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EXTENDED REPORT

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

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ABSTRACT

Objectives Develop recommendations for women's health issues and family planning in systemic lupus erythematosus (SLE) and/or antiphospholipid syndrome (APS).

Methods Systematic review of evidence followed by modified Delphi method to compile questions, elicit expert opinions and reach consensus.

Results Family planning should be discussed as early as possible after diagnosis. Most women can have successful pregnancies and measures can be taken to reduce the risks of adverse maternal or fetal outcomes. Risk stratification includes disease activity, autoantibody profile, previous vascular and pregnancy morbidity, hypertension and the use of drugs (emphasis on benefits from hydroxychloroquine and antiplatelets/anticoagulants). Hormonal contraception and menopause replacement therapy can be used in patients with stable/inactive disease and low risk of thrombosis. Fertility preservation with gonadotropin-releasing hormone analogues should be considered prior to the use of alkylating agents. Assisted reproduction techniques can be safely used in patients with stable/inactive disease; patients with positive antiphospholipid antibodies/APS should receive anticoagulation and/or low-dose aspirin. Assessment of disease activity, renal function and serological markers is important for diagnosing disease flares and monitoring for obstetrical adverse outcomes. Fetal monitoring includes Doppler ultrasonography and fetal biometry, particularly in the third trimester, to screen for placental insufficiency and small for gestational age fetuses. Screening for gynaecological malignancies is similar to the general population, with increased vigilance for cervical premalignant lesions if exposed to immunosuppressive drugs. Human papillomavirus immunisation can be used in women with stable/inactive disease.

Conclusions Recommendations for women's health issues in SLE and/or APS were developed using an evidence-based approach followed by expert consensus.

INTRODUCTION

Systemic lupus erythematosus (SLE) and the antiphospholipid syndrome (APS), SLE-associated or primary APS, affect mostly women of childbearing age. Several 'unmet needs' in the management of reproductive and other women's health issues may impact on personal relationships and the decision to have children.[1] Because of earlier recognition of disease and advances in medical treatment, family planning has gained greater importance.[2–4] Concerns include the effect of pregnancy on maternal disease, the impact of disease activity on fetal health and the safety of medications during pregnancy and breast feeding. Assessment of fertility and feasibility of assisted reproduction techniques (ARTs), use of contraception, management of menopause and surveillance against malignancies need to be addressed. We gathered a multidisciplinary panel of experts to develop evidence-based recommendations on the management of family planning and women's health issues in SLE and/or APS.

METHODS

We followed the European League Against Rheumatism (EULAR) standardised operating procedures[5] and the Appraisal of Guidelines Research and Evaluation instrument. Through a Delphi-based approach, the committee selected 12 research questions further edited for systematic literature review (see online supplementary table S1). We searched PubMed using arrays of relevant terms; all English-language publications up to December 2014 were considered. A hand search was also performed in October 2015. Retrieved items were refined based on abstract, full-text content and number of included patients. A detailed presentation of the literature review is given in the online supplementary table S2. Evidence was categorised based on the design and validity of available studies and the strength of the statements was graded (see online supplementary table S3). After rounds of

Table 1 Recommendations for women's health and the management of family planning, assisted reproduction, pregnancy and menopause in patients with systemic lupus erythematosus (SLE) and/or antiphospholipid syndrome (APS)

