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Management of Rheumatic Diseases During Pregnancy and Breastfeeding

Position Paper of the Working Group for Obstetrics and Prenatal Medicine in the German Society for Gynecology and Obstetrics e. V. (AGG – Section Maternal Diseases in Pregnancy)

Management von rheumatischen Erkrankungen in Schwangerschaft und Stillzeit

Positionspapier der Arbeitsgemeinschaft für Geburtshilfe und Pränatalmedizin in der Deutschen Gesellschaft für Gynäkologie und Geburtshilfe e. V. (AGG – Sektion Maternale Erkrankungen in der Schwangerschaft)

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Schlüsselwörter

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ABSTRACT

Purpose These recommendations issued by the AGG (Section Maternal Diseases in Pregnancy) were developed as a rapid orientation on maternal rheumatic diseases for counselling and disease management in pregnancy and breastfeeding.

Methods The standard literature, consensus and position papers, guidelines and recommendations by other specialist associations were evaluated by a task force of the Section and summarized in these recommendations following a joint consensus process.

Recommendations This paper provides an orientating overview of the physiology, pathophysiology and definitions of rheumatic diseases which is relevant for gynecologists and obstetricians. The recommendations focus on the maternal, fetal and neonatal diagnostic workup in cases with underlying maternal rheumatic disease.

ZUSAMMENFASSUNG

Zielsetzung Diese Empfehlungen der AGG (Sektion maternale Erkrankungen in der Schwangerschaft) sollen bei maternalen rheumatischen Erkrankungen eine schnelle Orientierung für Beratung und Management in Schwangerschaft und Stillzeit geben.

Methoden Die gängige Literatur, Konsensus- und Positionspapiere, Leitlinien und Empfehlungen anderer Fachgesellschaften wurden durch eine Arbeitsgruppe der Sektion bewertet und nach gemeinsamer Konsensusfindung in diese Empfehlungen gefasst.

Empfehlungen Das Manuskript gibt einen orientierenden Einblick in Physiologie, Pathophysiologie und Definitionen rheumatischer Erkrankungen, die für den Gynäkologen und Geburtshelfer relevant sein können. Die Empfehlungen beziehen sich auf mütterliche, fetale und neonatologische Diagnostik bei Vorliegen maternaler rheumatischer Grunderkrankungen.

1 Introduction

Anti-cellular autoantibodies (directed against human cell membranes, cellular and/or nuclear structures) may be circulating in the body years (!) before there is any clinical diagnosis of an autoimmune disease [1]. They can occur in the context of pathologies such as systemic lupus erythematosus (SLE), Sjögren's syndrome, systemic sclerosis, dermatomyositis and rheumatoid arthritis. Antiphospholipid antibodies (aPL) may appear as a secondary or even primary aspect of disease and can lead to antiphospholipid antibody syndrome (APS) with varying clinical presentations, principally in the form of thromboembolic events and complications of pregnancy. Pregnant women and their children who receive certain of these autoantibodies by transplacental transmission are exposed to particular risks (ranging from recurrent miscarriage, severe placental insufficiency and its attendant dangers for mother and infant to congenital lupus). Immunosuppressive therapy to maintain remission of the underlying disease is essential, particularly for SLE, before planning a pregnancy. Appropriate planning can often significantly reduce the risks for mother and child.

Conversely, the physiological changes of pregnancy may affect the course or the clinical appearance of rheumatic disease. For example, pregnancy-induced hypercoagulability may increase the risk of thrombosis which was possibly already present due to underlying disease. Normal changes of pregnancy (incl. chloasma gravidarum, anemia, diffuse arthralgias) may be wrongly interpreted as symptoms of the underlying rheumatic disease. Obtaining a differential diagnosis which differentiates preeclampsia and HELLP from flare-ups of lupus nephritis, vasculitis or a renal crisis in the context of systemic sclerosis requires interdisciplinary cooperation.

Most available studies are observational studies or, rarely, randomized controlled studies of usually small patient cohorts. The result is that many recommendations in this field are based less on evidence and more on expert opinions.

2 Methods

For this paper, the recommendations of relevant medical associations, specialist conferences and institutions on rheumatic disease in persons of child-bearing age with a special focus on lupus erythematosus and antiphospholipid syndrome were reviewed in March 2023 and evaluated to see whether they still reflected current knowledge. The literature included recommendations and statements by the following organizations, institutions and authors: the European League Against Rheumatism (EULAR) [2–4], the American College of Rheumatology Guideline (ACR) [5], the 16th International Congress on Antiphospholipid-Antibodies Task Force Report [6], the British Society for Rheumatology [7], and the German Society for Rheumatology [8].

In addition, meta-analyses, systematic overviews, guidelines, and other relevant publications (published between 1993 and 2022) were searched and evaluated. No systematic search and evaluation of evidence was carried out. The statements drafted after intensive debates therefore correspond to the level of evidence of an expert opinion. How the recommendations are worded is largely derived from the wording of guidelines, whereby "must" indicates a strong recommendation and "should" a moderate recommendation. The recommendations for action include the basis for the recommendation as well as relevant background information to provide a better understanding of the individual recommendations and/or their implementation in practice.

3 General Recommendation

AGG RECOMMENDATION (1)
Patients with rheumatoid disease who wish to have children should be informed that

- active inflammation – irrespective of the site where it manifests (e.g., joints, skin, internal organs such as kidneys, bowels) – is an unfavorable predictor for the course of pregnancy.
- Well-controlled disease activity is correlated with significantly better courses of pregnancy.
- The patient's medication must be adjusted to take account of the wish to have children/the pregnancy, and reliable contraception may be (temporarily) necessary.
- Higher doses of folic acid (5 mg/d) in women with risk factors such as diabetes, obesity, a medical history of risk factors for neural tube defects or taking sulfasalazine should already be initiated prior to conception.
- If there are identifiable risks of thromboembolism, an appropriate thromboembolism prophylaxis individualized according to the recommendations in the guidelines is necessary during pregnancy and/or breastfeeding.
- Administration of ASA 150 mg/d in the evening from week 11 of pregnancy is recommended as preeclampsia prophylaxis; patients with antiphospholipid syndrome should additionally receive low molecular-weight heparin.

