

Pregnancy and menopause in patients with systemic lupus erythematosus and/or antiphospholipid syndrome

Practical messages from the EULAR guidelines

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KEY WORDS

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ABSTRACT

Over the last few decades, reproductive medicine has observed an improvement in the management and outcome of pregnancy in connective tissue diseases, such as systemic lupus erythematosus (SLE) and antiphospholipid syndrome (APS). However, pregnancy and related issues remain a challenge in these patients. In routine clinical practice, health professionals dealing with SLE and APS need to consider the numerous aspects of the reproductive life of their patients, such as pregnancy, family planning, fertility, contraception, cancer surveillance, and menopause. The new European League Against Rheumatism recommendations for women's health and family planning reflect the need for a novel approach to communication in the patient–physician relationship. Preconception counseling is essential to ensure optimal pregnancy outcomes through a careful risk stratification involving disease activity, organ involvement, autoantibody profile, use of drugs, and previous pregnancy outcomes, as well as to ensure better preventive and therapeutic strategies to limit complications. In patients with stable/inactive disease and low risk of thrombosis, adequate hormonal contraception and menopausal replacement therapy should be recommended. Assisted reproductive techniques can be safely used in these patients, but anticoagulation or low-dose aspirin (or both) should be added in those with positive antiphospholipid antibody titers. All menstruating women should be counseled on the possibility to preserve fertility with gonadotropin-releasing hormone analogues if receiving alkylating agents. Strict clinical, serological, laboratory, and multidisciplinary monitoring during pregnancy is mandatory to early recognize and effectively treat disease flares or obstetric complications. Doppler ultrasonography and fetal biometry should be regularly performed, especially in the second and third trimesters. Physicians should recommend screening for cervical dysplasia related to human papillomavirus (HPV) infection, especially during immunosuppressive therapy, and HPV immunization can be used in women with stable/inactive disease.

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Introduction Autoimmune and systemic inflammatory disorders are common among women of child-bearing age because the onset of these disorders tends to overlap with patients' peak reproductive years, particularly in systemic lupus erythematosus (SLE) and antiphospholipid syndrome (APS).

Over the last few decades, we have observed an improvement in the management and outcome of pregnancy in connective tissue diseases, owing to improved control and management of

the underlying diseases and improved knowledge on such issues as the potential effects of disease activity on fetal health or the safety and usefulness of some medications during pregnancy and breastfeeding.¹ However, many aspects of the reproductive life of patients need to be considered, involving not only pregnancy and family planning but also fertility, contraception, and menopause.²⁻⁴ For this reason, new evidence-based recommendations on the management of family planning and women's health issues in SLE and

TABLE 1 Risk stratification for pregnancy women with systemic lupus erythematosus and/or antiphospholipid syndrome

Risk factors		Pregnancy-related complications
disease-related risk factors	SLE activity/flare	fetal morbidity and mortality (pregnancy loss, preeclampsia/eclampsia, preterm delivery, IUGR) ⁸³ increased risks for maternal disease activity (RR = 2.1 for flare during pregnancy and puerperium) ⁹
	lupus nephritis	any adverse maternal outcome (OR, 5.3), ¹⁰ renal flare during/after pregnancy (RR, 9.0), ⁸⁴ and poor fetal outcome (fetal loss, preterm delivery) ¹¹
	serological activity (low C3/C4 level, anti-dsDNA positivity)	increased risk of lupus flares during pregnancy, ⁹ pregnancy loss, and preterm birth ⁸
	end-stage organ damage	deterioration in renal function is higher with higher serum creatinine levels and the chance of successful pregnancy outcome is lower ¹²
	anti-Ro/SSA antibodies	neonatal lupus, ⁸⁵ CHB ⁸⁶
	previous adverse pregnancy outcome	in APS: increased risks for pregnancy complications ^{15,16}
	previous vascular thrombosis	in APS: increased risks for pregnancy morbidity ¹⁶
	aPL profile	increased risk of both maternal and fetal outcomes, especially for patients with lupus anticoagulant ⁷ or multiple aPL positivity and a moderate to high aPL titers ^{17,18} (high-risk aPL profile) maternal outcome: vascular thrombotic events during pregnancy, preeclampsia fetal outcome: IUGR, preterm birth, fetal loss
general risk factors	SLE	in APS: increased risks (OR, 6.0) for pregnancy morbidity ^{16,87}
	arterial hypertension	increased risk for preeclampsia, ⁸⁸ preterm birth, ⁸³ and IUGR ⁸⁹
	dyslipidemia	elevated triglycerides: increased risk for venous thrombosis ⁸⁷ ; hypercholesterolemia: increased risk for arterial thrombosis ⁹⁰
	diabetes mellitus	–
	thyroid disease	preterm delivery ⁹¹
	nicotine and alcohol use	–
	maternal age	–

Abbreviations: anti-dsDNA, anti-double-stranded DNA antibodies; aPL, antiphospholipid antibodies; CHB, congenital heart block; IUGR, intrauterine growth restriction; OR, odds ratio; RR, relative risk

APS have been recently developed by an international and multidisciplinary panel of experts.⁵

The recommendations have been developed following the methodology proposed by the European League Against Rheumatism (EULAR) standardized procedures for guidelines.⁵ In brief, the following techniques were applied: nominal group, Delphi surveys for prioritization, small group discussion, systemic literature review, and 2 rounds of Delphi technique for agreement. Twelve major unmet needs were identified and developed in this project: assessment of fertility, feasibility of assisted reproductive techniques (ARTs), use of contraception, management of menopause, and surveillance of malignancies.⁵

The aim of this paper was to review the new EULAR recommendations to improve the knowledge on pregnancy and women's health among physicians involved in the care of patients with SLE and/or APS, underlining the need for a novel approach in the physician-patient communication.