Statement/recommendation	LoA	
	Mean (SD)	Median (IQR)
1. Preconception counselling and risk stratification 1.1 In women with **SLE**, major risk factors for adverse maternal and fetal outcomes include active/flaring SLE **(1/A)**, especially active nephritis **(1/A)**, history of lupus nephritis **(2/B)** and presence of aPL/APS* **(1/A)**. 1.1.1 Blood pressure monitoring **(2/B)**, use of safe medications to control disease activity (emphasis on HCQ **(2/B)**) and limiting glucocorticoids exposure **(2/B)** are essential measures. 1.2 In women with **APS (primary or SLE-APS)**, risk factors include high-risk aPL profile (lupus anticoagulant, multiple aPL, moderate to high titre aPL) **(1/A),** coexisting SLE **(2/B),** history of vascular/thrombotic APS **(2/B)** and of previous adverse pregnancy complications **(2/B)**. 1.2.1 Blood pressure monitoring **(3/C)** and use of antiplatelet and/or anticoagulant therapy (*rated at statement 9*) are of fundamental importance.	10 (0.2)	10 (0)
2. Contraceptive measures 2.1 Women with SLE should be counselled about the use of effective contraceptive measures (oral contraceptives, subcutaneous implants, IUD), based on their disease activity and thrombotic risk (particularly aPL status). IUD can be offered to all the patients with SLE and/or APS free of any gynaecological contraindication **(1/A)**. 2.2 In patients with stable/inactive SLE and negative aPL, combined hormonal contraceptives can be considered **(1/A)**. In women with positive aPL with or without definite APS, hormonal contraception (with progesterone only) must be carefully weighed against the risk of thrombosis **(2/B)**.	9.9 (0.4)	10 (0)
3. Risk factors for reduced fertility Women with SLE who wish to plan a pregnancy should be counselled about fertility issues, especially the adverse outcomes associated with increasing age and the use of alkylating agents **(1/A)**. Treatment with alkylating agents should be balanced against the risk of ovarian dysfunction.	9.8 (0.4)	10 (0)
4. Preservation of fertility Fertility preservation methods, especially GnRH analogues, should be considered for all menstruating women with SLE who are going to receive alkylating agents **(2/B).**	9.5 (0.7)	10 (1)
5. Assisted reproduction techniques 5.1 Assisted reproduction techniques, such as ovulation induction treatments and in vitro fertilisation protocols, can be safely used in patients with SLE with stable/inactive disease **(3/C)**. 5.2 Patients with positive aPL/APS should receive anticoagulation (at the dosage as would be recommended during pregnancy) and/or low-dose aspirin **(3/D)**.	9.6 (0.6)	10 (1)
6. Predictive biomarkers for maternal disease activity in SLE pregnancy In pregnant women with SLE, assessment of disease activity **(1/A)**—including renal function parameters **(2/B)** and serological markers (serum C3/C4, anti-dsDNA titres) **(2/B)**—is recommended to monitor for obstetrical adverse outcomes and disease flares.	9.9 (0.3)	10 (0)
7. Pregnancy monitoring 7.1 Women with SLE and/or APS should undergo supplementary fetal surveillance with Doppler ultrasonography and biometric parameters, particularly in the third trimester to screen for placental insufficiency and small for gestational age fetuses **(3/D)**. 7.2 Fetal echocardiography is recommended in cases of suspected fetal dysrhythmia or myocarditis, especially in patients with positive anti-Ro/SSA and/or anti-La/SSB antibodies **(2/C)**†.	9.7 (0.5)	10 (1)
8. Drugs for the prevention and management of SLE flares during pregnancy 8.1 HCQ **(1/B)**, oral glucocorticoids, azathioprine, ciclosporin A and tacrolimus **(all 3/C)** can be used to prevent or manage SLE flares during pregnancy. 8.2 Moderate-to-severe flares can be managed with additional strategies, including glucocorticoids intravenous pulse therapy, intravenous immunoglobulin and plasmapheresis **(all 3/C)**. 8.3 Mycophenolic acid, cyclophosphamide, leflunomide and methotrexate should be avoided.	9.7 (0.7)	10 (0)
9. Adjunct treatment during pregnancy 9.1 HCQ is recommended preconceptionally and throughout pregnancy for patients with SLE **(2/B)**. 9.2 Women with SLE at risk of pre-eclampsia (especially those with lupus nephritis or positive aPL) should receive LDA **(2/C).** In women with SLE-associated APS or primary APS, combination treatment with LDA and heparin is recommended to decrease the risk of adverse pregnancy outcomes **(1/A)**. 9.3 Supplementation with calcium, vitamin D and folic acid should be offered as in the general population **(–/D)**. Measuring blood vitamin D levels should be considered after pregnancy is confirmed **(–/D)**.	9.8 (0.4)	10 (0)
10. Menopause and HRT HRT can be used for the management of severe vasomotor menopausal manifestations in SLE women with stable/inactive disease and negative aPL **(1/A)**. The use of HRT in patients with positive aPL should be carefully weighed against the risk of thrombosis and cardiovascular disease **(–/D).**	9.6 (0.6)	10 (1)
11. Screening for malignancies Women with SLE and/or APS should undergo screening for malignancies similar to the general population **(–/D)**. Women with SLE, especially those exposed to immunosuppressive drugs, are at higher risk of cervical premalignant lesions and should be monitored with vigilance **(2/B)**.	9.8 (0.4)	10 (0)
12. HPV vaccination HPV immunisation can be considered in women with SLE and/or APS and stable/inactive disease **(3/D)**.	9.2 (1.6)	10 (1)

For each statement or item, the LoE (range 1–3) and the GoR (range A–D) is given in parentheses (refer to online supplementary table S1). In the right-hand columns, the LoA among experts is reported as mean (SD) and median (IQR) values. A score of 10 represents the highest level of agreement.
*aPL and APS are defined according to the updated international consensus criteria.[6] For aPL assays, please see the footnotes of table 2.
†The substatement on fetal echo in women with SLE/APS and positive anti-Ro/La is rated with LoE=2 (ie, sufficient evidence for the association between anti-Ro/La and congenital heart block) but GoR=C due to lack of strong evidence for the clinical implications of this association, namely for the efficacy of interventions.
anti-dsDNA, anti-double-stranded DNA antibodies; aPL, antiphospholipid antibodies; GnRH, gonadotropin-releasing hormone; GoR, grade of recommendation; HCQ, hydroxychloroquine; HPV, human papillomavirus; HRT, hormone replacement therapy; IUD, intrauterine devices; LDA, low-dose aspirin; LoA, level of agreement; LoE, level of evidence.