Background information

Individual risks may be identified, assessed and a treatment plan set up based on the patient's medical history and clinical and laboratory tests. The obstetrician should also be familiar with the basics of serological and rheumatic test results and rheumatology treatment strategies to provide the appropriate care to women with autoantibodies and/or a relevant clinical diagnosis and be able to evaluate their risks.

AGG RECOMMENDATION (2)
Already prior to conception, obstetricians and rheumatologists should investigate the severity of disease, its activity, and compatible medications (if necessary, together with hemostaseology specialists, nephrologists, and cardiologists) and inform the patient about her individual risk profile with regards to complications of pregnancy.

AGG RECOMMENDATION (3)
Women with SLE, antiphospholipid syndrome, Sjögren's syndrome, systemic sclerosis and rheumatoid arthritis should be tested for autoantibodies (SS-A/SS-B, lupus anticoagulant, anticardiolipin, anti-β2-glycoprotein I) which are relevant for pregnancy at least once prior to or in the first trimester of pregnancy.

AGG RECOMMENDATION (4)
If the pregnancy is unplanned, persons with the relevant expertise (rheumatologists, obstetricians) should be involved without delay to determine the appropriate medication and the pregnancy risks as well as the timing of the necessary check-ups.

4 Pregnancy and Lupus Erythematosus

4.1 Preconception counselling

Background information

Large study cohorts have clearly shown that the course of pregnancies conceived and carried by women with active lupus disease, especially those of women with active lupus nephritis, is worse and includes higher numbers of early miscarriages, preterm births, and higher rates of preeclampsia. The longer SLE is in remission and the patient is receiving suitable therapy, the better the prognosis [9].

The importance of SLE activity on the course of pregnancy is well known. Rheumatologists use different indices, based on differently weighted clinical and laboratory parameters, to determine disease activity. One of the most common indices is SLEDAI (= Systemic Lupus Erythematosus Disease Index): a score of ≥ 4 in the 6 months prior to conception is associated with disease flare-ups and preeclampsia [9]. Moreover, a flare-up during pregnancy is predictive for preterm birth or miscarriage. The highest risk for preterm birth and preeclampsia is when a combination of high clinical and serological activity is present (hypocomplementemia or high levels of DNS antibodies) [10]. The prospective multiethnic PROMISSE observational study (= Predictors of Pregnancy Outcome: Biomarkers in Antiphospholipid Antibody Syndrome and Systemic Lupus Erythematosus) carried out in the USA investigated predictive factors for complications of pregnancy in women with stable SLE [11]. One third of patients had inactive kidney involvement with no functional limitations when they were pregnant, 60% were taking hydroxychloroquine (HCQ). More than 80% of pregnancies had no complications. 19% of the women experienced loss of pregnancy or preterm birth related to hypertensive complications. Predictors for a poor outcome included higher clinical SLE activity at conception, lupus anticoagulant positivity, non-white ethnicity, taking antihypertensives, and thrombocytopenia. An early history of lupus nephritis (LN) and low C4 complement levels in early pregnancy were independently associated

with a risk of renal flare [8, 12]. A first manifestation of lupus nephritis was rare and occurred in just 2% [12].

A Brazilian study of women with proliferative class III/IV lupus nephritis reported more SLE flare-ups and activity during pregnancy and even after the birth, which resulted in significantly more hospitalizations and higher rates of preeclampsia [8, 13].

In summary, the risk of a renal flare is highest if women have active LN in early pregnancy. The risk is lowest for women who have been in remission for a long time.

The most favorable time to plan a pregnancy is when LN is inactive (for at least 6 months and therapy is compatible with pregnancy), proteinuria values are < 0.5 g/24 h, and renal function and blood pressure are both normal [8].

AGG RECOMMENDATION (5)
Depending on maternal factors (e.g., renal involvement), a pregnancy should be planned after a period of at least 6 months during which SLE was inactive or mildly-to-moderately stable.

4.2 Risk of preeclampsia

Background information

The preeclampsia risk is significantly higher for women with SLE. It is even higher for women with LN and antiphospholipid antibodies [14]. A systematic search of the literature (10 studies with 6389 SLE patients) confirmed that the risk of developing preeclampsia was about 3 times higher compared to healthy controls [15]. In a Californian birth registry, hypertensive complications of pregnancy in women with SLE accounted for around 30% of preterm births and small-for-gestational-age infants [16]. Data from a Norwegian birth registry additionally showed that the probability of PE in women with active SLE was significantly higher compared to women with inactive SLE [17]. LN, higher doses of glucocorticoids, antiphospholipid antibodies and arterial hypertension are therefore all risk factors [8].

AGG RECOMMENDATION (6)
A patient with SLE, especially if antiphospholipid antibodies are also present, must be informed that her risk of preeclampsia is almost 3 times higher compared to healthy women (with an associated risk of FGR, IUGR, IUFD, placental insufficiency and preterm birth).

4.3 Prepartum management

4.3.1 Immunosuppression during pregnancy

The EULAR regularly publishes evidence-based recommendations on therapies during pregnancy and breastfeeding [4]. Ideally, a patient with SLE will continue with compatible immunosuppression and HCQ intake during pregnancy. Controlled studies have shown that women who continued to take HCQ during pregnancy had fewer flares and required fewer steroids [18]. A retrospective clinical observation showed that the preeclampsia rate was lower for SLE patients who continued to take HCQ (7.5 vs. 19.7, p = 0.032) and the birthweights of their newborns were higher (2757 vs. 2542 g, p = 0.01) compared to women who had discontinued HCQ [19]. A meta-analysis which analyzed 7 prospective cohorts with a total of 668 lupus patients during pregnancy with regards to HCQ found statistically significant positive effects in terms of reduced lupus activity when HCQ was taken during pregnancy and no impact on pregnancy outcomes [20]. Other studies have highlighted the risks of preterm birth and thrombosis in SLE patients [21].