Before conception: what health professionals need to know **Preconception counseling and risk stratification** Pregnancy planning in patients with SLE and/or APS is a crucial aspect in preventive medicine, and it is essential to increase the probability of a successful outcome. Therefore, the principal

aim of preconception counseling is to define and engage more appropriate preventive strategies to limit the risk of complications, to recognize and treat complications as early as possible, and to discuss a monitoring plan during and after pregnancy with patients and their relatives.

The major complications that patients with SLE and/or APS may experience during pregnancy are prematurity, fetal loss (spontaneous abortion and intrauterine fetal death), intrauterine growth restriction, small-for-gestational-age newborns, preeclampsia, HELLP syndrome (eclampsia/hemolysis, elevated liver enzyme levels, low platelet count), and premature rupture of membranes. All these aspects need to be carefully discussed and understood by patients and their partners.

Preconception counseling is based on risk assessment in an individual patient (TABLE 1). Risk factors for pregnancy complications can be divided into disease-related and general risk factors. Disease-related risk factors include maternal disease activity at conception or in the previous 6 to 12 months,⁷⁻⁹ active nephritis during pregnancy or a history of lupus nephritis,^{10,11} as well as severe organ involvement and end-stage organ damage, which are strongly associated with adverse outcomes.¹² Lupus nephritis flares during pregnancy can mimic preeclampsia, and differentiation between these 2 disorders can be

difficult. Preterm deliveries are associated with disease activity, as determined by the use of any medication throughout pregnancy and especially the use of glucocorticoids (at a prednisone dose of 10 mg/d or higher).¹³

In patients with APS or SLE with positive antiphospholipid (aPL) antibody titers, important risk factors are a history of pregnancy morbidity¹⁵ and thrombosis, the presence of lupus anticoagulant, and triple positivity of aPL antibodies.¹⁶⁻¹⁸ A complete aPL antibody profile should be determined and anticardiolipin and anti-B2-glycoprotein I antibody titers should be evaluated before a planned pregnancy. It may be helpful to repeat aPL antibody tests during pregnancy to assess maternal and fetal risks.

Obstetric risk factors common to the general population could also be present and should be assessed according with general obstetric practice and recommendations.¹⁹⁻²²

Contraceptive measures A safe pregnancy starts with adequate planning and therefore also with adequate contraception to avoid pregnancies during disease flares or while patients are taking potentially teratogenic drugs. However, counseling regarding contraceptive use is not common: in a prospective observational study on 86 patients with SLE who were at risk for unplanned pregnancy, 59% of the patients reported no contraceptive counseling in the past year despite the use of potentially teratogenic medications, 22% reported inconsistent contraceptive use, and 53% depended solely on barrier methods.²³ Women with SLE should be counseled about the use of effective contraceptive measures, and the best strategy should be discussed with patients according to disease activity and individual risk factors for thrombotic events.

Two randomized controlled trials have shown that combined estrogen and progestogen or progestogen-only contraceptives do not increase the risk for flares in women with inactive or stable active SLE and negative aPL titers and no history of thrombosis.^{24,25} Otherwise, in women with positive aPL titers (with or without APS), especially moderate or high titers, and with other thrombotic risks factors (hypertension, obesity, tobacco use), estrogen contraceptives should be avoided due to increased risk for thromboembolism. Even if few data are available, progestogen-only contraceptives are not correlated with disease flares and are considered safe for women with SLE, with the exception of those with positive aPL titers who are at the greatest risk of venous thromboembolism. In these patients, the use of progestogen-only contraceptives must be carefully weighed against the risk of thrombosis.²⁶ Unless gynecological contraindications are present, an intrauterine device, especially copper one, can be offered to all patients. Since patients with SLE and/or APS could be at increased risk for heavy menstrual bleeding due to treatment with anticoagulants or development of thrombocytopenia,

treatment with levonorgestrel-releasing intrauterine device should be considered only if the benefits outweigh the risk of thrombosis.²⁷

Assisted reproductive techniques Except for drug-induced ovarian failure and in the absence of severe active disease, primary infertility is not common among patients with SLE and/or APS, and, similarly to the general population, these patients may require ARTs (ovulation induction and in vitro fertilization). The presence of aPL antibodies does not cause infertility, hence routine screening is not warranted in the infertile population and therapeutic interventions are not justified, except in the case of women with recurrent miscarriages or pregnancy complications.²⁸ Efficacy of ARTs in terms of pregnancy rates in patients with SLE and APS is comparable with the general population, and these techniques are generally considered safe in patients with SLE with stable/inactive disease.²⁹ The most threatening conditions in women undergoing ovarian stimulation are disease flares, thrombosis, and ovarian hyperstimulation syndrome. Milder hormonal ovarian stimulation, single embryo transfer, administration of adjuvant therapy (anti-thrombotic), and use of natural estrogen or progestogen through a nonoral route may constitute the safest approach.³⁰ Patients with positive aPL antibody titers or with APS should receive anticoagulation or low-dose aspirin (or both), and the type and dosage of these treatments should be defined according to the individual risk profile, as during pregnancy. Patients with positive aPL antibody titers should receive heparin thromboprophylaxis from the time of embryo transfer to reduce the risk of thrombosis, which increases from the beginning of the luteal phase, while women with APS should be switched from oral anticoagulant therapy to therapeutic doses of heparin for ovarian stimulation. Therefore, it is essential to tailor ART procedures to the individual patient's profile.