Table 2 Checklist of parameters to be considered for preconception counselling and risk stratification in women with systemic lupus erythematosus (SLE) and/or antiphospholipid syndrome (APS)

Disease-related risk factors	Prognostic implications
SLE activity/flares* (in the last 6–12 months or at conception)	Increased risk for (i) maternal disease activity (RR 2.1 for subsequent flare during pregnancy and puerperium);[14] (ii) hypertensive complications (OR 1.8 for PE);[15] (iii) fetal morbidity and mortality (OR 5.7 for pregnancy loss,[16] 3.5 for IUGR[17] 6.5 for preterm delivery)[14 15 17–22]
Lupus nephritis (history or active at conception†)	Strong predictor of poor maternal (RR 9.0 for renal flare during/after pregnancy)[23] and fetal outcome(s) (OR 7.3 for fetal loss and 18.9 for preterm delivery)[24 25]
Serological (serum C3/C4, anti-dsDNA titres) activity	Increased risk for maternal SLE flares during pregnancy (OR 5.3)[14] and pregnancy loss[23 26 27]
Previous adverse pregnancy outcome(s)	APS: increased risk for pregnancy complications[28–30]
History of vascular thrombosis	APS: increased risk (ORs ranging 3.6–12.7) for pregnancy morbidity[31]
SLE diagnosis	APS: increased risk (OR 6.9) for pregnancy morbidity[31 32]
aPL profile‡	SLE: strong predictor of adverse maternal and fetal outcomes,[19 25 27 33 34] especially for patients with persistent moderate-to-high aPL titres, LA and multiple aPL positivity (high-risk aPL profile) APS: high-risk aPL profile correlates with increased risk of maternal vascular thrombotic events during pregnancy (OR 12.1),[35] (pre-)eclampsia (OR 2.3),[36 37] APS-related pregnancy morbidity (OR 9.2),[31] IUGR (OR 4.7),[36] preterm birth[38 39]
Anti-Ro/SSA, anti-La/SSB antibodies	Linked to development of neonatal lupus, including a low risk (0.7–2%) for CHB (especially if moderate-to-high anti-Ro titres);[40–43] weak association with other pregnancy complications[44]
End-stage organ damage and associated comorbidities	[45 46]
General risk factors	[47]
Maternal age	
Arterial hypertension	Increased risk for pregnancy loss (OR 2.4,[33] RR 2.9),[48] preterm birth[18 24 27] and IUGR (OR 6.8)[15]
Diabetes mellitus	[49]
Overweight/obesity	
Thyroid disease	[50]
Nicotine and alcohol use	[28]
Immunisations§	

*Diagnosed by validated SLE activity indices and/or physician judgement.
†Evaluated by renal function tests (serum creatinine, blood urea nitrogen) and urinalysis (proteinuria urine sediment).
‡Includes LA, aCL IgG/IgM, aβ2GPI IgG/IgM. The level of positivity of aCL and aβ2GPI antibodies (low vs medium–high) should be defined according to the single assay's characteristics.
§If negative serology, evaluate whether immunisations can be performed prior to pregnancy (eg, rubella).
aCL, anticardiolipin antibodies; aβ2GPI, anti-β2-GPI antibodies; anti-dsDNA, anti-double-stranded DNA antibodies; aPL, antiphospholipid antibodies; CHB, congenital heart block; IUGR, intrauterine growth restriction; LA, lupus anticoagulant; PE, pre-eclampsia; RR, relative risk.

discussions, the committee arrived at 12 final statements (table 1). Each member rated her/his agreement with each statement.

RESULTS AND DISCUSSION

Scope and overarching principles

These recommendations have been devised with the intention of helping physicians involved in the care of patients with SLE and/or APS and facilitating physician–patient communication. They recognise an implicit need for change in the mindset of health professionals, shifting from *caution against* pregnancy towards *embracement* of pregnancy. Accordingly, family planning should be discussed from the first physician–patient encounter and reinforced thereafter. Health professionals should support the patient and her family in their decisions regarding family planning by discussing individual pregnancy risks. Reports on the long-term follow-up of SLE and/or APS offspring are few,[7–10] showing a reassuring picture on the health conditions of the children, with the exception of some cases of neurodevelopmental alterations[11–13] that need further confirmation before they are linked to maternal disease.

Recommendations

Preconception counselling and risk stratification

Assessment of risk factors for adverse maternal and fetal outcomes in pregnant women with SLE and/or APS is crucial for preconception counselling and implementing appropriate preventive strategies and patient-tailored monitoring plan before and during pregnancy (table 2).