If ongoing prednisone intake during pregnancy is necessary, a low dose is recommended (≤ 7.5 mg/d). Higher doses or methylprednisolone as well as other immunosuppressive substances such as azathioprine or calcineurin inhibitors (such as cyclosporine A, tacrolimus) may be administered after a careful risk-benefit analysis to treat flares or for necessary immunosuppression [2, 8].

AGG RECOMMENDATION (7)
Women with SLE must continue to take HCQ in pregnancy (and if necessary, compatible immunosuppressive substances) if they began taking it prior to conception.

4.3.2 Preeclampsia prophylaxis during pregnancy

The probability of PE is reduced by more than 60% in patients at risk for PE by the prophylactic administration of 150 mg ASA. In the ASPRE study, women with a higher risk of PE received (double-blinded) either ASA (150 mg/d) or placebo (from weeks 11–14 until week 36 of gestation). The primary endpoint (PE with delivery of the infant before week 37 of gestation) occurred in 1.6% (13/798) of women in the ASA group compared with 4.3% (35/822) in the placebo group (OR for the ASA group: 0.38; 95% CI: 0.2–0.74) [22]. The effect is dose-dependent, with high rates of resistance against the effect of ASA on thrombocyte function if the dose is less than 100 mg/d [23]. Taking ASA at bedtime appears to be beneficial [24].

AGG RECOMMENDATION (8)
Low-dose acetylsalicylic acid (ASA) must be recommended as PE prophylaxis (150 mg taken at night) to all women with SLE (from week 11–14 until the end of week 36 of gestation).

4.3.3 Monitoring during pregnancy

Abnormal C-reactive protein, a high erythrocyte sedimentation rate, a differential blood cell count, urine analysis including the protein/creatinine ratio and anti-DNS, complement usage with decreasing levels of C3 or C4, transaminases and LDH may indicate a lupus flare, even in (still) asymptomatic patients. Lupus activity indices have now also been validated for pregnant women with lupus disease (including the LAI-P or BILAG2004 Pregnancy Index) [25, 26]. The angiogenesis markers sFlt1/PlGF may be used as an indication of placental involvement to obtain a differential diagnosis of preeclampsia. In a prospective multicenter observational study (PROMISSE), sFlt1 in the first trimester and the sFlt1/PlGF ratio in the second trimester were found to be the strongest

predictors for pregnancy outcomes in addition to such prognostically relevant predictive factors for pregnancy outcomes as medical history, status after thrombosis, preconception lupus activity, non-white ethnicity, the need for antihypertensive medication and thrombopenia [27].

AGG RECOMMENDATION (9)
SLE disease activity should be investigated at least once in every trimester of pregnancy based on the patient's medical history, a clinical examination and laboratory tests, as a lupus flare can significantly affect maternal prognosis and overall pregnancy prognosis.

Because of the increased risk of preeclampsia and the associated higher risk of fetal growth restriction (see above):

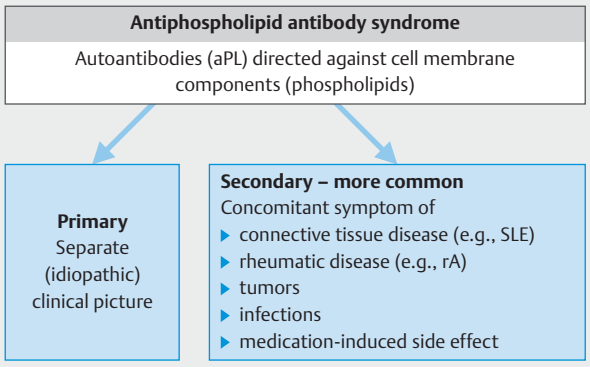
AGG RECOMMENDATION (10)
In addition to routine ultrasound screening in the 3rd trimester of pregnancy, a patient with SLE must have a biometric screening test and fetal as well as uterine Doppler sonography at least once every 4 weeks. First and second trimester screening including measurement of uterine artery resistance should be offered.

AGG RECOMMENDATION (11)
Determination of Flt1 in the first trimester and the sFlt1/PlGF ratio in the second and third trimester of pregnancy can be used as part of the differential diagnosis to determine prognosis when placental involvement is present.

5 Antiphospholipid Antibodies/ Lupus Anticoagulants

Antiphospholipid antibodies (aPL) are immunoglobulin (Ig) isotypes G and M, which can bind in vivo to phospholipid-protein complexes on membrane surfaces such as the endothelium or placental surfaces. In vitro they affect functional coagulation tests by binding phospholipids. This is used for diagnosis, and the association with systemic lupus has led to the coining of the term "lupus anticoagulants". Antiphospholipid antibodies can also be detected directly using immunological tests (ELISA); the most important in clinical practice are cardiolipin and β2-glycoprotein-I antibodies.

Clinically, the asymptomatic detection of phospholipid antibodies is differentiated from antiphospholipid syndrome. Antiphospholipid syndrome (APS) presents either as frequent atypical venous and arterial thromboembolisms (especially in younger people with no previously recognizable risk factors, significant cardiovascular events, immune thrombocytopenia) or as complications of pregnancy ("obstetric APS"). Certain criteria must be met for a diagnosis of APS, including tests which are positive for phospholipid antibodies or/and for lupus anticoagulants on two separate occasions with an interval of 12 weeks between tests [28].



▶ **Fig. 1** Antiphospholipid antibody syndrome – genesis.

Antiphospholipid syndrome (APS) rarely occurs as a primary idiopathic disease. Usually, it occurs secondarily as an attendant symptom of connective tissue disease (e.g., SLE), rheumatic disease (e.g., rheumatoid arthritis), tumors, infections, or as a result of taking medication (▶ **Fig. 1**) [29].