Therapy before conception: counseling and fertility preservation As previously mentioned, fertility is known to be normal in women with SLE; however, it can be reduced in the following situations: amenorrhea accompanying severe flares, renal insufficiency-related hypofertility, as well as menstrual irregularities and premature ovarian failure secondary to alkylating agents, such as cyclophosphamide.^{31,32} Since the effects of cyclophosphamide on fertility are age- and dose-dependent, physicians should consider preservation strategies, balancing the therapeutic effects against the risk of ovarian dysfunction, and should take into account all the possible factors with a negative impact on fertility (age, tobacco use, alcohol consumption). Therefore, all menstruating women should be counseled on the issue of fertility and on the possibility—if they are going to receive alkylating agents—to preserve it with gonadotropin-releasing hormone analogues (GnRH-a):

in fact, could start GnRH-a before or simultaneously with starting cyclophosphamide. As in patients with cancer, GnRH-a have a good safety profile and are effective in reducing amenorrhea rates, improving menstruation resumption, and increasing pregnancy rates in patients with SLE. However, the advantage of GnRH-a was shown only in observational studies but not in randomized controlled trials.³³

During pregnancy: treatment options and monitoring strategies

Predictive biomarkers to monitor disease activity The negative impact of disease activity on both maternal and fetal outcomes has been previously highlighted. Some physiologic changes reflected in laboratory test results (such as an increase in erythrocyte sedimentation rate and complement levels) as well as some pregnancy-related clinical manifestations (such as fatigue or peripheral edema) may mimic lupus activity. Therefore, the diagnosis of disease flares might be more difficult during pregnancy,³⁴ and validated lupus activity scales have been modified for pregnancy to offer possible guidance to physicians.^{35,36} A strict clinical, serological, and laboratory follow-up is mandatory during pregnancy, including evaluation of renal function (serum creatinine levels and glomerular filtration rate), urine sediment, proteinuria, serum uric acid, and blood pressure, as well as the levels of serological markers (complement proteins C3/C4 and anti-double stranded DNA [anti-dsDNA] antibodies). A decline in serum C3/C4 levels (even if still within the reference range) or the lack of elevated levels during the first period of pregnancy, as well as positive or increased titers of anti-dsDNA antibodies, if correlated with some clinical lupus activity, could help a physician early recognize a disease flare and to differentiate it from preeclampsia in the second part of pregnancy.^{7,37,38}

Pregnancy monitoring Pregnancy in patients with SLE and APL is at risk of intrauterine growth restriction (IUGR), and this condition exposes the fetus to an increased risk of complications; in fact, IUGR is a major determinant of adverse perinatal outcomes. Ultrasound markers of IUGR include alterations in biometric ratios, uteroplacental Doppler, and fetal growth velocity.³⁹ Pregnant women with SLE and/or APS should be followed with ultrasonographic protocols for high-risk pregnancy, including supplementary Doppler sonography in the second and third trimesters. Abnormal blood flow patterns in fetal circulation detected by Doppler ultrasound may indicate placental insufficiency and, consequently, poor fetal prognosis. Despite a good negative predictive value for placental-associated disorders such as preeclampsia and IUGR, umbilical and uterine artery Doppler sonography at 20 to 24 weeks had a modest positive value, especially in the absence of biometric alteration.^{40,41}

Fetal echocardiographic monitoring is a routine screening in women with anti-Ro/SSA or anti-La/SSB antibodies. The cardiac manifestations of neonatal lupus syndrome include conduction defects, structural abnormalities, cardiomyopathy, and congestive cardiac failure; however, the most common presentation is congenital heart block (CHB), which can lead to fetal death.⁴² CHB affects about 2% of children born to nulliparous women with anti-Ro antibodies, but the risk increases to 16% to 20% in consecutive pregnancies after the birth of an affected child. Numerous tests have been developed for early detection of CHB, but fetal Doppler echocardiography remains the most common. In the presence of maternal anti-Ro/SSA antibodies, it is proposed that fetuses are monitored with echocardiography every week from 16 to 26 weeks of gestation and every second week thereafter.⁴³ The detection of an early conduction defect such as prolonged PR interval should be considered a danger signal.

It has to be acknowledged that the risk for CHB in anti-Ro-positive women without previous CHB is low; therefore, the cost-effectiveness of intensive surveillance and its timing are still a matter of debate. Due to the high risk of recurrence, this monitoring should be offered to all patients with a previous pregnancy complicated with CHB.