In SLE women (with or without APS), prematurity, pre-eclampsia and eclampsia/Hemolysis, Elevated Liver enzyme levels, Low Platelet count (HELLP) rates approximate 25–35%, 10–15% and 1.0–1.5%, respectively.[19 24 25 44 51 52] In APS women (primary or SLE-related), the respective frequencies approximate 25–35%, 10–20% and 3.0–5.0%.[28 29 53 54]

During pregnancy, risk factors associated with adverse outcomes include active/flaring SLE (OR 12.7 for pre-eclampsia/eclampsia;[55] 19.0 for emergency caesarean section;[56] 3.0 for early fetal loss;[20] 5.5 for preterm delivery),[21 19] active nephritis (OR 5.3 for any adverse maternal outcome),[57] hypertension (OR 4.8–7.3 for pre-eclampsia;[52] relative risk (RR) 1.8 for preterm birth)[22] and use of glucocorticoids, especially at maintenance dose ≥10–20 mg/day of prednisone equivalent (OR 3.5 for preterm birth).[58 59] Discontinuation of hydroxychloroquine (HCQ) is related to an increased risk for SLE exacerbations during pregnancy,[24 33 56] and a single placebo-controlled study has suggested a beneficial effect of HCQ on maternal disease activity during pregnancy.[60]

Contraceptive measures

Women with SLE and/or APS should be counselled about contraception, especially for the prevention of unwanted pregnancies during high disease activity periods and intake of teratogenic drugs. Effective contraceptive measures should be

discussed with the patient by weighing the individual risk factors, including general (hypertension, obesity, tobacco use, family history of hormonal-dependent cancers)[61] and disease-related risk factors, particularly disease activity and thrombotic risk (emphasis on antiphospholipid antibodies (aPLs)).

The intrauterine device (IUD) can be offered to all patients unless there is a gynaecological contraindication. Copper IUD can be used in any patient, while levonorgestrel-containing IUD should be considered only if the benefits of the released hormone (such as the reduction of excessive menstrual bleeding due to anticoagulation)[62] outweigh the risk of thrombosis.[61]

The safety of the combined (oestrogen plus progestin) and progestin-only pill in SLE patients with inactive or stable active SLE and negative aPL has been demonstrated in randomised controlled trials (RCTs).[63 64] In women with *positive aPL* (*with or without definite APS*), contraception with combined hormones (oral pill, vaginal ring, transdermal patch) should be discouraged. In young women with myocardial infarction or ischaemic stroke and positive lupus anticoagulant, the use of the combined pill increased the risk of arterial events compared with non-users.[65] In fully anticoagulated patients carrying a low-risk aPL profile, oestrogens might be considered for persistent gynaecological disorders not otherwise managed. Compounds containing progestin only (pill, subcutaneous depot injections) are suitable for these women, although their use should be weighed against the risk of thrombosis. Progestin-only emergency contraception is not contraindicated in patients with SLE and/or APS.

Risk factors for reduced fertility

Few studies have assessed fertility in women with SLE and/or APS by means of hormonal levels (including the anti-Müllerian hormone) or antral follicle count (examined by ultrasound). There is no concrete evidence that the disease *per se* decreases fertility.[66–69]

However, active disease, especially lupus nephritis, and the use of immunosuppressive drugs may negatively impact on fertility. Alkylating agents such as cyclophosphamide (CYC) may cause menstrual irregularities and premature ovarian failure (POF), which is age- and dosage dependent.[70 71]

Similar to the general population, women with SLE and/or APS should be counselled on fertility issues, especially on the negative impact of increasing age (general tendency to postpone childbearing) and certain lifestyle exposures (tobacco use, alcohol consumption). In non-life-threatening disease, treatment with alkylating agents should be balanced against the risk of ovarian dysfunction; rather, less gonadotoxic regimens should be considered.[72] In the presence of multiple risk factors for impaired fertility, ovarian reserve may be assessed in patients with SLE at a younger age than recommended for the general population.[73]

Fertility preservation

Limited data are available on fertility preservation methods in menstruating women with SLE who require treatment with alkylating agents. Cryopreservation of ovarian tissue or oocytes/embryos are poorly investigated options[74 75] and require specialised centres, which may not be easily accessible.

The most extensively studied method for POF prevention in patients with SLE involves gonadotropin-releasing hormone analogues (GnRH-a), with a good safety and efficacy profile (RR 0.12).[76] GnRH-a have been efficacious in patients with cancer.[77 78] GnRH-a are likely to protect against POF, but there are no data on subsequent pregnancies in patients with SLE. They can cause menopause-like symptoms, which are fully reversible upon discontinuation. A study in childhood-onset patients with SLE aged <21 years suggested that GnRH-a should be administered 22 days before CYC is started or continued.[79] It is nevertheless recommended to start the GnRH-a prior to or concomitantly to initiation of the alkylating agent.

Assisted reproduction techniques

Evidence on the efficacy and safety of ARTs (ovulation induction therapy and in vitro fertilisation) in women with SLE and/or APS comes from observational studies.[80–83] Efficacy in terms of pregnancy rate is comparable with that in the general population (up to 30%). ARTs are generally safe if the patient has quiescent disease and is on appropriate antithrombotic treatment if aPL positive. Although it is challenging to define a single protocol, some general measures for prophylaxis in aPL-positive women undergoing ovarian stimulation can be suggested. The type (low-dose aspirin (LDA); low molecular weight heparin (LMWH)) and dosage (prophylactic vs full anticoagulant) of antithrombotic treatment should be recommended as during pregnancy according to the individual risk profile. LDA should be stopped three days before egg retrieval and resumed the following day. Patients taking LMWH should stop it at least 12 hours prior to the procedure and resume it the very same day as long as there is no bleeding. Patients with positive aPL who are not taking LDA during the ovarian stimulation period should start LDA on the day of the embryo transfer, usually in combination with LMWH (which will be continued during pregnancy).