With catastrophic APS, *thromboembolic manifestations in at least* 3 vascular areas or organs appear within the space of just one week. The reported mortality is about 50 %. To obtain a differential diagnosis, it is important to investigate primarily for disseminated intravascular coagulation (DIC) and thrombotic microangiopathies (TMA) (▶ **Fig. 2**).

To diagnose obstetric APS, a serological confirmation of a lupus anticoagulant and/or a moderate-to-high titer of IgG/IgM cardiolipin antibodies IgG/IgM antibodies against β2-glycoprotein-I [28] is required in addition to the clinical diagnosis (▶ **Table 1**).

AGG RECOMMENDATION (12)
If there is a suspicion of obstetric APS, the patient should be tested for anti-β2 glycoprotein IgG/IgM, and the antiphospholipid antibodies anticardiolipin IgG/IgM and lupus anticoagulants.

Background information

Antiphospholipid antibodies have been shown in different study cohorts to be distinct risk factors for significant complications of pregnancy including loss of pregnancy, especially in women with SLE. In the PROMISSE study, lupus anticoagulants [27] were found to be associated with the highest risk for complications of pregnancy in women with and without SLE (RR for adverse pregnancy outcome with lupus anticoagulant positivity was 12.15, 95 % CI: 2.92–50.54, p = 0.0006). Other independent risk factors for aPL-positive women are young age, a prior history of thromboembolism, and SLE.

▶ **Table 1** Laboratory definitions/risk profiles, Data from [3].

Laboratory definitions/risk profile of antiphospholipid antibodies for thromboembolic events or complications of pregnancy	
▪ IgG and/or IgM isotype aCL (titer > 40 U/ml) or > 99th percentile of a standardized laboratory test (ELISA), and/or	
▪ IgG and/or IgM isotype aβ2-GP I (titer > 40 U/ml) or > 99th percentile of a standardized laboratory test (ELISA), and/or	
▪ lupus anticoagulant (measured according to ISTH guidelines)	
Two tests confirming the presence of antibodies/anticoagulant carried out at an interval of at least 12 weeks are required.	
Definitions (EULAR): laboratory risk constellations for thromboembolism or complications of pregnancy	
High risk	lupus anticoagulant (measured according to ISTH guidelines), or
	aPL double positivity (every combination of LA, aCL or aβ2-GP I), or
	aPL triple positivity (detection of LA, aCL and aβ2-GP I), or
	consistently high aPL titer
Low risk	isolated aCL or aβ2-GP I with low-to-moderate titer levels, especially if confirmation is only transient

aCL: cardiolipin antibodies, aβ2-GP I: β2-glycoprotein-I antibodies, aPL: antiphospholipid antibodies, Ig: immunoglobulin, ISTH: International Society on Thrombosis and Haemostasis, LA: lupus anticoagulant

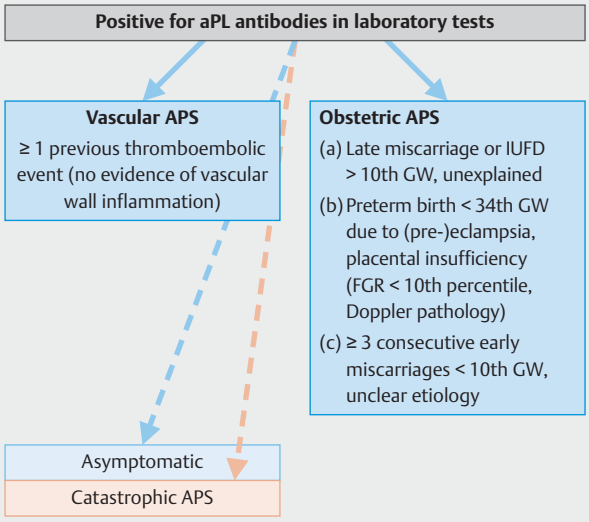
The European League against Rheumatism (EULAR) has defined a serological high-risk profile for APS (▶ **Table 1**) [3].

Excerpts of the recommendations of the EULAR for the treatment of women with antiphospholipid antibodies/lupus anticoagulant have been adopted [3, 8] (▶ **Table 2**).

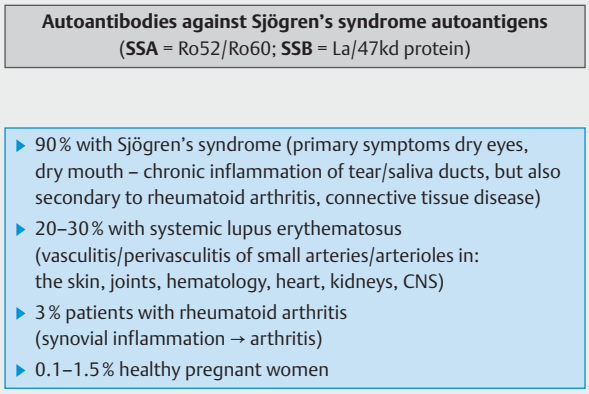
6 Neonatal Lupus Syndrome (for Maternal Autoantibodies with or without Sjögren's Syndrome)

The maternal autoantibodies SS-A (Ro52/Ro 60) and SS-B (La/47kd protein) are associated with a risk of neonatal lupus (NL) in the newborn (i.e., a passively acquired autoimmune disease). The risk increases if maternal antibody titers (> 50, especially > 100 U/l) are high or both autoantibodies are detected [30, 31].

These autoantibodies occur predominantly in women with Sjögren's syndrome but may also be present in patients with SLE, rheumatoid arthritis or in clinically healthy pregnant women (▶ **Fig. 3**). From around week 11 of gestation, maternal autoantibodies launch a passive transplacental attack on the infant during its intrauterine development. During vulnerable cardiac development stages (usually between week 16 and 24 of gestation) this may not just lead to myocarditis, cardiomyopathy and irreversible fibrotic remodeling of the AV node but can also lead to cutaneous signs of disease, hepatic damage and (pan)cytopenias in the neonate [30, 32, 33] (▶ **Fig. 3**).



