The Italian Society for Rheumatology guidelines on reproductive health in patients with rheumatic diseases

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Summary

Objective. To date, there is no shared national guideline in Italy for the management of reproductive health in rheumatic diseases (RHRD). The Italian Society for Rheumatology (SIR) has committed to developing clinical practice recommendations to provide guidance on both management and treatment regarding RHRD in Italy.

Methods. Using the GRADE-ADOLOPMENT methodology, a systematic literature review was conducted to update the scientific evidence that emerged after the publication of the reference recommendations from the American College of Rheumatology. A multidisciplinary group of 18 clinicians with specialist experience in rheumatology, allergy and clinical immunology, internal medicine, nephrology, gynecology and obstetrics, and neonatology, a professional nurse, a clinical psychologist, and a representative from the National Association of Rheumatic Patients discussed the recommendations in collaboration with the evidence review working group. Subsequently, a group of stakeholders was consulted to examine and externally evaluate the developed recommendations.

Results. Recommendations were formulated for each area of interest: contraception, assisted reproductive technology, preconception counseling, and use of drugs before, during, and after pregnancy and during breastfeeding, considering both paternal and maternal exposure.

Conclusions. The new SIR recommendations provide the rheumatology community with a practical guide based on updated scientific evidence for the management of RHRD.

Introduction

Given the frequency of rheumatic diseases (RD), reproductive health in patients with rheumatic diseases (RHRD) represents a transversal and priority issue in a nation with negative birth rates (1). There are several aspects to consider, and collaboration among different specialists is essential. Considering that the diagnosis of RD is often made in women of childbearing age, issues such as contraception, fertility, and family planning are highly relevant and must be addressed by a multidisciplinary team. Yet, RD can still influence family planning today (2, 3). In recent years, thanks to early diagnosis, the availability of various effective therapies, and multidisciplinary management, pregnancy outcomes in patients with RD have greatly improved. However, compared to the general population, an increased risk of complications in women with RD still exists (4-6). There are several aspects to consider during preconception counseling: disease activity, as poor control of maternal disease before conception can be associated with adverse maternal-fetal outcomes; the risk of disease flare during pregnancy; treatment modifications needed in case of drugs incompatible with pregnancy and breastfeeding, which must therefore be discontinued or replaced before conception (3, 7-13). It is also necessary to discuss situations that require particular monitoring or additional specific therapy during pregnancy. Those include positivity for anti-Ro/SSA and/or anti-La/SSB antibodies, associated with neonatal lupus and congenital heart block, or positivity for antiphospholipid antibodies (aPL), associated with increased obstetric and thrombotic morbidity (4, 11). If the pregnancy needs to be deferred due to disease-related reasons, or if the patient does not desire pregnancy, the initiation of an effective and safe contraceptive method requires proper evaluation. From this perspective, certain conditions, such as the presence of aPL, may contraindicate estrogen-based therapies due to an associated increased risk of thrombosis (4, 11). Furthermore, the issue of both male and female fertility must be considered, because fertility can be affected by the use of certain therapies in patients with RD. It is, therefore, necessary to evaluate the possibility of assisted reproductive technology (ART) procedures. ART must be adequately planned depending on the diagnosis and antibody positivity; where indicated, appropriate prophylaxis can be necessary (4, 11). Once pregnancy is established, it is essential that the patient with RD is followed by a multidisciplinary team. During pregnancy, it is extremely important to ensure continuous coordinated specialistic care that monitors the course of the underlying disease and implements appropriate adjustments if disease control is suboptimal. Therefore, constant collaboration with gynecologists/obstetricians and other specialists is crucial for the successful outcome of pregnancy, ensuring adequate multidisciplinary follow-up during the gestation period and postpartum. In the absence of national guidelines on this broad topic, the Italian Society for Rheumatology (SIR) has decided to develop national clinical practice guidelines for the management of RHRD in accordance with the requirements of the National Guidelines System of the Italian National Institute of Health.

Need for Italian guidelines

Although there are paths dedicated to individual diseases, in Italy there is to date no single shared national guideline on the management of reproductive health in patients with RD.

Objective

These guidelines aim to provide updated and evidence-based recommendations regarding the management of RHRD in Italy in accordance with the requirements of the National System of Guidelines of the Italian National Institute of Health.

Target population

Adult patients (≥18 years) with a diagnosis of RD formulated by a rheumatologist or other specialist or primary care doctor.

Covered areas

These guidelines include management strategies and pharmacological approaches in patients with RD regarding pregnancy (preconception counseling, management of anti-rheumatic therapy before and during pregnancy, paternal exposure, pharmacological safety during breastfeeding), contraception, and male and female fertility (ART and ovarian preservation).

The RDs covered by these guidelines are: rheumatoid arthritis, psoriatic arthritis, ankylosing spondylitis, juvenile idiopathic arthritis, systemic lupus erythematosus (SLE), Sjogren syndrome, polyarteritis nodosa, ANCA-associated vasculitis (microscopic polyangiitis, granulomatosis with polyangiitis, eosinophilic granulomatosis with polyangiitis), Behçet disease, Takayasu's arteritis, antiphospholipid syndrome (APS), systemic sclerosis, morphea, mixed connective tissue disease (MCTD), undifferentiated connective tissue disease (UCTD), idiopathic inflammatory myopathies.

Uncovered areas

These guidelines do not include diseases managed in the immuno-rheumatology field that are not specifically listed in the aforementioned covered areas, nor do they cover prevention, screening, and treatment activities for human papillomavirus infection and gynecological tumors.

Development approach of the guidelines and clinical questions

The Grading of Recommendations Assessment, Development, and Evaluation (GRADE)-ADOLOPMENT (14) methodology was used to identify existing and relevant guidelines on the topic and to adopt or adapt recommendations in accordance with the methodological manual for the production of clinical practice guidelines (version 1.3.2, April 2019) (15) and the operational manual (version 3.02, February 2020) (16) of the National Center for Clinical Excellence, Quality, and Safety of Care of the Italian National Institute of Health. The choice of the guideline topic, the activity plan, and the use of resources were approved by the Board of Directors of the SIR in the role of the Scientific and Technical Committee (July 7, 2021). For the application of the GRADE-ADOLOPMENT methodology, guidelines on RHRD issued by the American College of Rheumatology (ACR) in 2020 (11) were identified as references. The project was approved by the SIR Gender Medicine Study Group (58th SIR National Congress, November 25, 2021), and the final protocol for guideline development was approved by the panel (version 3.0, March 10, 2022).

Materials and Methods

Assembly of the working group

Upon approval from the Scientific and Technical Committee, the Developer (C.C.), the Co-Developer (N.U.), and the Evidence Review Team (S.S., S.T., F.C, M.O, G.C., A.Z., D.R.) of the SIR Study Center collaborated with a multidisciplinary experts panel of 18 clinicians with expertise in rheumatology, allergy and clinical

immunology, internal medicine, nephrology, gynecology and obstetrics, neonatology (A.T., A. L. B., M. S. C., P. C., G. C., E. D. P., M. F., M. C. G., M. G., A. H., A. I., M. L., D. M., M. M., M. M., M. P., M. L. U., S. Z.), a professional nurse (K.E.A.), a clinical psychologist (E.B.), and a representative (S.T.) from the National Association of Rheumatic Patients (ANMAR) through email discussions, web meetings, and participation in an online survey (*via* REDcap®). The participation of at least 75% of the working group members was considered a requirement for valid discussions and evaluations for the development of final recommendations.