Ovarian hyperstimulation syndrome can be avoided by milder hormonal stimulation or GnRH antagonist protocol.[84] The use of the 'natural cycle' method is another option, although associated with a lower rate of induced pregnancy. The ART induction protocol should be tailored to the individual patient, balancing the safety and effectiveness of the procedure.

Predictive biomarkers for maternal disease activity in SLE pregnancy

Active SLE during pregnancy, assessed by validated disease activity indices[22 56] and/or physician global assessment,[20] is associated with increased risk for maternal and/or fetal complications (*see also paragraph on Preconception counselling and risk stratification*). Pregnancy-specific SLE activity indices have been developed and validated for their sensitivity in detecting changes in disease activity and diagnosing flares (see online supplementary table S4).[85 86] Physicians should be aware of pregnancy physiological changes that can resemble SLE symptoms and signs.[87] Renal activity correlates with adverse pregnancy outcomes and should be monitored by means of urine protein excretion, urine sediment analysis (glomerular haematuria, urinary casts) and serum creatinine level/glomerular filtration rate.[33 49 52] Serological markers are useful in monitoring SLE activity and in the differentiation between disease exacerbation (declining serum C3/C4 levels (even within the normal range) and/or increasing anti-double stranded DNA titres) and pre-eclampsia.[88 89] Smaller increases in serum C3 levels from pregnancy onset to the second or third trimester[19] as well as serological activity (as defined above) that develops during pregnancy, especially in the context of clinical SLE activity, have been associated with increased risk for pregnancy loss,[19 90] intrauterine growth restriction (IUGR)[91] and preterm birth.[19 48 89 90 92]

Box 1 Ultrasonographic fetal surveillance recommended for pregnant women with systemic lupus erythematosus and/or antiphospholipid syndrome[43 45–48]

- Routine ultrasonographic screening
  - First trimester (11–14 weeks of gestation).
  - Second trimester (with Doppler, preferably at 20–24 weeks of gestation).
- Supplementary fetal surveillance in the third trimester at monthly intervals
  - Doppler sonography of the umbilical artery, uterine arteries, ductus venosus and middle cerebral artery (particularly in fetuses that have been identified to suffer from early intrauterine growth restriction (IUGR), ie, prior to 34 weeks of gestation).
  - In cases of late IUGR (diagnosed after 34 weeks), reduced abdominal circumference growth velocity and/or a reduced cerebroplacental ratio at Doppler investigation was shown to identify fetuses at higher risk of poor perinatal outcome (Doppler of the umbilical artery alone is insufficient).

Pregnancy monitoring

Pregnant women with SLE and/or APS should follow the local protocols applied to pregnancies at high risk for hypertensive disorders and/or placental insufficiency, adjusting the frequency and modality of fetal surveillance according to the maternal and/or fetal status (box 1). Fetal surveillance based on biometric and Doppler findings during the third trimester, and particularly the distinction between early and late IUGR, helps to better tailor the time of delivery and reduce perinatal morbidity and mortality.[93–97] Umbilical and uterine arteries Doppler sonography at 20–24 weeks has good negative predictive value but modest positive predictive value (especially in the absence of biometric signs of fetal growth restriction later in pregnancy) for placental-associated pregnancy disorders such as pre-eclampsia and IUGR. The mode (vaginal vs caesarean section) and timing of delivery are influenced by maternal (hypertensive disorders, anticoagulation status) as well as fetal conditions during pregnancy.

Fetal echocardiography is indicated if there is suspected fetal dysrhythmia or myocarditis, especially in the context of positive maternal anti-Ro/SSA or anti-La/SSB antibodies. Other tests (electrocardiogram plus Holter monitor, magnetocardiography, gated-pulsed Doppler technique, velocity-based fetal kinetocardiogram) might detect subtle signs of the development of congenital heart block (CHB), but are not currently recommended as standard practice.[98] CHB associated with anti-Ro/SSA and/or anti-La/SSB has 16% recurrence rate in women with a previously affected child; therefore, it is recommended to perform serial fetal echocardiograms weekly from 16 weeks of gestation onwards.[98] Considering the low risk (0.7–2%) for CHB in women with no previous CHB, it is unclear whether intensive monitoring (weekly/biweekly between 16 and 26 weeks of gestation and less frequently afterwards)[98] in the general population of anti-Ro/La-positive women is cost-effective. Moreover, there is no proven efficacy of protocols for the prevention or treatment of complete CHB.[99 100] The efficacy of maternal fluorinated steroids has not been established in large cohorts[101–104] despite initial reports of favourable effects in cases of incomplete CHB, cardiomyopathy, endocardial fibroelastosis and hydrops fetalis.[99] Given the potential of fluorinated steroids for major maternal and fetal side effects, the benefit for fetuses with CHB should be stratified according to the presence of risk factors for adverse outcome.[99] Despite its unproven benefit, the current practice of intensive surveillance for CHB onset in women with positive anti-Ro/SSA and/or anti-La/SSB antibodies and no previous child affected by CHB carries no risk and is well accepted by the mothers.[105]