▶ **Fig. 2** Antiphospholipid antibody syndrome – definitions.



▶ **Fig. 3** Presence of autoantibodies against Sjögren's syndrome autoantigens.

Clinical presentation

- fetal AV block (CHB), myocarditis, cardiomyopathy
- skin efflorescence typical for lupus (often triggered by UV light) which develops postnatally in the first few weeks of life
- rarely: anemia, leukopenia/thrombopenia, hepatic damage

AGG RECOMMENDATION (13)

Women with SS-A and/or SS-B antibodies should be informed about the CHB/conatal lupus risk of 0.7–2 %. If a woman has already given birth to one child with CHB/conatal lupus, she should be informed about the significantly higher risk of 15–20 %.

▶ **Table 2** Recommendations for the therapy of women with antiphospholipid antibodies before and during pregnancy (data from [3, 8]).

Primary prophylaxis for aPL-positive non-pregnant women	**Not pregnant**
Prophylactic therapy with low-dose ASA (75–100 mg/d) is recommended for asymptomatic carriers of aPL (who do not meet any vascular or obstetric criteria for APS) with a high-risk aPL profile, with or without traditional risk factors.	
Women with SLE without previous thromboembolism or complications of pregnancy	
a. Prophylactic therapy with low-dose ASA (75–100 mg/d) is recommended for patients with a high-risk aPL profile. b. Prophylactic therapy with low-dose ASA (75–100 mg/d) is recommended for patients with a low-risk aPL profile.	
Prophylactic therapy with low-dose ASA is recommended for non-pregnant women with a history of purely obstetric APS (with or without SLE) after weighing up the risks and benefits (aPL profile, other cardiovascular risk factors, tolerability of ASA).	
Therapy for aPL-positive women in pregnancy	**Pregnant**
Treatment with low-dose ASA during pregnancy should be considered for women with a high-risk aPL profile but without a prior history of thrombosis or complications of pregnancy (with or without SLE).	
For women with a history of pregnancy complications from APS only (no thrombotic events), with or without SLE:	
a. If there is a prior history of > 3 recurrent spontaneous miscarriages before week 10 of gestation and/or miscarriage after the 10th week of gestation (without other causes), administering a combination of low-dose ASA (150 mg/d) and LMWH prophylactically during pregnancy is recommended. b. If there is a previous history of delivery before week 34 of gestation due to eclampsia, severe preeclampsia, or placental insufficiency, prophylactic treatment with low-dose ASA or a combination of ASA (150 mg/d) and LMWH is recommended which takes account of the individual risk profile. c. If the clinical criteria have not been sufficiently met for a diagnosis of prior obstetric APS, for example, 2 recurrent spontaneous miscarriages before week 10 of gestation or delivery ≥ 34th week of gestation due to severe preeclampsia or eclampsia, treatment with low-dose ASA (150 mg/d) alone or in combination with LMWH may be considered, always based on the individual risk profile. d. If treatment consists of prophylactic doses of LMWH during pregnancy for obstetric APS, continuing the prophylactic doses of LMWH for 6 weeks after the birth may be considered to reduce the risk of maternal thrombosis.	
For women who meet the criteria of obstetric APS with recurrent complications of pregnancy despite receiving a combination of LMWH and low-dose ASA (150 mg/d) a. increase the LMWH dose to achieve therapeutic levels, or b. administer HCQ, or c. low-dose prednisolone in the 1st trimester of pregnancy, or d. consider administering intravenous immunoglobulins in very specific cases.	
A combination of low-dose ASA and therapeutic doses of LMWH during pregnancy and the puerperium is recommended for APS patients with a prior history of thromboembolism.	

APS: antiphospholipid syndrome, aPL: antiphospholipid antibodies, HCQ: hydroxychloroquine, LMWH: low molecular-weight heparin, LoE: level of evidence, GW: week of gestation, SLE: systemic lupus erythematosus

6.1 Congenital AV block, cardiac involvement

The cardiac impact of NL is the most clinically important: irreversible fibrotic remodeling of the AV nodal region with congenital AV block (CHB). The CHB risk of children born to SS-A/SS-B-antibody-positive mothers is 0.7–2% in the first pregnancy. The risk of recurrence (the mother has already given birth to one child with NL/CHB) is significantly higher at 15–20% [8, 32]. Most CHB are diagnosed in utero between week 20 and 24 of gestation. The overall mortality is around 20%, of which one quarter die in utero and just under half of the children die in the first 3 months of life. Two thirds require a pacemaker already as an infant. The cumulative 10-year survival rate of a liveborn neonate with CHB is about 85%. The prognosis is mainly determined by the concomitant cardiomyopathy (fibrotic replacement of cardiac muscle tissue/myocarditis) [8, 32].

CHB develops within a very short time (< 24 h) and can be neither reliably predicted with currently tested examination methods (such as mechanical measurement of PR intervals or serial home monitoring) [34] nor is it (ideally reversibly) treatable [35]. In most cases, the detection of CHB has no direct clinical consequences subsequently in terms of initiating drug therapy [36]. This means that serial echocardiography carried out in women who are “only” SS-A/SS-B positive with no previous history of an infant with NL or CHB only leads to an unnecessary use of resources and maternal disquiet. However, serial screening is recommended for women with a high risk of CHB.

The obstetrician and neonatologist are responsible for initiating serial echocardiography monitoring of a fetus with CHB and making the decision when to deliver the infant. The obstetric setting of infants with CHB requires interdisciplinary cooperation even before the birth.

AGG RECOMMENDATION (14)
Women who are positive for SS-A and/or SS-B antibodies should be screened in the second and third trimesters of pregnancy, and screening should include fetal echocardiography. When routine screening is carried out as required by the German guidelines on maternity policy and care, bradycardia screening should be carried out every 4 weeks (e.g., by auscultation, CTG or ultrasound).