Stakeholder involvement

A multidisciplinary, multiprofessional, and national group of physicians, healthcare professionals from the FOR-RHeUMA, and representatives from ANMAR were invited to evaluate and vote on the outcomes and text of these recommendations. These recommendations were developed without any contribution or collaboration with any pharmaceutical company or industry.

Audience

Physicians [rheumatologists, clinical immunologists, immunologists and allergists, gynecologists/obstetricians, internal medicine specialists, and general practitioners (primary care)] and all healthcare professionals involved in the management of patients with RD (secondary care) in primary, secondary, and tertiary healthcare settings, both at the community and hospital levels. Patients, policymakers, and organizers of care regarding reproductive health in patients with RD in the Italian National Health Service.

Search strategy, inclusion and exclusion criteria, data extraction, and synthesis into the evidence profile

Starting from structured clinical questions according to the Population, Intervention, Comparator, Outcome (PICO) framework of the reference guideline (11), disease outcomes were evaluated by the panel (March 13-24, 2022) and stakeholders (April 15-29, 2022) (17). Outcomes assessed as "important and essential" or "important but not essential" were used to guide the systematic search for scientific evidence.

The literature search was based on the key words and strings adopted by the reference recommendations and in accordance with the outcome voting (17). The Evidence Review Team assessed the quality of the ACR reference recommendations using the online tool Appraisal of Guidelines Research and Evaluation (AGREE) II, and five evaluators (C.C., S.S., S.T., F.C, M.O) assigned a score and an overall judgment for each guideline (17). An initial update of the scientific evidence was conducted by performing a systematic literature review from the end date of the reference guideline search (May 8, 2018) to April 6, 2022, and a second update to January 22, 2023. The following databases were queried: Medline (*via* PubMed), Embase (*via* Ovid), and Cochrane Library (*via* Cochrane Central). The Evidence Review Team conducted study selection and data extraction (by at least two members independently). For the scientific literature search, the following inclusion criteria were applied: English, Italian, or other languages with available translations; relevance to the clinical questions; and all study designs (experimental and observational clinical studies, case reports with a sample size of at least 2). Publications such as recommendations, guidelines, consensus statements, case reports, or those in languages for which translation was not available, and those not relevant to the clinical questions were excluded. The flow of study selection is depicted in Figure 1. The results of data extraction were synthesized, meta-analyzed, and reported in summary tables (Summary of Findings, SoF) divided by PICO (17).

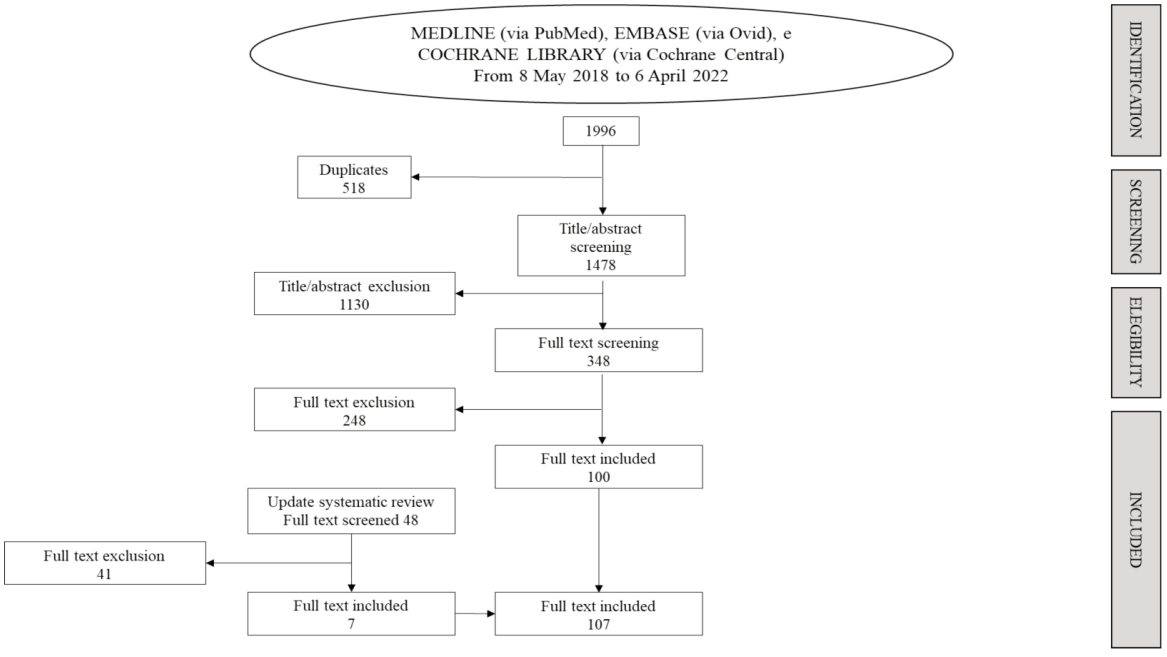

Figure 1. Steps in the systematic reviews on the development of guidelines on reproductive health in rheumatic diseases.

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Critical appraisal of quality

The Evidence Review Team assessed the quality of evidence (QoE) retrieved from systematic search following the GRADE method by assessing the following domains: limitations (Quantification of Bias Risk), inconsistency, indirectness, imprecision, and publication bias (through visualization of funnel plots and Egger's test). The risk of bias was assessed with the following tools: Risk Of Bias In Non-randomised Study - of Interventions (ROBINS-I) (18), Revised Cochrane risk-of-bias tool for randomized trials (19), and the Quality in Prognostic Studies (20) for treatment and prognosis (17). Finally, an overall judgment on quality was assigned to the evidence using the terms "high", "moderate", "low", and "very low" based on the expected impact on the confidence placed in the estimate of the effect (*Supplementary Table 1*). The judgment "not assessable" was assigned if the evidence was deemed insufficient to make an assessment.

From the evidence profile to the evidence-to-decision framework and the development of the recommendations

The results of the SoF tables and the quality assessment were structured into the evidence-to-decision (EtD) framework, which served to conduct the debate on the recommendations among panel members *via* web meetings (October 11 and 18, November 29, and December 13, 2022). Hence, considering the available scientific evidence, the scarcity, and heterogeneity of the studies, a judgment on the strength of the recommendations was made, and the statements were considered either strong or conditional in accordance with the views of patients, clinicians, and policymakers (*Supplementary Table 1*). During the recommendation discussion process, the latest British Society for Rheumatology guideline on prescribing drugs in pregnancy and breastfeeding (12, 13) became available and was considered by the Panel to solve contentious issues or as additional discussion points. The panel's considerations on the strength of recommendations, risks and benefits, and applicability were reported in the EtD tables based on the updated evidence (17). The AGREE checklist for guideline publication was used as a guide for the final version of these recommendations (21).

Approval of the recommendations and stakeholders' consultations

The members of the panel rated the draft of the recommendation by using a 1(worst)-to-9(best) score *via* an online survey (January 28 - February 20, 2023; 21/21 complete responses, response rate 100%). An average score >7 was defined *a priori* to consider the final recommendation to be valid and approved for clinical practice. The outcome of the vote for each recommendation is reported in the document published on the Italian National Institute of Health website (17). Stakeholders were consulted to externally review and rate (1-to-9-point scoring) the draft of the recommendations *via* an online survey (April 2-14, 2023, *via* REDcap®). The comments from those who responded were taken into account for the development of the final version of the recommendations (17).

Results

Key to understanding this guidance

Each recommendation is reported with the QoE, strength of the recommendation, and level of agreement among the members of the panel (*Supplementary Table 1*). The text supporting each recommendation is structured as follows: i) *supporting evidence* - list of the evidence; ii) *from evidence to recommendation* – Panel's discussion based on the evidence and the clinical experience used to develop the recommendation. A summary of all recommendations is provided in the Italian National Institute of Health document (17).