The effectiveness of treatment with fluorinated steroids has not been proved in established third-degree heart block⁴⁴; however, a recent study on anti-Ro/SSA-positive women suggests that, despite its unproven benefit, the Doppler screening protocol is well accepted by patients.⁴⁵

Therapy during pregnancy: prevention and management of complications

Drug treatment during pregnancy in patients with SLE and/or APS may be required to control maternal disease, which can adversely affect fetal well-being and pregnancy outcome, as well as to prevent complications. Adjustment of therapy in a patient who is planning pregnancy is aimed at introducing drugs that can control disease activity and are considered safe for the fetus.¹

Hydroxychloroquine (HCQ) should be recommended in women with SLE before conception and should be continued during pregnancy.^{46,47} Its beneficial effect has also been demonstrated in a randomized controlled trial.⁴⁸ In addition, there are data suggesting that the use of HCQ during pregnancy might reduce the risk of CHB,⁴⁹ especially in subsequent pregnancies of women with a previous child with CHB.⁵⁰ The protective role of HCQ in pregnant women with aPL antibody positivity is controversial due to its anti-inflammatory, antiaggregant, and immunoregulatory properties,⁵¹ and future prospective studies are necessary to clarify whether HCQ should be routinely recommended in clinical practice for women positive for aPL antibodies.

Although many drugs used to treat SLE are potentially harmful in pregnancy, there are some safe options that should be used during

this period. Corticosteroids represent the treatment of choice in cases of reactivation of SLE during pregnancy and can be used as prednisone or prednisolone, which is inactivated by enzyme 11- β -hydroxysteroid dehydrogenase 2 and reduce fetal exposure to approximately 10% of maternal dosage⁵²; therefore, the use of these drugs does not replace the use of betamethasone or dexamethasone when they are indicated for fetal lung maturation. Exposure to steroids should be limited to a minimum dose during pregnancy for an increased risk of diabetes, hypertension, and premature rupture of membranes.⁵³ However, in case of moderate to severe flares, short courses of high-dose and/or intravenous-pulse glucocorticoids can be used.⁵

Azathioprine and calcineurin inhibitors (cyclosporine A, tacrolimus) are therapeutic resources available for active SLE during pregnancy. Azathioprine has documented safety, can control disease activity, and is not associated with teratogenicity.^{14,54} The dose should be limited to a maximum of 2.5 mg/kg/d to avoid risk of fetal cytopenia and immune suppression.⁵³

Cyclophosphamide, mycophenolate mofetil, leflunomide, and methotrexate have teratogenic effects and should not be used during pregnancy.⁵⁵ In case of severe disease flare during pregnancy, intravenous immunoglobulin and plasmapheresis remain alternative options as additional therapies.

There are scarce data on the use and safety of belimumab and rituximab during pregnancy; therefore, these drugs should be used only when other pregnancy-compatible drug cannot effectively control maternal disease.⁵⁶

Low-dose aspirin should be considered and added before conception and during pregnancy to decrease the risk of preeclampsia, especially in patients with lupus nephritis or those with positive aPL antibody titers.^{57,58} However, all patients with positive titers should be stratified for the risk of maternal and fetal complications during pregnancy, and a combination therapy of low-dose aspirin and heparin should be considered.

Heparin and low-dose aspirin are widely recognized as the current treatments of choice for APS in pregnancy.⁵⁹⁻⁶¹ Heparin is initiated after a positive pregnancy test and needs to be continued for 6 weeks postpartum. Patients with prior systemic thrombosis should receive full therapeutic doses of heparin throughout pregnancy, while those with obstetric APS—prophylactic doses. Low-molecular-weight heparin has demonstrated similar efficacy to unfractionated heparin in prospective studies on obstetric APS.^{62,63} In patients refractory to these treatment strategies, an additional use of steroids, intravenous immunoglobulin, and plasmapheresis has shown benefit in case reports.⁶⁴⁻⁶⁶

Eventually, physicians should consider adjunct supplementation with vitamin D and calcium to support bone health, especially for patients on steroids and heparin.⁶⁷

Beyond pregnancy: medical issues related to women's health

Menopause and hormone replacement therapy

Menopause is associated with significant physiologic changes, particularly in the cardiovascular, skeletal, and central nervous systems. Three randomized controlled trials have investigated the effects of hormone replacement therapy (HRT) in postmenopausal patients. No increased risk of severe disease flare was reported, although there was a small increase in the risk of mild to moderate flare (relative risk, 1.34), as compared with placebo.^{68,69}

However, an apparently increased risk of thrombosis seems to be a real threat in women with SLE who receive HRT,⁷⁰ even if these findings are limited by the exclusion of patients with aPL antibodies and a history of thrombosis. Moreover HRT does not seem to increase the risk of cardiovascular events.^{71,72} Therefore, HRT can be considered for short-term (up to 1- to 2-year) management of severe menopausal symptoms after the assessment of the patient's risk profile, preferably in stable inactive disease and with negative aPL titers. The benefit should be balanced against the risk of flare and thrombotic risk.

Screening for malignancies

Multicenter studies and meta-analyses have demonstrated that patients with SLE are at higher risk for cervical dysplasia (especially high-grade squamous intraepithelial lesions) and vaginal and vulvar cancers than general population, due to a higher frequency of human papillomavirus (HPV) infection.⁷³⁻⁷⁵ A relationship between cervical abnormalities and previous use of immunosuppressive drugs, particularly those exposed to cyclophosphamide in a cumulative dose-dependent way, has been reported.^{76,77} Thus, a preventive counseling about cancer surveillance appears relevant in sexually active patients with SLE who receive immunosuppressive therapy, and gynecologic visits at shorter intervals than in general population seem to be a reasonable approach in these patients. No increased risk for breast, ovarian, and endometrial cancer has been observed; therefore, the same screening protocols as in general population are applied.⁷⁸

Human papillomavirus vaccination

Prospective studies have shown a good safety and efficacy profile of a HPV vaccine in patients with SLE, with no increase in lupus activity or flares and excellent seroconversion rates.^{79,80} The quadrivalent HPV vaccine has been associated with venous thromboembolic events, even if the significance of these findings is not clear.⁸¹ Starting from the previous considerations about HPV infection and increased incidence of cervical dysplasia in SLE patients, HPV vaccination should be considered in young women with SLE and/or APS with stable/inactive disease, carefully weighing against thrombotic risks.⁸²

Conclusions The development of new EULAR recommendations for women's health and family planning reflects the need for a novel approach in the patient-physician relationship, in which health professionals could support the patient's decision to start a family by discussing from the first visit individual pregnancy risks, providing the best care and the best preventive measures and shifting the attention from post- to preconception issues.

