Clinical manifestations of pregnancy in patients with Takayasu arteritis: experience from a single tertiary center. *Arch Gynecol Obstet*. 2012;285(2):377-385.
59. Reed NR, Smith MT. Periarteritis nodosa in pregnancy: report of a case and review of the literature. *Obstet Gynecol*. 1980;55(3): 381-384.
60. Uzun S, Alpsoy E, Durdu M, Akman A. The clinical course of Behçet's disease in pregnancy: a retrospective analysis and review of the literature. *J Dermatol*. 2003;30(7):499-502.
61. Noel N, Wechsler B, Nizard J, et al. Behçet's disease and pregnancy. *Arthritis Rheum*. 2013;65(9):2450-2456.