Recommendations

Contraception

Details are reported in *Supplementary Table 2*.

Good clinical practice

- In women with RD of childbearing age, it is suggested to discuss contraceptive strategies and potential plans for pregnancy early on, either during the first visit or in the early stages of disease management, or whenever treatment with potentially teratogenic drugs begins.
- The counseling regarding contraceptive methods for each individual patient should be based on the effectiveness and safety of the various proposed strategies, as well as the woman's individual values and preferences.
- In women with RD for whom the use of other, more effective, forms of birth control is contraindicated, we suggest using barrier contraceptive methods over other less effective options or no contraception at all.

Supporting evidence for recommendations 1.1.a and 1.1.b

The most suitable contraceptive method for each woman should be evaluated based on individual characteristics (type and activity of the disease, presence of thrombotic risk factors, and patient preferences). The thrombotic risk associated with the use of progestin-only pills compared to no use of hormonal contraception has been addressed by one randomized controlled trial (RCT) (22) and three observational studies (23-25), with indirect evidence. The available evidence does not report a higher incidence of adverse events in women receiving hormonal therapy with progestin-only pills.

From evidence to recommendations 1.1.a and 1.1.b

This recommendation is broad in nature and aims to provide a framework for subsequent specific recommendations on different contraceptive methods and/or pathological contexts. The panel acknowledged that the correct timing of conception is achieved through a reasoned and shared choice of the most effective and safe contraceptive for women with RD. For this reason, despite the lack of evidence for most of the treated PICO questions, this recommendation was voted as conditional in favor.

Supporting evidence for recommendation 1.2

As for women with other RD, contraceptive choices for women with SLE without aPL are based on limited evidence. The available studies explore only some aspects of contraception. In particular, the recommendation regarding the use of combined hormonal contraception (pill, patch, or vaginal ring) compared to no hormonal contraception on the risk of thrombosis is based on the presence of direct evidence [1 RCT (26) and 1 observational study (23)] as well as indirect evidence [1 RCT (22), 2 observational studies (24, 27)]. Studies supporting the safety and efficacy of hormonal contraceptives on the risk of nephritis and exacerbation of

non-nephritis diseases have been separately analyzed for the use of combined estrogen-progestin contraception (pill, patch, or vaginal ring) and progestin-only pill, in both cases compared to no hormonal contraception. In the first case, the risk of disease flare was addressed by two RCTs (22, 26) and two observational studies (24, 28) with direct evidence. An additional observational study provided indirect evidence (27). In the second case, data are available from one RCT (22) and one observational study (25). Another observational study indirectly addressed the issue (29).

From evidence to recommendations 1.2

SLE causes an increased risk of pregnancy complications for both the mother and fetus. Despite the increased risk of pregnancy complications in women with SLE compared to healthy women, the consensus now recognizes that tight control of the disease before and throughout gestation, together with appropriate therapies, is the key factor for a favorable pregnancy outcome.

Panelists found an agreement in recommending, even strongly, the use of forms of hormonal contraception over their non-use in patients with stable disease (low disease activity), despite the quality of the evidence being low/moderate or absent. Likewise, even in the absence of evaluable evidence, in women with SLE with moderate or severe disease (including active lupus nephritis), the panelists strongly recommended the use of progestin-only contraceptives (progesterone pill, progestin implant) or intrauterine device (IUD) and to avoid the use of combined estrogen-progestin contraceptives. The use of depo-medroxyprogesterone has not been discussed as it refers to a medicinal formulation not available in Italy.

Evidence to support recommendations 1.3

Patients with aPL positivity have an increased thromboembolic risk. Studies that have explored the safety and effectiveness of hormonal contraception, including estrogen-progestin, in women with aPL are very scarce. The impact of estrogen-progestin contraception (pill, patch or vaginal ring) compared to the absence of hormonal contraception on the risk of thrombosis was addressed by an observational study with indirect evidence (30).

From evidence to recommendations 1.3

The recognized pro-thrombotic state due to the presence of aPL requires caution in the use of estrogen-progestin contraception. Given this consideration, the panelists, even in the absence of evaluable evidence, strongly advise against the use of combined estrogen-progestin therapy. The use of emergency contraception (post-coital), even in the absence of available dedicated studies, can be recommended conditionally in conditions of necessity.

Evidence to support the recommendations 1.4

No clinical studies have been identified that explored the safety and effectiveness of different contraceptive options in relation to the different conditions specified in the PICOs in question, such as, for example, the use of immunosuppressive therapy.

From evidence to recommendations 1.4

The choice of contraceptive strategy in women taking immunosuppressive therapy must consider multiple aspects, including the nature and activity of the disease, the presence of thrombotic risk factors, and the specific type of immunosuppressant being used. Despite the absence of evaluable studies, the panelists conditionally recommend the use of an IUD (copper or progestin). In women taking mycophenolate mofetil or mycophenolic acid, the use of one IUD (alone) or the combined use of two alternative methods of contraception is conditionally recommended, also to reduce the risk of ongoing unplanned pregnancies of therapy not compatible with gestation.

Assisted reproduction

Details are reported in *Supplementary Table 3*.

Evidence to support recommendation 2.1.a

This recommendation arises from data coming from indirect evidence (31).

From evidence to recommendation 2.1.a

We would like to point out that the positivity of aPL itself does not represent an absolute contraindication to ART procedures. In fact, both a careful patient evaluation and risk stratification are necessary.

Evidence to support the recommendations 2.2

Recommendations regarding this topic derive only from indirect evidence (31).

From evidence to recommendations 2.2

Disease activity represents an element that influences the prognosis of pregnancy. For this reason, also in the case of ART, preconception counseling is recommended in order to plan the pregnancy timing and the phases in which the disease presents with moderate-severe activity. There is no evidence regarding the effectiveness of introducing or increasing the dosage of prednisone before ART, unless necessary for the control of the disease itself and for the reduction of disease activity.

Evidence to support the recommendations 2.3

There are no works in the literature that address the topic, only indirect evidence is available.

From evidence to recommendations 2.3

Regarding recommendation 2.3.d, patients with thrombotic APS are already being treated with oral anticoagulant: therefore, in the case of ART, the anticoagulant drug is replaced with a drug compatible with pregnancy while maintaining a therapeutic dosage. Details regarding the management of patients with aPL with or without clinical manifestations can be found in the dedicated section (Recommendation 3.4: pregnancy counseling in women affected by APS).

Evidence to support recommendation 2.4.a

For this recommendation, only indirect evidence (31).

From evidence to recommendation 2.4.a

Although the available data are limited and therefore the quality of the evidence cannot be assessed, the panel considered it important to recommend, in a conditional manner, to continue immunosuppressive and/or biological therapies (except for cyclophosphamide) during ovarian stimulation and recovery of oocytes. It is recommended to follow ovarian preservation options, including the use of gonadotropin-releasing hormone, to protect ovarian function and fertility.

Pregnancy counseling

Details are reported in *Supplementary Table 4*.

Good clinical practice

Shared management with a rheumatologist or another specialist with experience in pregnancy management is preferable.

In women with SLE during pregnancy, it is strongly recommended to monitor disease activity with laboratory tests at least once per trimester.

In women with RD who are considering pregnancy or who are already pregnant, we strongly suggest counseling patients as follows: maternal and pregnancy outcomes are more favorable when the disease is in a quiescent or low activity state prior to conception. In males with RD undergoing cyclophosphamide therapy who are not planning to have a child, we suggest - where possible and when future conception is desired - to proceed with sperm cryopreservation, ideally before starting cyclophosphamide therapy.