Drugs for prevention and management of SLE flares during pregnancy

A single randomised, placebo-controlled study[60] as well as non-randomised evidence[24 33 56] supports the beneficial role of HCQ in controlling disease activity and preventing flare-ups during pregnancy. Uncontrolled studies suggest an acceptable benefit/risk ratio of oral glucocorticoids,[22 106] azathioprine[59 107] and calcineurin inhibitors (ciclosporin A, tacrolimus)[108 109] in controlling SLE activity during pregnancy. In moderate-to-severe flares, additional modalities can be considered, such as high-dose glucocorticoids (including pulse intravenous therapy),[110 111] intravenous immunoglobulin[20 22] and plasmapheresis (may be also used in refractory nephrotic syndrome).[112 113] CYC should not be administered during the first trimester of pregnancy due to risk for fetal loss (OR 25.5)[20 114] and should be reserved only for the management of severe, life-threatening or refractory SLE manifestations during the second or third trimester. Available data are not sufficient to evaluate the risk of using belimumab in pregnancy[115] and the drug should not be used unless the benefit outweighs the risk to the fetus. Mycophenolic acid, methotrexate and leflunomide should be avoided due to known or possible teratogenicity.[116] To this end, collaborative groups have developed recommendations for the use of antirheumatic drugs before and during pregnancy and lactation.[111 117 118]

Adjunct treatment during pregnancy

Use of HCQ is recommended in women with SLE preconceptionally and throughout pregnancy.[33 56 60] A beneficial role has also been suggested for APS pregnancies,[119–121] but at present there is insufficient data to recommend its routine use in these patients. HCQ may reduce the odds of CHB occurrence in fetuses exposed to maternal anti-Ro/SSA antibodies, especially in mothers who already had a child with CHB.[40 122]

The protective role of LDA against preterm and severe pre-eclampsia has been established in non-autoimmune patients.[123 124] Accordingly, women with SLE at higher risk of pre-eclampsia including those with lupus nephritis or positive aPL will benefit from LDA, preferably given preconceptionally or no later than gestational week 16.[123 124]

In women with definite obstetric APS, combination treatment with LDA and heparin is recommended to decrease the risk of adverse pregnancy outcomes.[16 125–127] Statistically significant results have been demonstrated only for unfractionated heparin in RCTs. However, LMWH is preferable for practical reasons and has shown comparable efficacy in prospective studies.[128 129] Moreover, patients with positive aPL but with no definite classification of APS will benefit from combination therapy if they are considered at moderate to high risk of maternal and fetal complications (see online supplementary table S5).

In addition, other regimens such as prednisolone 10 mg/day in the first trimester, intravenous immunoglobulin or plasmapheresis can be considered for selected patients with APS (refractory obstetric APS, women with previous thrombosis, particularly previous or new cerebrovascular events, women with triple aPL positivity).[119 130–133]

Box 2 Points to consider and research agenda

- Reproductive issues are of paramount importance for women with systemic lupus erythematosus (SLE) and/or antiphospholipid syndrome (APS) and should be addressed on a regular basis by healthcare providers.
- Preconception counselling and risk stratification are essential for prevention of unwanted complications during pregnancy.
- The use of hormonal contraception or replacement therapy is feasible but must be weighed against the individual risk of thrombosis.
- The preservation of fertility should be mentioned while counselling about lifestyles and considered in the treatment choice. Validated protocols for assisted reproduction techniques in patients with SLE and/or APS are needed.
- Predictive biomarkers for maternal disease activity during SLE pregnancy should be expanded with particular focus on the prediction of pre-eclampsia.
- Pregnancy monitoring in SLE and/or APS women should aim at the identification of placental insufficiency with fetal growth restriction in order to decide the best timing for delivery and reduce the risk of perinatal morbidity and mortality.
- The cost-effectiveness of intensive surveillance with fetal echocardiography in patients with positive anti-Ro/SSA and anti-La/SSB antibodies and no previous child with congenital heart block remains to be established.
- Hydroxychloroquine is beneficial during pregnancy to reduce the risk of SLE flares and of poor obstetrical outcomes. More data are needed to support its benefit in APS pregnancies.
- The benefits of cancer surveillance and prevention of gynaecological malignancies need to be communicated to patients.

As recommended in the general population, supplementation with calcium, vitamin D and folic acid should be offered to patients with SLE and/or APS, with particular consideration to those with low circulating levels of 25-OH vitamin D in the first trimester of gestation and receiving glucocorticoids and/or heparin for their detrimental effects on bone mass.