REFERENCES

- Götestam Skorpen C, Hoeltzenbein M, Tincani A, et al. The EULAR points to consider for use of antirheumatic drugs before pregnancy, and during pregnancy and lactation. *Ann Rheum Dis.* 2016; 75: 795-810.
- Ntali S, Damjanov N, Drakakis P, et al. Women's health and fertility, family planning and pregnancy in immune-mediated rheumatic diseases: a report from a south-eastern European Expert Meeting. *Clin Exp Rheumatol.* 2014; 32: 959-968.
- Østensen M, Andreoli L, Brucato A, et al. State of the art: Reproduction and pregnancy in rheumatic diseases. *Autoimmun Rev.* 2015; 14: 376-386.
- Kavanaugh A, Cush JJ, Ahmed MS, et al. Proceedings from the American College of Rheumatology Reproductive Health Summit: the management of fertility, pregnancy, and lactation in women with autoimmune and systemic inflammatory diseases. *Arthritis Care Res.* 2015; 67: 313-325.
- Andreoli L, Bertias GK, Agmon-Levin N, et al. EULAR recommendations for women's health and the management of family planning, assisted reproduction, pregnancy and menopause in patients with systemic lupus erythematosus and/or antiphospholipid syndrome. *Ann Rheum Dis.* 2016. [Epub ahead of print].
- Dougados M, Betteridge N, Burmester GR, et al. EULAR standardised operating procedures for the elaboration, evaluation, dissemination, and implementation of recommendations endorsed by the EULAR standing committees. *Ann Rheum Dis.* 2004; 63: 1172-1176.
- Buyon JP, Kim MY, Guerra MM, et al. Predictors of pregnancy outcomes in patients with lupus: a cohort study. *Ann Intern Med.* 2015; 163: 153-163.
- Clowse MEB, Magder LS, Witter F, Petri M. The impact of increased lupus activity on obstetric outcomes. *Arthritis Rheum.* 2005; 52: 514-521.
- Yang H, Liu H, Xu D, et al. Pregnancy-related systemic lupus erythematosus: clinical features, outcome and risk factors of disease flares – a case control study. *PLoS One.* 2014; 9: e104375.
- Wagner SJ, Craici I, Reed D, et al. Maternal and foetal outcomes in pregnant patients with active lupus nephritis. *Lupus.* 2009; 18: 342-347.
- Smyth A, Oliveira GHM, Lahr BD, et al. A systematic review and meta-analysis of pregnancy outcomes in patients with systemic lupus erythematosus and lupus nephritis. *Clin J Am Soc Nephrol.* 2010; 5: 2060-2068.
- Lv J, Wang W, Li Y. Clinical outcomes and predictors of fetal and maternal consequences of pregnancy in lupus nephritis patients. *Int Urol Nephrol.* 2015; 47: 1379-1385.
- Clark CA, Spitzer KA, Nadler JN, Laskin CA. Preterm deliveries in women with systemic lupus erythematosus. *J Rheumatol.* 2003; 30: 2127-2132.
- Fischer-Betz R, Specker C, Brinks R, et al. Low risk of renal flares and negative outcomes in women with lupus nephritis conceiving after switching from mycophenolate mofetil to azathioprine. *Rheumatol Oxf Engl.* 2013; 52: 1070-1076.
- Jeremic K, Stefanovic A, Dotlic J, et al. Neonatal outcome in pregnant patients with antiphospholipid syndrome. *J Perinat Med.* 2015; 43: 761-768.
- Ruffatti A, Tonello M, Visentin MS, et al. Risk factors for pregnancy failure in patients with anti-phospholipid syndrome treated with conventional therapies: a multicentre, case-control study. *Rheumatol Oxf Engl.* 2011; 50: 1684-1689.
- Lockshin MD, Kim M, Laskin CA, et al. Prediction of adverse pregnancy outcome by the presence of lupus anticoagulant, but not anticardiolipin antibody, in patients with antiphospholipid antibodies. *Arthritis Rheum.* 2012; 64: 2311-2318.
- Simchen MJ, Dulitzki M, Rofe G, et al. High positive antibody titers and adverse pregnancy outcome in women with antiphospholipid syndrome. *Acta Obstet Gynecol Scand.* 2011; 90: 1428-1433.
- Gante I, Amaral N, Soares J, Almeida MC. Impact of gestational weight gain on obstetric and neonatal outcomes in obese diabetic women. *BMC Pregnancy Childbirth.* 2015; 15: 249.
- Aktun LH, Yorgunlar B, Karaca N, Akpak YK. Predictive Risk factors in the treatment of gestational diabetes mellitus. *Clin Med Insights Womens Health.* 2015; 8: 25-28.
- Giacobbe AM, Grasso R, Triolo O, et al. Thyroid diseases in pregnancy: a current and controversial topic on diagnosis and treatment over the past 20 years. *Arch Gynecol Obstet.* 2015; 292: 995-1002.
- Moroni G, Doria A, Giglio E, Tani C, Zen M, Strigini F, et al. Fetal outcome and recommendations of pregnancies in lupus nephritis in the 21st century. A prospective multicenter study. *J Autoimmun.* 2016; 74: 6-12.
- Yazdany J, Trupin L, Kaiser R, et al. Contraceptive counseling and use among women with systemic lupus erythematosus: a gap in health care quality? *Arthritis Care Res.* 2011; 63: 358-365.
