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


INTRODUCTION
Systemic lupus erythematosus (SLE) and the antiphospholipid syndrome (APS) are autoimmune diseases that can affect various systems, including the reproductive system. Women with these conditions may face unique challenges related to family planning, assisted reproduction, pregnancy, and menopause. This study aimed to develop evidence-based recommendations to address these issues.

METHODS
The European League Against Rheumatism (EULAR) standardised operating procedures for developing guidelines and the Appraisal of Guidelines Research and Evaluation instrument were used. A Delphi-based approach was employed, with the committee selecting 12 research questions to be addressed. A systematic review of the literature was conducted, and recommendations were made based on evidence from multiple sources.

RESULTS
The EULAR committee made recommendations on family planning, assisted reproduction, pregnancy, and menopause in women with SLE and/or APS. These recommendations included considerations for fertility, contraception, anticoagulation, and the safety of medications during pregnancy. The committee aimed to provide guidance to healthcare professionals and patients.

Conclusions
The EULAR recommendations were developed using an evidence-based approach and are intended to support both healthcare providers and patients in making informed decisions regarding family planning, assisted reproduction, pregnancy, and menopause.
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).

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.

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).

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).

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 titre) (2/B)—is recommended to monitor for obstetrical adverse outcomes and disease flares.

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-LaSS8 antibodies (2/C).

8. Drugs for the prevention and management of SLE flares during pregnancy
8.1 HCQ (1/B), oral glucocorticoids, azathioprine, cyclosporin 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. 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 (1/D). Measuring blood vitamin D levels should be considered after pregnancy is confirmed (2/D).

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 (2/D).

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).

12. HPV vaccination
HPV immunisation can be considered in women with SLE and/or APS and stable/inactive disease (3/D).

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.†For aPL assays, please see the footnotes of table 2.

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)

<table>
<thead>
<tr>
<th>Statement/recommendation</th>
<th>LoA</th>
<th>Mean (SD)</th>
<th>Median (IQR)</th>
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<tbody>
<tr>
<td>1. Preconception counselling and risk stratification</td>
<td></td>
<td>10 (0.2)</td>
<td>10 (0)</td>
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<tr>
<td>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)</td>
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<tr>
<td>1.1.1 Blood pressure monitoring (2/B), use of salicylates to control disease activity (emphasis on HCQ (2/B)] and limiting glucocorticoids exposure (2/B) are essential measures.</td>
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<td>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).</td>
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<tr>
<td>1.2.1 Blood pressure monitoring (3/C) and use of antplatelet and/or anticoagulant therapy (rated at statement 9) are of fundamental importance.</td>
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<tr>
<td>2. Risk factors for reduced fertility</td>
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<td>9.9 (0.4)</td>
<td>10 (0)</td>
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<td>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).</td>
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<td>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).</td>
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</table>
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)

<table>
<thead>
<tr>
<th>Disease-related risk factors</th>
<th>Prognostic implications</th>
</tr>
</thead>
<tbody>
<tr>
<td>SLE activity/flares* (in the last 6–12 months or at conception)</td>
<td>Increased risk for (i) maternal disease activity (RR 2.1 for subsequent flare during pregnancy and puerperium); (ii) hypertensive complications (OR 1.8 for PE); (iii) fetal mortality and morbidity (OR 5.7 for pregnancy loss, 3.5 for IUGR 15.6.5 for preterm delivery)</td>
</tr>
<tr>
<td>Lupus nephritis (history or active at conception)</td>
<td>Strong predictor of poor maternal (RR 9.0 for renal flare during/after pregnancy) and fetal outcome(s) (OR 7.3 for fetal loss and 18.9 for preterm delivery)</td>
</tr>
<tr>
<td>Serological (serum C3/C4, anti-dsDNA titres) activity</td>
<td>Increased risk for maternal SLE flares during pregnancy (OR 5.3) and pregnancy loss</td>
</tr>
<tr>
<td>Previous adverse pregnancy outcome(s)</td>
<td>APS: increased risk for pregnancy complications</td>
</tr>
<tr>
<td>History of vascular thrombosis</td>
<td>APS: increased risk (ORs ranging 3.6–12.7) for pregnancy morbidity</td>
</tr>
<tr>
<td>SLE diagnosis</td>
<td>APS: increased risk (OR 6.9) for pregnancy morbidity</td>
</tr>
<tr>
<td>aPL profile</td>
<td>SLE: strong predictor of adverse maternal and fetal outcomes, especially for patients with persistent moderate-to-high aPL titres, LA and multiple aPL positivity (high-risk aPL profile)</td>
</tr>
<tr>
<td>Anti-Ro(SSA), anti-La(SSB) antibodies</td>
<td>Linked to development of neonatal lupus, including a low risk (0.7–2%) for CHB (especially if moderate-to-high anti-Ro titres), weak association with other pregnancy complications</td>
</tr>
</tbody>
</table>