Evidence to support the recommendations 3.1

In general, the evidence from the systematic literature review for this recommendation is scarce, coming from a limited number of patients and limited to some drugs. For this reason, the strength of the recommendation is very low (32-40). The evidence supporting recommendation 3.1.c comes mainly from indirect data on predominantly descriptive studies (41-49). Recommendation 3.1.d is based on indirect data from predominantly descriptive studies (44-46, 48, 50-61).

From evidence to recommendations 3.1

The panelists recommend consistently assessing the desire for pregnancy in patients of childbearing age to select a treatment that is compatible with their reproductive goals. In the case of a patient already on treatment, compatibility must be verified when planning a pregnancy. In the case of a drug that is not compatible with it, it will be advisable to plan a therapeutic switch in advance and have time to evaluate both the tolerability and effectiveness of the new therapeutic choice. The panel deemed it appropriate to specify that the search for anti-Ro/SSA and anti-La/SSB antibodies is necessary for every woman affected by RD "at least once" or during counseling or at the beginning of pregnancy. Conversely, it was deemed not necessary to repeat the dosage of these antibodies, unless particular situations existed throughout the pregnancy. Also, regarding aPL, their research is necessary for every woman affected by RD who is pregnant or planning a pregnancy. It was deemed appropriate to specify that it is preferable to search for these antibodies in the pre-conceptional phase; the search must include all aPL (anti-cardiolipin IgG and IgM, anti-β_2-glycoprotein I IgG and IgM, Lupus Anticoagulant).

Evidence to support the recommendations 3.2

Recommendation 3.2.a. arises from evidence coming only from observational studies [direct: (62-64); indirect: (65-72)]. Recommendations 3.2.b., 3.2.c., 3.2.d are based on data from observational studies only (49, 62, 65-69, 71-85).

From evidence to recommendations 3.2

Given the known risk of neonatal lupus and fetal cardiac complications, the use of hydroxychloroquine (HCQ) is recommended during pregnancy in women with RD and anti-Ro/SSA and anti-La/SSB antibodies, unless there are contraindications. The risk of cardiac complications in case of positive anti-Ro/SSA and anti-La/SSB antibodies is well known, even in the absence of a history of congenital heart block; therefore, the panelists recommend an ultrasound screening in these patients. In these cases, the frequency of the fetal ultrasound may vary based on clinical judgment and the characteristics of the patient. However, given that the risk of complete heart block increases greatly (from 2-18%) in case of history of a child born with congenital heart block or neonatal lupus, experts recommend an ultrasound screening every week starting from 16th-18th weeks of gestation up to the 26th weeks of gestation.

In case of 1st-2nd degree heart block, the use of the steroid (dexamethasone) at the same dosage of 4mg orally per day is therefore recommended. In the case of 3rd degree heart block, however, dexamethasone must be taken into consideration only in the presence of signs of inflammation.

Regarding the presence of anti-Ro/SSA and anti-La/SSB antibodies and cardiac involvement in the fetus, it is worth underlining that, in some particular situations, treatment with plasmapheresis can also be considered. The guidelines of the American Apheresis Society suggest the use of plasmapheresis in pregnant women, with anti-Ro/SSA and anti-La/SSB antibodies, with great caution, only in selected cases and only after multidisciplinary discussion (grade 2C recommendation, category III). The literature on the topic supporting the recommendation is scarce and based on a few patients. The proposed treatment regimen varies from 3 times a week up to once a month, all patients received steroids and therapy with intravenous immunoglobulin (IVIG) or azathioprine was often associated (86).

Evidence to support the recommendations 3.3

Pregnancy counseling in women with aPL without APS (*i.e.*, in the absence of previous thrombotic events or pregnancy morbidity attributable to the classification criteria for APS) is based on a small number of studies. One RCT study (87) provides no direct evidence regarding the use of low-dose acetylsalicylic acid (LDA) during pregnancy versus no treatment to improve maternal and pregnancy outcomes in women with aPL and recurrent miscarriages as the only manifestation of pregnancy morbidity. In contrast, the role of the use of LDA during pregnancy is supported by several observational studies (67, 88-91). Indirect evidence is also provided by two RCTs (92, 93). The systematic use of HCQ during pregnancy compared to no treatment is not supported by evidence. Furthermore, no further evidence can be evaluated to support the use of heparin prophylaxis or low-molecular-weight heparin (LMWH) in association with LDA in women who do not meet the criteria for obstetric or thrombotic APS and who do not have a high-risk profile.

From evidence to recommendations 3.3

The management of pregnancy in women with APS is based on the use of LDA and LMWH, at prophylactic or therapeutic doses depending on the history of thrombosis and the patient's previous history of pregnancy morbidity. Prophylactic choices in women with aPL without established APS are based on a limited number of studies, lack of direct evidence, or studies with a high risk of bias. For these reasons, in light of the quality of the available evidence, the panelists conditionally recommend the use of LDA during pregnancy in order to improve maternal and pregnancy outcomes. Furthermore, in the absence of full-blown APS, the use of heparin prophylaxis or LMWH in association with LDA is not recommended, albeit conditionally. The use of HCQ in women with aPL is currently being studied in at least one RCT (94).

Evidence to support recommendation 3.4.a

The management of pregnancy in women affected by obstetric APS without a previous history of thrombosis is based on the use of prophylactic dose heparin or LMWH in association with LDA.

This recommendation is based on evidence from three head-to-head RCTs (95-97) and five head-to-head observational studies (93, 98-101). The results provided by direct RCT studies show a favorable effect of LMWH + LDA compared to the use of LDA alone across different pregnancy outcomes. The results of the observational studies provide further evidence to support the use of prophylactic dose heparin or LMWH in combination with LDA to improve various pregnancy outcomes, except intrauterine growth restriction.

From evidence to recommendation 3.4.a

The available evidence, although heterogeneous in terms of study design and sample analyzed, overall supports the use of prophylactic dose heparin or LMWH in association with LDA for the management of pregnancy in women affected by obstetric APS without a previous history of thrombosis. Given the moderate QoE (which includes the presence of at least 3 RCTs) the panelists agreed to strongly support this recommendation.

Evidence to support recommendations 3.4.b, 3.4.c, 3.4.d, 3.4e

The management of pregnancy in women with obstetric APS who have failed standard therapy is based on a limited number of studies of low or very low quality. As regards the use of IVIG in addition to prophylactic heparin and LDA, in one RCT (102) a favorable direct effect was observed only for some pregnancy outcomes (more marked for preterm birth, less on preeclamptic complication). The results are also confirmed in a second RCT (103) and in observational studies (104). The latter shows a slight advantage in using IVIG in addition to prophylactic heparin and LDA.

The use of prednisone in addition to heparin or LMWH in combination with LDA is addressed by three observational studies (105-107) and one observational study with indirect evidence (108). In the 2014 Ruffatti study, the live birth rate in the LDA group was 68.8% and in the LDA + heparin + IVIG group it was 75%. In Deguchi 2017 (105), the use of prednisolone was identified as a risk factor for the onset of hypertension. The 2017 Ye study (108) compared prednisone + HCQ + LDA + LMWH with LDA + LMWH. The results showed a favorable effect on some outcomes (fetal loss and small for gestational age) but not on others (preterm birth). The use of therapeutic doses of heparin or LMWH in association with LDA in obstetric APS women who have failed standard therapy is not supported by evaluable evidence and is judged by the panelists as a viable option only if not contraindicated. Furthermore, although in the absence of evaluable evidence, in pregnant women with thrombotic APS, heparin at therapeutic dosage in association with LDA is recommended over the use of non-heparin anticoagulation. In the same context, albeit in the absence of analyzable evidence, the panelists agree in suggesting the suspension of therapy with vitamin K antagonists and the initiation of heparin at therapeutic doses once the pregnancy has been confirmed.