- Petri M, Kim MY, Kalunian KC, et al. Combined oral contraceptives in women with systemic lupus erythematosus. *N Engl J Med.* 2005; 353: 2550-2558.
- Sánchez-Guerrero J, Uribe AG, Jiménez-Santana L, et al. A trial of contraceptive methods in women with systemic lupus erythematosus. *N Engl J Med.* 2005; 353: 2539-2549.
- Culwell KR, Curtis KM, del Carmen Cravioto M. Safety of contraceptive method use among women with systemic lupus erythematosus: a systematic review. *Obstet Gynecol.* 2009; 114 (2 Pt 1): 341-353.
- Pisoni CN, Cuadrado MJ, Khamashta MA, Hunt BJ. Treatment of menorrhagia associated with oral anticoagulation: efficacy and safety of the levonorgestrel releasing intrauterine device (Mirena coil). *Lupus.* 2006; 15: 877-880.
- Practice Committee of American Society for Reproductive Medicine. Anti-phospholipid antibodies do not affect IVF success. *Fertil Steril.* 2008; 90: S172-S173.
- Orquevaux P, Masseur A, Le Guern V, et al. [In vitro fertilization and systemic lupus erythematosus or antiphospholipid syndrome: An update]. *Rev Med Interne.* 2015; 36: 154-158. [French].
- Bellver J, Pellicer A. Ovarian stimulation for ovulation induction and in vitro fertilization in patients with systemic lupus erythematosus and antiphospholipid syndrome. *Fertil Steril.* 2009; 92: 1803-1810.
- Ioannidis JPA, Katsifis GE, Tzioufas AG, Moutsopoulos HM. Predictors of sustained amenorrhea from pulsed intravenous cyclophosphamide in premenopausal women with systemic lupus erythematosus. *J Rheumatol.* 2002; 29: 2129-2135.
- Mayorga J, Alpizar-Rodríguez D, Prieto-Padilla J, et al. Prevalence of premature ovarian failure in patients with systemic lupus erythematosus. *Lupus.* 2016; 25: 675-683.
- Ben-Aharon I, Gafter-Gvili A, Leibovici L, Stemmer SM. Pharmacological interventions for fertility preservation during chemotherapy: a systematic review and meta-analysis. *Breast Cancer Res Treat.* 2010; 122: 803-811.
- Khamashta MA, Ruiz-Irastorza G, Hughes GR. Systemic lupus erythematosus flares during pregnancy. *Rheum Dis Clin North Am.* 1997; 23: 15-30.
- Buyon JP, Kalunian KC, Ramsey-Goldman R, et al. Assessing disease activity in SLE patients during pregnancy. *Lupus.* 1999; 8: 677-684.
- Yee C-S, Akil M, Khamashta M, et al. The BILAG2004-Pregnancy index is reliable for assessment of disease activity in pregnant SLE patients. *Rheumatol Oxf Engl.* 2012; 51: 1877-1880.
- Buyon JP, Cronstein BN, Morris M, et al. Serum complement values (C3 and C4) to differentiate between systemic lupus activity and pre-eclampsia. *Am J Med.* 1986; 81: 194-200.
- Clowse MEB, Magder LS, Petri M. The clinical utility of measuring complement and anti-dsDNA antibodies during pregnancy in patients with systemic lupus erythematosus. *J Rheumatol.* 2011; 38: 1012-1016.
- Sovio U, White IR, Dacey A, et al. Screening for fetal growth restriction with universal third trimester ultrasonography in nulliparous women in the Pregnancy Outcome Prediction (POP) study: a prospective cohort study. *Lancet Lond Engl.* 2015; 386: 2089-2097.
- Lees C, Marlow N, Arabin B, et al. Perinatal morbidity and mortality in early-onset fetal growth restriction: cohort outcomes of the trial of randomized umbilical and fetal flow in Europe (TRUFFLE). *Ultrasound Obstet Gynecol Off J Int Soc Ultrasound Obstet Gynecol.* 2013; 42: 400-408.
- Alfirevic Z, Stampalija T, Gyte GML. Fetal and umbilical Doppler ultrasound in high-risk pregnancies. *Cochrane Database Syst Rev.* 2013; CD007529.
- Brito-Zerón P, Izmirly PM, Ramos-Casals M, et al. The clinical spectrum of autoimmune congenital heart block. *Nat Rev Rheumatol.* 2015; 11: 301-312.
- Buyon JP, Clancy RM, Friedman DM. Cardiac manifestations of neonatal lupus erythematosus: guidelines to management, integrating clues from the bench and bedside. *Nat Clin Pract Rheumatol.* 2009; 5: 139-148.
- Izmirly PM, Saxena A, Sahl SK, et al. Assessment of fluorinated steroids to avert progression and mortality in anti-SSA/Ro-associated cardiac injury limited to the fetal conduction system. *Ann Rheum Dis.* 2016; 75: 1161-1165.
- Tingström J, Hjelmstedt A, Welin Henriksson E, et al. Ro/SSA autoantibody-positive pregnancy: reactions to serial fetal Doppler echocardiographic surveillance. *Lupus.* 2015; 24: 1540-1545.
- Clowse MEB, Magder L, Witter F, Petri M. Hydroxychloroquine in lupus pregnancy. *Arthritis Rheum.* 2006; 54: 3640-3647.
- Sperber K, Hom C, Chao CP, et al. Systematic review of hydroxychloroquine use in pregnant patients with autoimmune diseases. *Pediatr Rheumatol Online J.* 2009; 7: 9.