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, RR 2.9), preterm birth (OR 2.4 27), and IUGR (OR 6.8) |
| Diabetes mellitus | 49 |
| Overweight/obesity | 50 |
| 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, a2GPI IgG/IgM. The level of positivity of aCL and a2GPI 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).
αCL, antiphospholipid antibodies; a2GPI, 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.

**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

**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. In APS women (primary or SLE-related), the respective frequencies approximate 25–35%, 10–20% and 3.0–5.0%, and a single placebo-controlled study has suggested a beneficial effect of HCQ on maternal disease activity during pregnancy.60

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

**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, showing a reassuring picture on the health conditions of the children, with the exception of some cases of neurodevelopmental alterations that need further confirmation before they are linked to maternal disease.
discussed with the patient by weighing the individual risk factors, including general (hypertension, obesity, tobacco use, family history of hormonal-dependent cancers) 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 gynecological 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) outweigh the risk of thrombosis.

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). 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. 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.

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.

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 childbirth) and certain lifestyle exposures (tobacco use, alcohol consumption). In non-life-threatening disease, treatment with alkylating agents should be balanced against the risk of infertility. Alkylating agents such as cyclophosphamide (CYC) may cause menstrual irregularities and premature ovarian failure (POF), which is age- and dosage dependent.

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 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). GnRH-a have been efficacious in patients with cancer. 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. 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. 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. 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 and/or physician global assessment, 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). Physicians should be aware of pregnancy physiological changes that can resemble SLE symptoms and signs. 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. 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. Smaller increases in serum C3 levels from pregnancy onset to the second or third trimester 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 and/or intrauterine growth restriction (IUGR) and preterm birth.
Recommendations

Box 1 Ultrasonographic fetal surveillance recommended for pregnant women with systemic lupus erythematosus and/or antiphospholipid syndrome

- 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. 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. 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.

Considering the low risk (0.7–2%) for the congenital heart block, but are not currently recommended as standard practice. 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.

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Despite initial reports of favourable effects in cases of incomplete CHB, cardiomyopathy, endocardial fibroelastosis and hydrops fetalis, 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. 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.

Drugs for prevention and management of SLE flares during pregnancy

A single randomised, placebo-controlled study as well as non-randomised evidence 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, azathioprine and calcineurin inhibitors (ciclosporin A, tacrolimus) 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), intravenous immunoglobulin and plasmapheresis (may be also used in refractory nephrotic syndrome). CYC should not be administered during the first trimester of pregnancy due to risk for fetal loss (OR 2.5) 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 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. To this end, collaborative groups have developed recommendations for the use of antirheumatic drugs before and during pregnancy and lactation.

Adjunct treatment during pregnancy

Use of HCQ is recommended in women with SLE preconceptionally and throughout pregnancy. A beneficial role has also been suggested for APS pregnancies, 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.

The protective role of LDA against preterm and severe pre-eclampsia has been established in non-autoimmune patients. 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.

In women with definite obstetric APS, combination treatment with LDA and heparin is recommended to decrease the risk of adverse pregnancy outcomes. 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. 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 S3).

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).
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. 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.

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.

HRT, it seems reasonable to start it as early as possible to gain an added benefit for bone protection. 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.

Screening for malignancies

Women with SLE are not at increased risk of breast, ovarian and endometrial cancer compared with the general population, 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), 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. 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.

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).

Prospective studies have demonstrated efficacy and safety of HPV vaccination in patients with SLE, 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. In accordance with the EULAR recommendations, 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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