AGG RECOMMENDATION (15)
Starting in week 16–24 of gestation, weekly monitoring of the fetal heart rate and second and third trimester screening including fetal echocardiography should be carried out in women who have already given birth to a child with congenital AV block (CHB) and/or neonatal lupus.

AGG RECOMMENDATION (16)
An infant with congenital AV block (CHB) must be delivered in a level I perinatal center with the facilities to provide immediate cardiac emergency care.

AGG RECOMMENDATION (17)
An infant who appears to be in good cardiac health during the pregnancy born to a mother with SS-A/SS-B antibodies should have an ECG postnatally.

6.2 Cutaneous neonatal lupus

In the first weeks of life the neonate may develop the skin efflorescence typical for lupus due to a (passively acquired) antibody-mediated autoimmune response with histopathological findings such as those associated with cutaneous lupus erythematosus. Rarer diagnoses include Coombs-positive hemolytic anemia, thrombopenia, leukopenia or organ involvement (e.g., from elevated transaminase levels). These presentations are usually self-limiting and disappear within 6–9 months.

In prospective studies, cutaneous NL developed in 16–40% of infants [37, 38]. The skin presentations are usually reversible. However, a retrospective study found sequelae in 34% of 106 children with NL (13% had telangiectasias, 17% had disorders of pigmentation, 9% had atrophic scars) [39].

AGG RECOMMENDATION (18)
Women who have already given birth to a child with CHB and/or neonatal cutaneous lupus affecting the above-mentioned organ systems should be followed up with weekly monitoring of the fetal heart rate from week 16 to 24 of gestation and second and third trimester screening should include fetal echocardiography.

6.3 Drug therapy

The antimalarial hydroxychloroquine (HCQ) has been used for decades as a well-tolerated immune-modulating substance to treat SLEs. It reduces disease activity as well as the required glucocorticoid doses. The half-life of HCQ is assumed to be 50–60 days (probably caused by long binding in tissue), and at low doses (< 5 mg/kg/d), the toxicity is relatively low. The most commonly debated risk is retinopathy, but this appears to be dose-dependent and cumulative after 10 years' intake and occurs in just 2%. An ophthalmic examination is therefore recommended before or at the start of therapy, followed by annual ophthalmic examinations over the course of therapy [40]. Registry data have shown that maternal HCQ therapy reduces the risk of CHB recurrence by more than 60% [36]. A prospective phase-2 study has recently confirmed these data. The study included 54 women who had previously already given birth to an infant with CHB. The mothers were given HCQ (400 g/d) before week 10 of gestation. Four of 54 (7.4%) fetuses went on to develop 2° or 3° CHB. This means that the CHB rate was significantly ($p = 0.02$) lower than in historic cohorts [41]. HCQ also appears to have a protective effect against the disease activity of SLE in the puerperium, indicating that the continued intake of HCQ (at least for women who additionally have SLE) should be discussed [42].

AGG RECOMMENDATION (19)
Women who have already given birth to a child with CHB and/or neonatal lupus must be treated with 400 mg/d HCQ starting at the latest in week 10 of gestation and continuing until the end of the puerperium.

AGG RECOMMENDATION (20)
Prophylactic therapy with 400 mg/d HCQ should be discussed and generously prescribed for women who are positive for SS-A and/or SS-B antibodies.

7 Peripartum Management

AGG RECOMMENDATION (21)
A pregnancy in a woman with rheumatic disease is considered a risk pregnancy and the care offered should be analogous to the care provided to women at risk for preeclampsia/placental insufficiency.

AGG RECOMMENDATION (22)
Induction of labor or elective caesarean section is not indicated for women with asymptomatic rheumatic disease. Induction of labor may be offered and recommended from week 39 + 0 of gestation. The decision in cases with active symptomatic disease must be taken on an individual basis.

8 Postpartum Management

8.1 Medication

There are some study data which indicate that the rate of SLE flares increases postpartum [43, 44]. The patient's individual risk of thrombosis must also be taken into consideration, especially for women with antiphospholipid syndrome who have an increased risk of thrombosis. Please consult current guidelines and recommendations issued by specialist medical associations [45].

AGG RECOMMENDATION (23)
SLE-specific medication must be administered during pregnancy and in the puerperium. Rheumatological control examinations at 12 and 24 weeks postpartum must be recommended.

AGG RECOMMENDATION (24)
If there is no peripartum infection from other causes, biological agents (such as TNF-α or IL inhibitors) may be restarted 24 h after vaginal delivery or 48 h after caesarean section.

8.2 Breastfeeding

AGG RECOMMENDATION (25)
Women must be recommended to breastfeed for at least 6 to 12 months. Disease-specific medications must be continued using drugs compatible with lactation.

Raynaud's phenomenon of the nipple (extremely painful transient ischemia where the affected area first turns white, then blue, followed by periareolar erythema) is reported in the literature as an underdiagnosed, often wrongly diagnosed, problem of pregnant women and breastfeeding mothers. A number of case reports are available but there are no systematic studies [46, 47]. Possible trigger factors include induced digital vasospasm, cold and stress. It is assumed that women with rheumatic disease, for whom Raynaud's phenomenon of fingers and toes is often a symptom of underlying disease, are more commonly affected. The symptoms are relatively easy to treat, and treatment consists of warmth or, if necessary, the administration of vasodilating substances such as nifedipine (10–60 mg retard) [48].

AGG RECOMMENDATION (26)
Pregnant women with rheumatic disease should be actively asked about Raynaud's phenomenon of the nipple, informed, and treated if necessary.

Fischer-Betz and Haase [8] compiled an overview of the recommendations for management pre- and post-conception, during pregnancy, and in the postpartum period, which has been added to by the AGG authors (▶ **Table 3**).