The use of prophylactic dose heparin (unfractionated or LMWH) during the postpartum period is recommended in women with obstetric APS, albeit in the absence of evaluable studies. Its use is suggested for 6 weeks in the post-partum period, as already indicated in other contexts (109), although in the absence of strong evidence. Finally, in pregnant women with obstetric and/or thrombotic APS +, the use of HCQ is based on a very low level of evidence, in the absence of RCTs or direct evidence.

From evidence to recommendations 3.4.b, 3.4.c, 3.4.d, 3.4e

The management of pregnancy in women with obstetric APS who have failed standard therapy is based on low or very low-quality evidence or, sometimes, for some therapeutic approaches, on the absence of studies providing direct evidence. The available studies often involve small sample sizes. On the one hand, this fact is justified by the relatively low prevalence of the disease, on the other, the low sample size cannot fail to impact the precision of the estimates of the effects of the various treatments. In some cases, such as for the use of HCQ, we relied on a very low level of evidence, often extrapolated from other areas of these recommendations (impact on the pregnancy of continuing the drugs compared to stopping the drugs before or during pregnancy for women with RD). However, the panelists agreed to offer recommendations in support of specific therapeutic strategies, occasionally with strong conviction despite limited evidence, to ensure a pragmatic and effective approach in clinical practice.

Evidence to support the recommendations 3.5

The use of HCQ and LDA in women with SLE in the context of pregnancy is based on evidence provided by observational studies and on indirect evidence extrapolated from other areas of these recommendations (impact on the pregnancy of continuing medications compared to discontinuation of medications before or during pregnancy for women with RD). A case-control study showed similar flare rates between HCQ-exposed and HCQ-unexposed pregnancies (62% *vs*. 58%) (110). One observational study showed a higher rate of disease flare in women who discontinued HCQ during pregnancy (55%) vs those who continued taking it (30%) or never took it (36%) (111).

From evidence to recommendations 3.5

The continuation of HCQ intake in women with SLE during pregnancy is considered by the panelists as a strategy to be implemented systematically, unless there are contraindications, despite the low level of evidence. There is no new evidence available to support the initiation of HCQ therapy in women who were not taking this therapy before pregnancy.

There is currently no clear evidence to support the systematic use of LDA in all women with SLE during pregnancy. For this reason, also in light of experiences present in the scientific literature on this topic (112), its use is currently recommended in a conditional manner.

Evidence to support recommendation 3.6

Despite the importance of this particular clinical condition, the data in the literature are scarce and heterogeneous.

From evidence to recommendation 3.6

Scleroderma renal crisis is burdened by high mortality even today. The introduction of specific antihypertensive strategies, based on the use of angiotensin-converting enzyme inhibitor or an angiotensin receptor blocker, has reduced mortality by almost 30% in recent years. Therefore, this approach remains indicated even in pregnancy (11). However, the panelists underline the teratogenicity of such drugs. In fact, they act by blocking the renin-angiotensin system, leading, in the second/third trimesters, to abnormal renal development in the fetus, a condition known as Fetal Renin-Angiotensin System Blockade Syndrome (113).

A systematic review of the literature also reported a significant risk of cardiovascular malformations, miscarriages, and stillbirths in women taking such therapies (114).

Evidence to support the recommendations 3.7

This recommendation arises from data derived from a single observational study (115).

From evidence to recommendations 3.7

In formulating recommendation 3.7a, the panel of experts deemed it appropriate to specify that the washout time for cyclophosphamide is 12 weeks.

Medications before/during/after pregnancy - paternal exposure

Details are reported in *Supplementary Table 5*.

Good clinical practice

In male patients with RD who are planning to have a child, it is suggested to discuss the use of medications before planning a pregnancy (Figure 2).

Evidence supporting the recommendations 4.1

From the systematic literature review, very low-quality indirect evidence emerged from a limited number of studies. In these studies, only some of the medications reported in the recommendation were considered and often mentioned as a class (anti-tumor necrosis factor (TNF) α drugs as a class; certolizumab pegol; nonsteroidal anti-inflammatory drugs (NSAIDs); methotrexate; sulfasalazine; tofacitinib) (17). For other drugs, no evidence has emerged to support this recommendation.

From evidence to recommendations 4.1

In general, the evidence from systematic literature reviews for this recommendation is scarce and limited to a few drugs. For this reason, the strength of the recommendation was discussed by the expert panel, acquiring also some information that emerged recently from the guidelines by the British Society for Rheumatology, published during the discussion with the expert panel (12). Therefore, given the limited data available, it is recommended to always evaluate the risk-benefit ratio when choosing whether to continue therapy. Although there is no evidence regarding the use of cyclophosphamide in male patients with rheumatological disease who are planning a pregnancy, the expert panel strongly recommends its discontinuation, at least 12 weeks before conception due to the mechanism of action of the drug and its teratogenic and mutagenic potential. There is no evidence available also regarding thalidomide. However, it is conditionally suggested to stop the drug at least 4 weeks before conception due to the known female teratogenicity and the finding of the molecule in male seminal fluid. Even in the absence of evidence deriving from the systematic review of the literature, the panel of experts strongly recommends continuing therapy with HCQ considering its benefits and the possible flare of RD in case of discontinuation. Despite the absence of evidence, the panel of experts strongly recommends the continuation of azathioprine/6-mercaptopurine, after a careful evaluation of the risks-benefits of its discontinuation. Similarly, the panel of experts expressed its opinion in favor of the continuation of anti-TNFα drugs; the strength of the recommendation, despite the very low quality of the evidence, is given by the risk of disease flare in case of drug interruption. No evidence emerged regarding colchicine therapy; the panel of experts recommends its continuation after a careful risk-benefit assessment. In the absence of evidence regarding recommendations 4.1.g and 4.1.h, the expert panel conditionally recommends the continuation of therapy with leflunomide and mycophenolate mofetil. Although no direct evidence exists specifically for selective cyclooxygenase-2 (COX-2) inhibitors, the panel of experts includes them in the recommendations by extrapolating from the indirect evidence currently avail-