- 48 Levy RA, Vilela VS, Cataldo MJ, et al. Hydroxychloroquine (HCQ) in lupus pregnancy: double-blind and placebo-controlled study. *Lupus*. 2001; 10: 401-404.
- 49 Tunks RD, Clowse MEB, Miller SG, et al. Maternal autoantibody levels in congenital heart block and potential prophylaxis with anti-inflammatory agents. *Am J Obstet Gynecol*. 2013; 208: 64.e1-e7.
- 50 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: 76-82.
- 51 Sciascia S, Branch DW, Levy RA, et al. The efficacy of hydroxychloroquine in altering pregnancy outcome in women with antiphospholipid antibodies. Evidence and clinical judgment. *Thromb Haemost*. 2016; 115: 285-290.
- 52 Jain V, Gordon C. Managing pregnancy in inflammatory rheumatological diseases. *Arthritis Res Ther*. 2011; 13: 206.
- 53 Østensen M, Khamashta M, Lockshin M, et al. Anti-inflammatory and immunosuppressive drugs and reproduction. *Arthritis Res Ther*. 2006; 8: 209.
- 54 Al Maimouni H, Gladman DD, Ibañez D, Urowitz MB. Switching treatment between methotrexate and azathioprine in lupus patients: indications and outcomes. *Arthritis Care Res*. 2014; 66: 1905-1909.
- 55 Østensen M, Förger F. How safe are anti-rheumatic drugs during pregnancy? *Curr Opin Pharmacol*. 2013; 13: 470-475.
- 56 Danve A, Perry L, Deodhar A. Use of belimumab throughout pregnancy to treat active systemic lupus erythematosus: a case report. *Semin Arthritis Rheum*. 2014; 44: 195-197.
- 57 Roberge S, Villa P, Nicolaidis 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: 141-146.
- 58 Wu CQ, Kustec VE, Brown RN, et al. The medical management of antiphospholipid syndrome in pregnancy: a meta-analysis. *Obstetrics & Gynecology*. 2014. doi:10.1097/01.AOG.0000447195.12926.b9.
- 59 Mak A, Cheung MW-L, Cheak AA, Ho RC-M. Combination of heparin and aspirin is superior to aspirin alone in enhancing live births in patients with recurrent pregnancy loss and positive anti-phospholipid antibodies: a meta-analysis of randomized controlled trials and meta-regression. *Rheumatol Oxf Engl*. 2010; 49: 281-288.
- 60 de Jesús GR, Rodrigues G, de Jesús NR, Levy RA. Pregnancy morbidity in antiphospholipid syndrome: what is the impact of treatment? *Curr Rheumatol Rep*. 2014; 16: 403.
- 61 Empson M, Lassere M, Craig J, Scott J. Prevention of recurrent miscarriage for women with antiphospholipid antibody or lupus anticoagulant. *Cochrane Database Syst Rev*. 2005; (2): CD002859.
- 62 Ruffatti A, Gervasi MT, Favaro M, et al. Adjusted prophylactic doses of nadroparin plus low dose aspirin therapy in obstetric antiphospholipid syndrome. A prospective cohort management study. *Clin Exp Rheumatol*. 2011; 29: 551-554.
- 63 Fouda UM, Sayed AM, Abdou A-MA, et al. Enoxaparin versus unfractionated heparin in the management of recurrent abortion secondary to antiphospholipid syndrome. *Int J Gynaecol Obstet Off Organ Int Fed Gynaecol Obstet*. 2011; 112: 211-215.
- 64 Bramham K, Thomas M, Nelson-Piercy C, et al. First-trimester low-dose prednisolone in refractory antiphospholipid antibody-related pregnancy loss. *Blood*. 2011; 117: 6948-6951.
- 65 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.
- 66 El-Haieg DO, Zanati MF, El-Foual FM. Plasmapheresis and pregnancy outcome in patients with antiphospholipid syndrome. *Int J Gynaecol Obstet*. 2007; 99: 236-241.
- 67 ACOG Committee on Obstetric Practice. ACOG Committee Opinion No. 495: Vitamin D: Screening and supplementation during pregnancy. *Obstet Gynecol*. 2011; 118: 197-198.
- 68 Cravioto M-D-C, Durand-Carbajal M, Jiménez-Santana L, et al. Efficacy of estrogen plus progestin on menopausal symptoms in women with systemic lupus erythematosus: a randomized, double-blind, controlled trial. *Arthritis Care Res*. 2011; 63: 1654-1663.
- 69 Buyon JP, Petri MA, Kim MY, et al. The effect of combined estrogen and progesterone hormone replacement therapy on disease activity in systemic lupus erythematosus: a randomized trial. *Ann Intern Med*. 2005; 142 (12 Pt 1): 953-962.
- 70 Sánchez-Guerrero J, González-Pérez M, Durand-Carbajal M, et al. Menopause hormonal therapy in women with systemic lupus erythematosus. *Arthritis Rheum*. 2007; 56: 3070-3079.