9 Rheumatoid Arthritis (rA), Seronegative Spondyloarthritis (SpA), Psoriatic Arthritis (PsA)

A systematic review combined with a meta-analysis has shown that the disease activity of rA improves by 60 % during pregnancy but worsens again by 50 % postpartum [49]. Another meta-analysis found a 1.4 to 2.2 higher risk for poor fetomaternal outcomes (such as increased rates of spontaneous miscarriage, gestational hypertension, preeclampsia, SGA/FGR, preterm birth) compared to healthy controls [50]. There are fewer data on PsA; disease remains stable in around ⅓ of all cases during pregnancy, is exacerbated in ⅓ and improves in ⅓ of cases [51]. The data on SpA is equally controversial, with very variable courses of disease (ranging from stable to exacerbated) reported during pregnancy. However, what all these diseases have in common is that a significant percentage of patients will experience worsening of disease again in the postpartum months [52]. Here too, drugs which are compatible with pregnancy and breastfeeding to control disease activity are essential (▶ **Table 4**). There has been a paradigm shift in recent years with regards to the use of TNF-α inhibitors which have been used for more than 20 years to treat the arthritic diseases discussed here. Most of these substances (infliximab, adalimumab, golimumab, etanercept) have IgG structures and are transferred to the fetus through the placenta, although transmission of etanercept to the fetal circulation is lower due to its specific molecular structure. The TNF blocker certolizumab, which consists of an anti-TNF PEGylated Fab fragment, has the lowest trans-

▶ **Table 3** Recommendations for examinations and measures to be taken prior to conception, during and after pregnancy for women with systemic lupus erythematosus (SLE); data from [8], with the addition of obstetrically relevant recommendations.

Prior to conception	
Generally	Previous pregnancies/complications of pregnancy?
	Comorbidities (e.g. hypertension, diabetes, thromboembolic events)?
	Vaccinations?
	Take folic acid starting 4 to 12 weeks before the planned conception
	Vitamin D substitution (if necessary, determine vitamin D levels)
SLE-specific	Severity of disease (especially renal, pulmonary, cardiac impact; if necessary, interdisciplinary cooperation with a review of contraindications); review records of the last cardiopulmonary check-up, update where necessary? Current renal values?
	Review current SLE activity and SLE activity in the last 6 to 12 months (ideally with a validated instrument, e.g., SLEDAI; target SLEDAI is ≤ 4)[a]
	Drug therapy: contraindicated? → adjust therapy
	Continue with hydroxychloroquine or initiate treatment with hydroxychloroquine
	Lab tests: erythrocyte sedimentation rate (before the start of pregnancy)/C-reactive protein, complete blood count including thrombocytes, creatinine/creatinine clearance, LDH, CK, liver values
	Check urine status, possibly albumin excretion (protein/creatinine ratio)
	Check complement (C3 and C4 or CH50) levels, DNS antibodies, **SS-A/SS-B antibodies, antiphospholipid antibodies, lupus anticoagulant**
In pregnancy	
	In every trimester of pregnancy:
	Review disease activity (ideally using a validated instrument, e.g., SLEDAI)
	Review/adjust therapy
	Administer low-dose aspirin (150 mg/d) as preeclampsia prophylaxis, starting at the latest between week 11–16 of gestation and continuing until the end of week 36 of gestation
	Long-term glucocorticoid intake: 75 g OGTT screening test
	Routine ultrasound screening, additional recommendation for ▪ first trimester screening to include Doppler sonography of the uterine arteries[b] ▪ second trimester screening to include Doppler sonography of the uterine arteries[b] ▪ third trimester: monthly biometric tests and feto-(maternal) Doppler sonography[b,c]; intensify controls if fetal growth appears to be levelling off/fetal growth retardation is apparent; if necessary carry out additional examination using sFlt1/PlGF ratio[d]
	SS-A/SS-B-positive women should be screened for fetal bradycardia by a specialist at every examination; echocardiography during first, second, and third trimester screening is recommended.
	SS-A/SS-B-positive women: information about 1–2 % probability of neonatal lupus syndrome (AV block/myocarditis, cutaneous lupus)
Postpartum	
	SS-A/SS-B positive women: newborns should have an ECG.
After 12 and 24 weeks: SLE activity should be reviewed.	

[a] SLEDAI = Systemic Lupus Erythematosus Activity Index, a score of > 4 in the 6 months prior to conception is associated with a higher probability of flares/preeclampsia [1].

[b] Doppler sonography of the uterine arteries to estimate the individual risk of preeclampsia.

[c] Biometric tests.

[d] sFlt/PlGF ratio to estimate and obtain differential diagnosis of placental involvement in the disease process.

mission-to-fetal-circulation rate. Nevertheless, a patient whose disease is already controlled well with a different TNF blocker should not be switched to certolizumab. Certolizumab may be considered if TNFα therapy needs to be initiated in pregnancy or if the patient wished to become pregnant [53].

TNF blockers are still detectable at low concentrations in infants several months after the birth, which is why the intake of these substances should be paused in the 3rd trimester of pregnancy in cases with stable disease and restarted again after the birth. There are no long-term data about children after the 2nd–5th years of life; however, there are currently no data which indicate a negative immunocompromising effect. As a precaution, infants who were exposed in utero should not be vaccinated with active vaccines in their first months of life [54, 55]. In 2022, the EULAR recommended discontinuing adalimumab and infliximab intake around week 20 of gestation and etanercept intake between weeks 30–32 of gestation and, with little evidence, to administer certolizumab in specific cases during entire pregnancy [53].

Antinuclear antibodies such as SS-A and SS-B, which have been associated with the above-mentioned complications of pregnancy

▶ **Table 4** Antirheumatic medications in pregnancy and breastfeeding. Data from EULAR recommendations [4, 8].