Menopause and hormone replacement therapy

The efficacy and safety of hormone replacement therapy (HRT) (oestrogen plus progestin) in selected patients with SLE has been illustrated in RCTs.[134–136] Benefit was demonstrated mainly in vasomotor and other hypoestrogenism symptoms. No significantly increased risk of severe lupus exacerbations during 12–24 months of HRT was found, although there was a modest increase in mild-to-moderate flares.[132] There was no increased risk of thrombosis and cardiovascular events, although one of the RCTs included only patients with negative aPL and no previous cardiovascular events[132] and another did not detail the aPL profile.[63] Two cohort studies with long-term follow-up did not report significantly increased risk of cardiovascular events during HRT,[137 138] although limitations in power and design preclude firm conclusions. Consequently, HRT should be reserved for the management of severe and disabling vasomotor menopausal symptoms, preferably in SLE women with stable/inactive disease and negative aPL. In patients with positive aPL, the use of HRT should be carefully weighed against thrombotic and cardiovascular risks. If menopause symptoms necessitate HRT, it seems reasonable to start it as early as possible to gain an added benefit for bone protection.[139] Optimal duration of HRT in patients with SLE and/or APS is not known, but it seems reasonable to recommend it for the shortest possible duration.[140 141]

Screening for malignancies

Women with SLE are not at increased risk of breast, ovarian and endometrial cancer compared with the general population,[142 143] and, therefore, should follow the current population screening protocols for these malignancies. Conversely, women with SLE are at higher risk of cervical dysplasia (but not cervical cancer),[144–147] vagina and vulva cancers,[142 147] likely associated with human papillomavirus (HPV) infection. Women with SLE exposed to immunosuppressive drugs, particularly CYC in a cumulative dose-dependent fashion, are at higher risk of cervical dysplasia.[148–151] The suggested timing for Papanicolaou (PAP) smear examination would be once a year in heavily immunosuppressed patients or according to the local screening programme in low-risk patients. Subgroups of women with SLE (Caucasian, younger age, lower education, high SLE damage) may be at risk for poorer adherence to screening programmes.[152 153]

HPV vaccination

HPV vaccination is currently offered to female and male adolescents for preventing precancerous growths and cancer in the cervix and in the genital area. There are reports of venous thromboembolic events (VTEs) associated with the quadrivalent HPV vaccine. However, of the 31 cases (0.2/100 000 doses vaccine) with documented VTE, 90% had a known risk factor for VTE (APS in two cases).[154]

Prospective studies have demonstrated efficacy and safety of HPV vaccination in patients with SLE,[155 156] although seroconversion rates may be lower in patients receiving steroids and immunosuppressive agents. A few cases of severe SLE flares or abrupt SLE onset after HPV vaccination have been reported.[157–159] In accordance with the EULAR recommendations,[160] we recommend that HPV vaccination be offered to young women with stable/inactive SLE and/or APS, according to local protocols, with particular caution in those with high-risk aPL profile.

The points to consider and the research agenda suggested by the Task Force Members are reported in box 2.

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Women's health in lupus and APS

This is the lay version of the EULAR recommendations for the management of women's health and family planning in women with lupus and/or antiphospholipid syndrome. The original publication details the recommendations on use of medications, clinical focus points and treatment options. It can be downloaded from the EULAR website: www.eular.org.

Andreoli L, 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 2017;76:476–485. doi:10.1136/annrheumdis-2016-209770

Introduction

Recommendations give advice to doctors and patients about the best way to treat and manage diseases. EULAR has written recommendations on family planning, pregnancy and menopause for women who have systemic lupus erythematosus (also called lupus or SLE) and/or antiphospholipid syndrome (often shortened to APS).

The recommendations were written by a multidisciplinary team of medical specialties, other healthcare providers and patient representatives. They looked at the scientific evidence on the management of people with lupus and/or APS. They also discussed their expert opinion to achieve a level of agreement.

What do we already know?

Lupus is an autoimmune disease that can affect the joints, skin and internal organs. Lupus is often linked to APS, which is characterised by increased levels of antiphospholipid antibodies in the blood. People with antiphospholipid antibodies have a higher than normal risk of getting blood clots and pregnancy losses.

Women with lupus or APS are often diagnosed during their childbearing years. The disease can have an effect on a woman's ability to get pregnant and her chances of miscarriage. Lupus and some of the medications used for treatment increase the risk of complications during pregnancy, both for the mother and the baby.

What do the recommendations say?

Overall, there are 12 main statements or recommendations. These recommendations recognise an important need for doctors to move away from undue caution against pregnancy for women with lupus, and instead to embrace pregnancy and help their patients to have children if they want them, provided that the individual risks for each patient are discussed. The recommendations aim to help you to manage your fertility, family planning and menopause. Each recommendation is based on available scientific evidence or expert opinion. The more stars a recommendation has the stronger the evidence is.