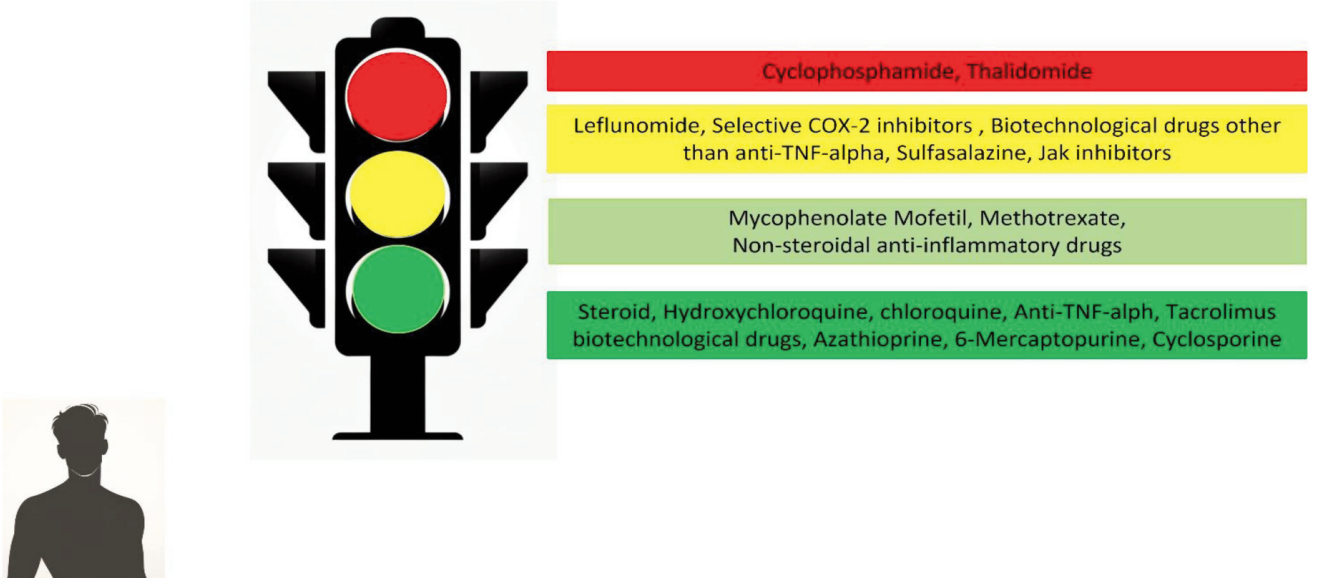

Figure 2. Summary of recommendations for paternal drug exposure in male patients with rheumatic diseases. In red: recommendation against (strongly or conditionally); in yellow: recommendation in favor conditionally or absence of conclusive scientific evidence; in light green: absence of clear evidence against and/or absence of consolidated use in clinical practice; in dark green: strong recommendation in favor. COX-2, cyclooxygenase-2; TNF, tumor necrosis factor; JAK, Janus kinase.

able on non-selective NSAIDs. Regarding sulfasalazine, the panel of experts evaluated the limited evidence deriving from the systematic review of the literature and three additional reviews exploring paternal exposure to anti-rheumatic drugs (116-118). Since there was no evidence of adverse outcomes or teratogenic potential, the panel recommends continuing the drug. Given the potential fertility problems found in patients treated with sulfasalazine (asthenozoospermia and oligospermia) and given their reversibility after discontinuing therapy, in case of difficulty in conceiving it is useful to consider stopping the drug. Given the absence of evidence deriving from the systematic literature review, recommendations 4.1.n and 4.1.o, regarding the continuation of ciclosporin and tacrolimus respectively, were judged as strong recommendations based on the opinion of the panel of experts, also supported by the fact that these drugs are more frequently used in Italy than in other countries. As regards non-anti-TNFα/small molecule biological drugs [anakinra, rituximab, abatacept, apremilast, belimumab, secukinumab, tocilizumab, ustekinumab, Janus kinase (JAK) inhibitors], because of limited data (12), the expert panel conditionally recommends their continuation.

Medications before/during/after pregnancy - maternal exposure

Recommendations on the safety of drugs (conventional - *Supplementary Table 6a*; biological - *Supplementary Table 6b*; glucocorticoids - *Supplementary Tables 6c and 6d*) for pregnant women with RD or those planning a pregnancy.

Good clinical practice

It is suggested to discuss the use of medications before planning a pregnancy. It is also suggested to discuss future pregnancy when starting treatment with any drugs that can affect fertility such as cyclophosphamide. In women inadvertently exposed to teratogenic drugs during pregnancy, it is strongly suggested to consider discontinuing therapy and consulting a maternal-fetal medicine specialist or geneticist.

Evidence supporting the recommendations 4.2

The evidence supporting this recommendation comes from mostly indirect evidence of very low quality. In fact, from the systematic literature review, a limited number of studies with small case series emerged, often heterogeneous and in which only some of the drugs (NSAIDs, methotrexate, cyclophosphamide, leflunomide, sulfasalazine, azathioprine/6-mercaptopurine) were considered and then reported in the recommendation (17). For other drugs, no evidence emerged to support this recommendation.

From evidence to recommendations 4.2

Given that the evidence supporting this recommendation from the systematic literature review is scarce and limited to certain drugs, and in some cases only specific scenarios, the strength of the recommendation was thoroughly discussed by the panel of experts. In addition to considering the current guidelines, they also incorporated insights from the guidelines published by the British Society for Rheumatology (12). Considering the lack of evidence regarding the use of COX-2 drugs during the conception period and taking note of what is stated in the British Society for Rheumatology guidelines which contraindicate the use of COX-2 drugs in this period, the panel of experts expressed a preference for the use of NSAIDs compared to COX-2 during the conception period. Furthermore, the panel members point out that the intake of NSAIDs at this stage could cause narrowing or premature closure of the arterial duct of Botallo and expose the fetus to renal dysfunction with possible renal failure with oligohydramnios.

Regarding the timing of discontinuation of methotrexate before conception, the panel members underline the need to suspend the drug "at least one menstrual cycle" and preferably 3 months before conception.

Due to the mechanism of action of drugs such as thalidomide and mycophenolate mofetil and their teratogenic and mutagenic potential, although in the absence of studies that have evaluated the use of the drugs in pregnant women with RD, their interruption is strongly recommended by the panel.

In the event of pregnancy occurring during treatment with leflunomide, the panel agrees to indicate a washout with cholestyramine lasting eleven days (as reported in the drug's technical data sheet) and in any case until the drug levels are detectable in the blood.

Evidence supporting the recommendations 4.3

Studies evaluating the impact of biologics on pregnancy outcomes evaluated pregnancies in women with autoimmune diseases taking mainly anti-TNFα drugs, but also rituximab, abatacept, tocilizumab, ustekinumab, and anakinra (17). There is indirect evidence coming from observational studies. No stratified analysis of birth outcomes for the different drugs is available. Overall, the authors of these studies found no increased risk of miscarriage, neonatal mortality, or congenital anomalies in patients exposed to biologic drugs. Limited data are present regarding the use of biosimilars compared to originator drugs.

From evidence to recommendations 4.3

The anti-TNFα drugs currently available have different pharmacokinetic and pharmacodynamic characteristics (half-life, bioavailability, placental transfer rates,...). These differences are not negligible and require careful consideration regarding their use during pregnancy. In the past, the varying rates of placental transfer of different anti-TNFα agents, along with the timing of drug exposure during the second and/or third trimester of pregnancy, have influenced the decision to avoid administering live vaccines during the first 7 months of the newborn's life. Considering the new evidence on the placental transfer of specific drugs, it is recommended to delay the administration of live vaccines to children exposed in utero with a variable timing depending on the different drugs (119). A single distinction regards certolizumab pegol which is only minimally transferred across the placenta. It is unlikely that children born from women who used certolizumab pegol during pregnancy will experience sufficient levels of TNFα inhibition significantly affecting the immune response.

Regarding the use of rituximab, while there are no direct reports of teratogenicity and only exposure during the second or third trimester has been associated with neonatal B cell depletion, there remains insufficient evidence to determine whether in-utero exposure to rituximab increases the risk of miscarriage, congenital malformations, low birth weight, intrauterine death, or adverse neurodevelopmental outcomes. For these assumptions, the panel suggests continuing rituximab during conception and, only in cases of severe maternal disease, at risk of maternal death or with risk of permanent organ damage, even during pregnancy.

Limited evidence has not demonstrated that non-anti-TNFα biologics are teratogenic; however, there is not enough evidence to be sure that they are compatible with pregnancy. For this reason, experts conditionally recommend continuing therapy during conception and suspending it at a positive pregnancy test.