Medication	Comment[a]	Breastfeeding[a]
Non-selective COX inhibitors (classic NSAIDs)	Can be taken in the first and second trimester of pregnancy.	Compatible
Selective COX inhibitors	Should be avoided.	Celecoxib is the only selective COX inhibitor that has been sufficiently investigated; it is compatible.
Azathioprine	Can be continued; dose of 2 mg/kg/d should not be exceeded.	Compatible
Cyclosporine	Can be continued at the lowest effective dose; dose of 2–3.5 mg/kg/day should not be exceeded.	Compatible
Cyclophosphamide	Teratogenic in humans. Discontinue 3 months prior to planned pregnancy (consider in life-threatening situations from the 2nd trimester of pregnancy).	No data, avoid
Hydroxychloroquine	Dosages the same as outside of pregnancy.	Compatible
Chloroquine	Dosages the same as outside of pregnancy.	Compatible
Leflunomide	Teratogenic in animal studies, should be avoided. Insufficient data for humans; a washout period is necessary before planning a pregnancy.	No data, avoid
Methotrexate	Teratogenic for humans, discontinue 1–3 months prior to planned pregnancy, afterwards folic acid substitution (1–5 mg/d) until the 1st trimester of pregnancy.	Data insufficient, avoid
Mycophenolate mofetil	Teratogenic for humans, discontinue at least 1.5 months prior to planned pregnancy.	No data, avoid
Prednisone, prednisolone	Continue intake at lowest effective dose.	Compatible
Methylprednisolone	Can be administered during acute flare-ups.	Administer in cases of acute flare-up.
Sulfasalazine	Continue, do not exceed 2 g/d + must be accompanied by supplementation with folic acid.	Compatible
Tacrolimus	Continue at the lowest effective dose; if necessary, adjust dose according to plasma levels.	Compatible
Colchicine	Continue, do not exceed 1 mg/d.	Compatible
Intravenous immunoglobulin	Continue.	Compatible
Tofacitinib	Avoid, discontinue 2 months prior to conception.	No data, avoid
Infliximab	Continue until week 20 of gestation; administration possible during entire pregnancy with rigorous monitoring.	Compatible
Adalimumab	Continue until week 20 of gestation; administration possible during entire pregnancy with rigorous monitoring.	Compatible
Golimumab	Limited data; administration possible during entire pregnancy with rigorous monitoring if there is no alternative.	Compatible
Etanercept	Continue until week 30–32 of gestation; administration possible during entire pregnancy with rigorous monitoring.	Compatible
Certolizumab	Continue.	Compatible
Rituximab	Limited data[b]. Preferably switch to a different therapy or administer shortly before conception. Administration in the 2nd and 3rd trimester may result in B-cell depletion in the infant.	Limited data[c]
Anakinra	May be continued if there are no alternatives.	No data, avoid
Ustekinumab	Limited evidence – opt for alternative drugs if possible.	No data, avoid
Belimumab	Limited data[b]. Preferably switch to a different therapy; Germany has a Belimumab pregnancy registry.	No data[c]

[a] After carefully weighing up the risks and benefits, and depending on disease severity and activity after the patient has received individually tailored detailed information.

[b] Based on case series of unplanned pregnancies with maternal exposure in the 1st trimester, there does not appear to be a pattern of congenital anomalies. Can be used in pregnancy if there is no other therapy which adequately controls disease activity.

[c] Biological DMARDs (disease-modifying antirheumatic drugs) for which there are no or only limited data with regards to breast feeding should be avoided during breastfeeding if the disease activity can be effectively controlled using other therapies. Based on the pharmacological properties of biological DMARDs, women should not be advised against taking these substances when breastfeeding if no other options are available.

and disease, should also be monitored in patients with rA (▶ **Fig. 3**).

AGG RECOMMENDATION (27)
Women with rA, SpA and PsA should be informed at the start of their pregnancy that their disease may be associated with a higher risk of poor fetomaternal outcomes. Regular rheumatic check-ups and therapy before and during pregnancy are therefore recommended to stabilize the disease process.

AGG RECOMMENDATION (28)
Women with rA and other autoimmune diseases should, after consulting with the treating rheumatologist, be tested once for SS-A and SS-B antibodies prior to or early in pregnancy.

Postpartum flare-ups in the months following the pregnancy occur in around half of all women [49].

10 Mixed Connective Tissue Disease/ Undifferentiated Connective Tissue Disease

Mixed connective tissue disease is a defined disease entity with a specific autoantibody constellation (detection of U1-RNP antibodies) and clinical signs of systemic lupus erythematosus, systemic sclerosis, dermatomyositis and Sjögren's syndrome. The above-mentioned risks are expected in patients with mixed connective tissue disease and antiphospholipid antibodies, lupus anticoagulant and/or SS-A/SS-B antibodies [56].

AGG RECOMMENDATION (29)
Women with mixed or other connective tissue disease should be informed, preferably before or at the start of pregnancy, that the disease may be associated with a higher risk of poor fetomaternal outcomes, and that regular rheumatic monitoring and therapy before and during pregnancy are recommended to ensure that disease activity remains stable.

AGG RECOMMENDATION (30)
Women with mixed or other connective tissue disease should be tested once for SS-A/SS-B and antiphospholipid antibodies before conception or in early pregnancy.

11 Vasculitis

Vasculitis can affect small (e.g., granulomatosis with polyangiitis or microscopic polyangiitis), medium-sized (polyarteritis nodosa) and large vessels (Takayasu's arteritis). Behçet's disease and IgA vasculitis are also considered as part of this group of rheumatic diseases. These diseases are associated with an increased risk of preeclampsia, placental insufficiency, SGA, FGR, preterm birth and hypertension [57].

AGG RECOMMENDATION (31)
Low-dose acetylsalicylic acid (ASA) must be recommended to all women with vasculitis (from week 11–14 of gestation until the end of week 36 of gestation) as PE prophylaxis (150 mg taken at night).

AGG RECOMMENDATION (32)
Monitoring during pregnancy and patient management peripartum and in the postpartum period should be analogous to that provided to women at risk for hypertension, preeclampsia. and placental insufficiency.

EULAR has compiled a systematic overview of the existing data on experiences with and safety aspects of common antirheumatic drug therapies during pregnancy and breastfeeding which includes expert consensuses [4]. The most important aspects of these expert consensuses are summarized in ▶ **Table 4**.

Conflict of Interest

The authors state that they have no conflict of interest.

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