- 71 Hochman J, Urowitz MB, Ibañez D, Gladman DD. Hormone replacement therapy in women with systemic lupus erythematosus and risk of cardiovascular disease. *Lupus*. 2009; 18: 313-317.
- 72 Fernández M, Calvo-Alén J, Bertoli AM, et al. Systemic lupus erythematosus in a multiethnic US cohort (LUMINA L II): relationship between vascular events and the use of hormone replacement therapy in postmenopausal women. *J Clin Rheumatol Pract Rep Rheum Musculoskel Dis*. 2007; 13: 261-265.
- 73 Bernatsky S, Ramsey-Goldman R, Labrecque J, et al. Cancer risk in systemic lupus: an updated international multi-centre cohort study. *J Autoimmun*. 2013; 42: 130-135.
- 74 Santana IU, Gomes A do N, Lyrio LD, et al. Systemic lupus erythematosus, human papillomavirus infection, cervical pre-malignant and malignant lesions: a systematic review. *Clin Rheumatol*. 2011; 30: 665-672.
- 75 Zard E, Arnaud L, Mathian A, et al. Increased risk of high grade cervical squamous intraepithelial lesions in systemic lupus erythematosus: A meta-analysis of the literature. *Autoimmun Rev*. 2014; 13: 730-735.
- 76 Klumb EM, Araújo ML, Jesus GR, et al. Is higher prevalence of cervical intraepithelial neoplasia in women with lupus due to immunosuppression? *J Clin Rheumatol Pract Rep Rheum Musculoskel Dis*. 2010; 16: 153-157.
- 77 Ognenovski VM, Marder W, Somers EC, et al. Increased incidence of cervical intraepithelial neoplasia in women with systemic lupus erythematosus treated with intravenous cyclophosphamide. *J Rheumatol*. 2004; 31: 1763-1767.
- 78 Bernatsky S, Ramsey-Goldman R, Foulkes WD, et al. Breast, ovarian, and endometrial malignancies in systemic lupus erythematosus: a meta-analysis. *Br J Cancer*. 2011; 104: 1478-1481.
- 79 Soybilgic A, Onel KB, Utset T, et al. Safety and immunogenicity of the quadrivalent HPV vaccine in female Systemic Lupus Erythematosus patients aged 12 to 26 years. *Pediatr Rheumatol Online J*. 2013; 11: 29.
- 80 Mok CC, Ho LY, Fong LS, To CH. Immunogenicity and safety of a quadrivalent human papillomavirus vaccine in patients with systemic lupus erythematosus: a case-control study. *Ann Rheum Dis*. 2013; 72: 659-664.
- 81 Slade BA, Leidel L, Vellozzi C, et al. Postlicensure safety surveillance for quadrivalent human papillomavirus recombinant vaccine. *JAMA*. 2009; 302: 750-757.
- 82 van Assen S, Agmon-Levin N, Elkayam O, et al. EULAR recommendations for vaccination in adult patients with autoimmune inflammatory rheumatic diseases. *Ann Rheum Dis*. 2011; 70: 414-422.
- 83 Chakravarty EF, Colón I, Langen ES, et al. Factors that predict prematurity and preeclampsia in pregnancies that are complicated by systemic lupus erythematosus. *Am J Obstet Gynecol*. 2005; 192: 1897-1904.
- 84 Imbasciati E, Tincani A, Gregorini G, et al. Pregnancy in women with pre-existing lupus nephritis: predictors of fetal and maternal outcome. *Nephrol Dial Transplant*. 2009; 24: 519-525.
- 85 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: 678-683.
- 86 Ambrosi A, Wahren-Herlenius M. Congenital heart block: evidence for a pathogenic role of maternal autoantibodies. *Arthritis Res Ther*. 2012; 14: 208.
- 87 Danowski A, de Azevedo MNL, de Souza Papi JA, Petri M. Determinants of risk for venous and arterial thrombosis in primary antiphospholipid syndrome and in antiphospholipid syndrome with systemic lupus erythematosus. *J Rheumatol*. 2009; 36: 1195-1199.
- 88 Bramham K, Hunt BJ, Bewley S, et al. Pregnancy outcomes in systemic lupus erythematosus with and without previous nephritis. *J Rheumatol*. 2011; 38: 1906-1913.
- 89 Kwok LW, Tam LS, Zhu T, et al. Predictors of maternal and fetal outcomes in pregnancies of patients with systemic lupus erythematosus. *Lupus*. 2011; 20: 829-836.
- 90 Gíron-González JA, García del Río E, Rodríguez C, et al. Antiphospholipid syndrome and asymptomatic carriers of antiphospholipid antibody: prospective analysis of 404 individuals. *J Rheumatol*. 2004; 31: 1560-1567.
- 91 Stagnaro-Green A, Akhter E, Yim C, et al. Thyroid disease in pregnant women with systemic lupus erythematosus: increased preterm delivery. *Lupus*. 2011; 20: 690-699.