Regarding the use of small-molecule-targeted JAK inhibitors and apremilast (by analogy with small-molecule-targeted, due to the short half-life and in the absence of pronouncements from other guidelines), in the absence of evidence, the panel expressed conditionally regarding the suspension of these drugs at least 2 weeks before trying to conceive. Based on the expert opinion, the panel suggests using contraception for at least 4 weeks after the last dose of tofacitinib or upadacitinib, and at least one week for baricitinib and filgotinib. Although the scientific evidence for the use of biosimilars in pregnancy and breast milk exposure is very limited compared to original biologics, it is expected that they may have comparable effects. Therefore, the recommendations referring to the active substances of biological drugs with available biosimilars can be considered valid based on indirect scientific evidence also for equivalent biosimilar drugs authorized on the market in Italy.

Evidence supporting recommendations 4.4 and 4.5

In support of this recommendation, there are several low-quality studies in the literature, mostly observational cohort studies, which have evaluated pregnancy outcomes, especially in patients with chronic arthritis and SLE (17).

From evidence to recommendations 4.4 and 4.5

Recent evidence describes a dose-dependent association of the use of prednisone with the risk of preterm birth (120) for which the panel of experts suggests, where necessary and in non-severe forms of the disease, to consider instead infiltrative therapy with steroids. However, in cases of high disease activity, the panel expressed its opinion on the possibility of evaluating treatment with intravenous glucocorticoids.

Breastfeeding

Recommendations for the use of drugs (conventional – *Supplementary Table 7a*; immunosuppressants – *Supplementary Table 7b*; biologics – *Supplementary Table 7c*; glucocorticoids – *Supplementary Table 7d*) during breastfeeding in women with RD.

Good clinical practice

Breastfeeding is strongly suggested if possible.

Disease control should be maintained with drugs compatible with breastfeeding and with a risk-benefit ratio assessed with the patient and her particular situation.

Evidence supporting the recommendations 4.6

From the systematic literature review, very low-quality evidence from a very limited number of studies emerged regarding piroxicam and HCQ (17, 121, 122). For other drugs, no evidence has emerged to support this recommendation.

From evidence to recommendations 4.6

Given that the evidence deriving from the systematic literature review for this recommendation is scarce and limited to some drugs, the panel of experts discussed the strength of the recommendation also referring to what is reported in the database regarding drug exposure in breastmilk (123). If necessary, the panel of experts suggests the use of NSAIDs during breastfeeding; among these, ibuprofen is the molecule to be preferred, considering its short half-life, the low levels found in breast milk, and its use also in children, as reported on LactMed® (123). Regarding the use of selective COX-2 inhibitors during breastfeeding, after consulting the LactMed® database, the panel of experts recommends, if necessary, choosing celecoxib, the only molecule of this class for which there is data in breastfeeding (123, 124). Despite the presence of low-quality evidence, if necessary, the panel of experts strongly recommends the use of HCQ during breastfeeding as its suspension could represent a risk for the patient, such as a disease flare. No evidence emerged from the systematic literature review regarding sulfasalazine therapy during breastfeeding. The panel of experts recommends evaluating possible therapeutic alternatives but, if necessary, recommends continuing the therapy conditionally, advising to delay the drug intake from feeding. If it is necessary to take colchicine during breastfeeding, the panel of experts recommends delaying breastfeeding, thus avoiding the peak concentration in breast milk that occurs 2-4 hours after taking the drug (123); the panel of experts suggests preferring alternative drugs.

Evidence supporting the recommendations 4.7

From the systematic review of the literature, no evidence emerged on the use of these drugs during breastfeeding.

From evidence to recommendations 4.7

Given the absence of evidence deriving from the systematic literature review for this recommendation, the expert panel discussed the strength of the recommendation also referring to what was reported in the LactMed® database (123). In the absence of literature data on the use of leflunomide during breastfeeding and in the absence of information available on LactMed® (123), the panel strongly recommends not using this drug in women who are breastfeeding, not knowing the amount of the excretion of the molecule into breast milk and its possible effects on the newborn. Similarly, regarding the use of mycophenolate during breastfeeding, the strength of the recommendation is equally justified. As regards cyclophosphamide, despite the absence of evidence deriving from the systematic review of the literature, the expert panel strongly recommends not using it in women who are breastfeeding as the drug is not considered compatible. Similarly, regarding the use of thalidomide during breastfeeding, the strength of the recommendation is equally justified. There is no evidence regarding the use of methotrexate during breastfeeding. LactMed® (123) reports some data relating to the finding of low doses of methotrexate in women who were breastfeeding and taking methotrexate at a medium-low dose (as in the treatment of rheumatoid arthritis. For these reasons, the panel of experts suggests not using methotrexate while breastfeeding. There is no evidence of the use of azathioprine/6-mercaptopurine, ciclosporin and tacrolimus during breastfeeding. If it is necessary to take one of these drugs during breastfeeding, the panel of experts recommends delaying breastfeeding and, if possible, preferring alternative drugs.

Evidence to support the recommendations 4.8

From the systematic review of the literature, no evidence emerged regarding the use of these drugs during breastfeeding.

From evidence to recommendations 4.8

Due to the lack of evidence, the panel of experts discussed the strength of the recommendation also referring to what was reported in the LactMed® database (123). The panel strongly recommends the use of anti-TNFα drugs, as a class, or rituximab, during breastfeeding, if necessary, as they are compatible drugs. For the other biological drugs (belimumab, tocilizumab, anakinra, abatacept, secukinumab and ustekinumab), the panel of experts recommends their use during breastfeeding considering their biochemical nature: high molecular weight proteins with expected low

excretion into maternal milk and possible partial digestion in the gastrointestinal tract of the newborn. As regards JAK inhibitor drugs, in the absence of evidence deriving from the systematic review of the literature, based on the indications of the guidelines by the British Society for Rheumatology (12) regarding the prescription of drugs during pregnancy and breastfeeding and also considering the lack of data from LactMed® (123) regarding such therapies, the expert panel recommends not using JAK inhibitors and apremilast during breastfeeding.

Evidence to support the recommendations 4.9

No evidence emerged from the systematic review of the literature.

From evidence to recommendations 4.9

In the absence of supporting evidence, the panel of experts, based on their expert opinion, strongly recommend the use of prednisone (or non-fluorinated equivalent), if necessary, during breastfeeding as it is a compatible drug. If the need for steroid doses is higher than 20 mg/day, the panel believes that breastfeeding should be delayed and breast milk discarded for the next four hours. During breastfeeding, regarding the use of drugs not covered in the previous recommendations, but which can be used in patients with RD (for example IVIG, LDA, heparin, direct oral anticoagulants (DOACs), warfarin) the panel recommends referring to LactMed® (123). Figure 3 details the summary of the recommendations about drug safety (conventional, immunosuppressive and biologics) for women with RD who are pregnant, or planning to become pregnant, and while breastfeeding.

Reflections on perinatal psychological health

The perinatal period constitutes a phase of great psychological complexity due to the important somatic, affective and relational changes that the birth of a child entails. Motherhood is often associated with an increased risk of depression and anxiety in the general population. This risk may increase in the presence of particular conditions, including RD. Perinatal psychological disorders can have important consequences for the mother, the family and the child's development.

Psychological health screening is the most effective tool for providing care to the greatest number of women, preferring, in outpatient and inpatient hospital settings, generic tools for detecting psychological distress, for reasons of organizational and clinical timing, unlike the screening already structured in Family Advice Centers. Whenever possible, screening should be offered during pregnancy and the first year post-partum. Women should be informed of the outcome and the opportunity for a meeting with a psychologist and, if necessary, psychiatric care.