One star (*) means it is a weak recommendation with limited scientific evidence.

Two stars (**) means it is a weak recommendation with some scientific evidence.

Three stars (***) means it is a strong recommendation with some scientific evidence.

Four stars (****) means it is a strong recommendation with a lot of scientific evidence.

- **Women should receive counselling and advice before they decide to have a baby.******
  Very severe or flaring lupus, or having APS can have very serious consequences for a pregnant woman and her baby. This should be discussed before a woman decides to have a baby. Each woman's risks, such as her type of lupus and her individual treatment regime, should be assessed to help develop the best strategy for a safe pregnancy.

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- **Women with lupus should be counselled about the use of effective contraception.******
  Your doctor should talk to you about your contraceptive options, including the pill, a coil, or an implant. Using contraceptives is especially important to prevent unwanted pregnancies when your disease is very active or when you are taking drugs that could be dangerous for a foetus. A combined pill may not be suitable if you have APS, or if your doctor thinks you are at high risk of developing blood clots. In such cases, the progesterone-only pill and a coil may be suitable options.

- **Women should receive counselling about fertility.*****
  If you wish to have a baby, either now or in the future, you should discuss general and disease-related risk factors with your doctor. Your lupus (especially lupus nephritis), your age, the drugs you take for your lupus, certain lifestyle exposures (such as tobacco use or alcohol consumption) may affect your ability to get pregnant. There may be lifestyle changes you can make to improve your fertility, such as limiting how much alcohol you drink, or stopping smoking.

- **There are methods available to preserve fertility.****
  Drugs called alkylating agents (for example, cyclophosphamide) can affect your fertility. If your doctor prescribes you an alkylating agent, he/she should also consider fertility preservation methods or drugs if you are still getting your period and might want to have a baby in the future.

- **IVF and treatments to induce ovulation can be used in women with Lupus.***
  As long as your lupus is stable or inactive, you can have *in vitro* fertilization (IVF) or treatments to help make you ovulate. If you have APS you might need to take medicines to prevent you getting blood clots, such as anticoagulation medications or low-dose aspirin.

- **Women with lupus should be closely monitored during pregnancy.******
  While you are pregnant, your doctor should assess your disease activity. This might include testing your kidney function or blood tests to check your antibody levels.

- **The babies of women with lupus or APS should be closely monitored during pregnancy.***
  You may need to have more ultrasound scans than normal during your pregnancy to monitor the baby's development. This is especially important during your third trimester, to make sure that your baby is the right size, and that your placenta is working properly.

- **Women with lupus can take some anti-lupus drugs during pregnancy.*****
  Drugs such as hydroxychloroquine, oral glucocorticoids, azathioprine, ciclosporin A and tacrolimus can be used to prevent or manage flares of your lupus while you are pregnant. Other strategies such as glucocorticoid intravenous pulse therapy, intravenous immunoglobulin and plasmapheresis can be used to manage moderate-to-severe flares. Mycophenolic acid, cyclophosphamide, leflunomide and methotrexate should be avoided because of their potential to cause malformations.

- **Other drugs may be needed to limit risks during pregnancy.******
  Women with lupus who are at risk of pre-eclampsia (especially those with disease that affects their kidneys, or who have tested positive for antiphospholipid antibodies) should receive low-dose aspirin. If you have APS you may need combination treatment with low-dose aspirin and heparin. Consider taking folic acid supplements when you plan to become pregnant or when you find out that you are pregnant. Check your vitamin D levels during the first trimester and discuss adequate vitamin D and calcium supplementation with your doctor.

- **Women with lupus may need hormone replacement therapy when they reach the menopause.******
  Hormone replacement therapy (HRT) may be helpful when you reach the menopause and if you have severe symptoms that negatively impact on your quality of life. If you have antiphospholipid antibodies

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in your blood, discuss with your doctor the benefits of HRT against the risk of you getting blood clots or heart disease.

- **Women with lupus or APS should be screened for female cancers.*****
  If you have lupus, you may have a higher than normal risk of cervical premalignant lesions. You should attend all screening appointments. Your doctor may recommend a more intensive schedule if you are taking immunosuppressive drugs. Regarding breast, ovarian and endometrial malignancy, women with SLE and/or APS should undergo screening similar to the general population.

- **Women with lupus can have the HPV vaccination.***
  The HPV vaccine protects you against Human Papilloma Virus, a sexually transmitted infection which is linked to women developing cervical cancer. If you have lupus and/or APS that is stable or inactive, you can receive the HPV vaccine as normal (according to local health policies).

Summary

Overall, the recommendations say that it is important for you and your doctor to work together to help you manage your fertility, family planning and menopause. If you have lupus and/or APS these recommendations will give you tips about what to expect from your doctor throughout your life and your pregnancies.

Recommendations with just 1 or 2 stars, which are based mainly on expert opinion and not backed up by appropriate clinical studies, may be as important as those with 3 and 4 stars.

If you have any questions or concerns about your disease or your medication, you should speak to your doctor.

Further reading

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