Discussion

As already emphasized, there is no single national document that serves as an Italian guideline on the management of reproductive health in the course of RD, although there are dedicated pathways for individual diseases, attempts at standardization, and coding of disease-specific paths at the regional level, or Regional Diagnostic Therapeutic Care Pathways containing sections dedicated to the subject of these guidelines.

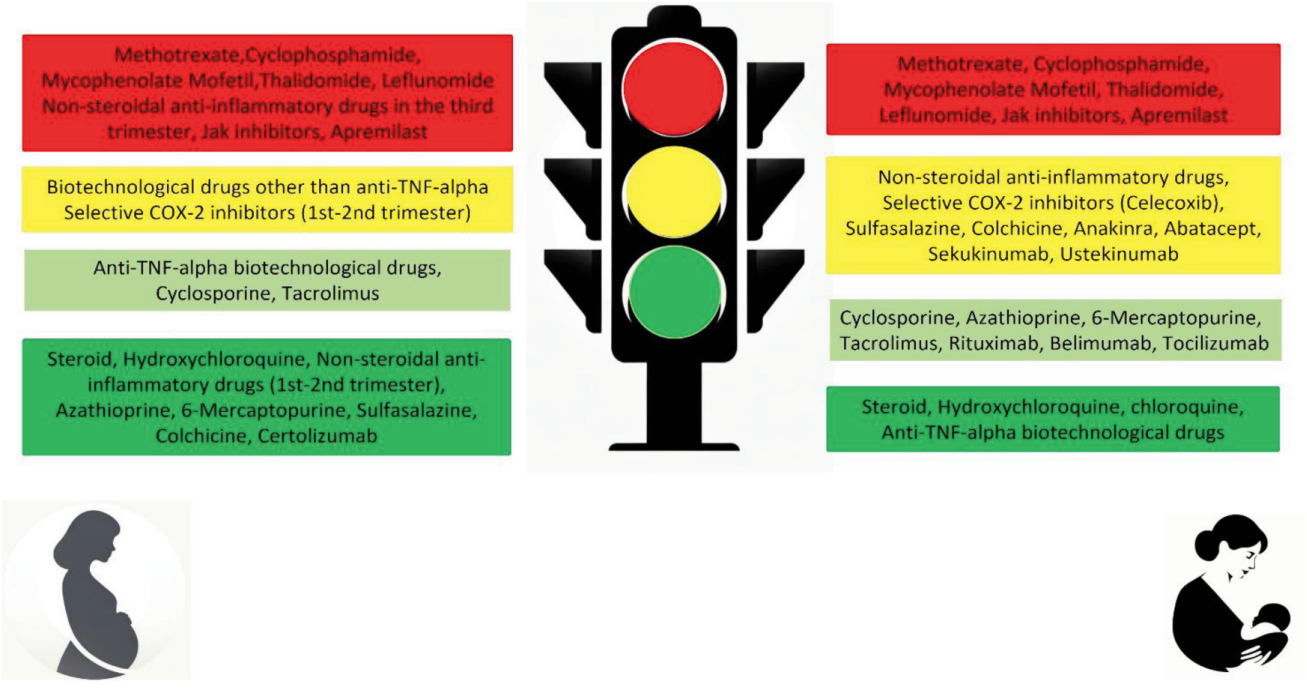

Figure 3. Summary of the recommendations about drug safety (conventional, immunosuppressive and biologics) for women with rheumatic diseases who are pregnant, or planning to become pregnant, and while breastfeeding. COX-2, cyclooxygenase-2; TNF, tumor necrosis factor.

In the absence of national recommendations, the current reference is the recommendations issued in 2016 by the European Alliance of Associations for Rheumatology (EULAR) for SLE and APS, the EULAR 'points to consider' on the use of anti-rheumatic drugs during pregnancy and lactation, and, more recently, the 2020 guidelines of the ACR for RD (4, 10, 11). The GRADE-ADOLOPMENT methodology (14) was chosen in analogy with the latest guidelines promulgated by SIR (125), due to the advantage it offers in terms of containing economic resources, human resources, and time-labor compared to the development of new guidelines. Moreover, for the development of this update, a systematic strategy was adopted aimed at the identification, analysis, and synthesis of international guidelines (11) and their adaptation to the Italian health context. Compared to the reference guidelines, it was decided to organize the recommendations by major areas of intervention (contraception, assisted fertilization, pre-pregnancy counseling, drugs before, during, and after pregnancy), including sections dedicated to paternal, maternal exposure, and breastfeeding to ensure easier use in specific contexts. In line with the ACR guidelines, the importance of multidisciplinary management was emphasized, and the key points regarding the management of the various issues related to reproductive health have remained substantially unchanged.

During the process of adapting the ACR's reference guidelines from 2020 (11), the BSR guidelines (12) were also published, which have not been the subject of a new adaptation but have provided an additional evidence support tool for the panelists in case of grey areas, such as, for example, in reference to maternal and paternal exposure to certain drugs (*e.g.*, abatacept, apremilast, belimumab, secukinumab, tocilizumab, ustekinumab, JAK-inhibitors).

These updated recommendations have some limitations. Firstly, the last update of the bibliographic research is conditioned to the end date of the search (January 3, 2023), and studies published after this date were not included in the discussion of the scientific evidence. However, at the time of drafting this version, these recommendations are the most up-to-date available. Secondly, most of the recommendations are based on low or very low-quality evidence, mainly from retrospective studies and indirect evidence; in such circumstances, the panelists sometimes had to express their opinions on the different statements by resorting to their own expertise. Finally, it should be noted that there were no studies included that explored aspects of health economics. However, when possible, the aspects of efficiency and effectiveness of specific strategies have been considered in this version to best adapt to the Italian health context.

Update plan

The need for updating will be re-evaluated after 3 years. In case of significant scientific novelties published in the literature, a partial or complete revision of these guidelines will be considered.

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Online supplementary material:
Supplementary Table 1. Guidance for the appraisal of the quality of evidence and strength of the recommendations in accordance with the Grades of Recommendation Assessment, Development and Evaluation approach.
Supplementary Table 2. Recommendations for contraception in women with rheumatic diseases.
Supplementary Table 3. Recommendations on assisted reproduction for women with rheumatic diseases.
Supplementary Table 4. Recommendations on pregnancy counseling for women with rheumatic diseases.
Supplementary Table 5. Recommendations on paternal drug exposure in male patients with rheumatic diseases.
SupplementaryTable 6a. Safety of conventional drugs for pregnant women with rheumatic diseases or those planning a pregnancy (recommendations 4.2).
Supplementary Table 6b. The safety of biological drugs for pregnant women or women planning a pregnancy with rheumatic diseases (recommendations 4.3).
Supplementary Table 6c. The use of non-fluorinated glucocorticoids during pregnancy and childbirth in women with rheumatic diseases (recommendations 4.4).
Supplementary Table 6d. The use of non-fluorinated glucocorticoids in women on chronic therapy with low doses of glucocorticoids during delivery (recommendations 4.5).
Supplementary Table 7a. The use of conventional drugs during breastfeeding in women with rheumatic diseases (recommendations 4.6).
Supplementary Table 7b. The use of immunosuppressive drugs during breastfeeding in women with rheumatic diseases (recommendations 4.7).
Supplementary Table 7c. The use of biological drugs during breastfeeding in women with rheumatic diseases (recommendations 4.8).
Supplementary Table 7d. The use of glucocorticoid drugs during breastfeeding in women with rheumatic diseases (recommendations 4.9).