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**Guidelines**



Guidelines

# Executive Summary: British Society for Rheumatology guideline on prescribing drugs in pregnancy and breastfeeding: comorbidity medications used in rheumatology practice

**Karen Schreiber[1,2,3,†], Margreta Frishman[4,†], Mark D. Russell[5], Mrinalini Dey[6], Julia Flint[7], Alexander Allen[8], Amy Crossley[9], Mary Gayed[10], Kenneth Hodson[11], Munther Khamashta[12], Louise Moore[13], Sonia Panchal[14], Madeleine Piper[15], Clare Reid[9], Katherine Saxby[16], Naz Senvar[17], Sofia Tosounidou[18], Maud van de Venne[19], Louise Warburton[20,21], David Williams[22], Chee-Seng Yee[23], Caroline Gordon[24], Ian Giles[25,*], for the BSR Standards, Audit and Guidelines Working Group[‡]**

[1]Thrombosis & Haemophilia Centre, Guy's and St Thomas' NHS Foundation Trust, London, UK
[2]Department of Rheumatology, Danish Hospital for Rheumatic Diseases, Sonderborg, Denmark
[3]Department of Regional Health Research, University of Southern Denmark, Odense, Denmark
[4]Obstetrics and Gynaecology, North Middlesex University Hospital NHS Trust, London, UK
[5]Centre for Rheumatic Diseases, King's College London, London, UK
[6]Institute of Life Course and Medical Sciences, University of Liverpool, Liverpool, UK
[7]Department of Rheumatology, Robert Jones and Agnes Hunt Orthopaedic Hospital NHS Foundation Trust, Shropshire, UK
[8]Clinical Affairs, British Society for Rheumatology, London, UK
[9]Patient representative, London, UK
[10]Rheumatology, University Hospital Birmingham NHS Foundation Trust, Birmingham, UK
[11]UK Teratology Information Service, Newcastle upon Tyne, UK
[12]Division of Women's Health, Lupus Research Unit, King's College London, London, UK
[13]Rheumatic and Musculoskeletal Disease Unit, Our Lady's Hospice and Care Service, Dublin, Ireland
[14]Rheumatology, South Warwickshire NHS Foundation Trust, Warwickshire, UK
[15]Royal National Hospital for Rheumatic Diseases, Royal United Hospital, Bath, UK
[16]Pharmacology, University College London Hospitals NHS Foundation Trust, London, UK
[17]Obstetrics and Gynaecology, St George's University Hospitals NHS Foundation Trust, London, UK
[18]Lupus UK Centre of Excellence, Sandwell and West Birmingham NHS Trust, Birmingham, UK
[19]Women's Health, Frimley Park Hospital, Surrey, UK
[20]Shropshire Community NHS Trust, Shropshire, UK
[21]Primary Care and Health Sciences, Keele University, Keele, UK
[22]Obstetrics, University College London Hospitals NHS Foundation Trust, London, UK
[23]Department of Rheumatology, Doncaster and Bassetlaw, Teaching Hospitals NHS Foundation Trust, Doncaster, UK
[24]Rheumatology Research Group, Institute of Inflammation and Ageing, University of Birmingham, Birmingham, UK
[25]Centre for Rheumatology, Department of Inflammation, Division of Medicine, University College London, London, UK

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*Correspondence to: Ian Giles, Centre for Rheumatology, Department of Inflammation, Division of Medicine, University College London, Room 411, Rayne Institute, 5 University Street, London NW1 2PG, UK. E-mail: i.giles@ucl.ac.uk

[†]Shared authorship.

[‡]See supplementary data available at *Rheumatology* online for a list of the BSR Standards, Audit and Guidelines Working Group members.

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## Scope and purpose

### Background

The rationale behind this update on the 2016 British Society for Rheumatology (BSR) guidelines on prescribing anti-rheumatic drugs in pregnancy and breastfeeding [1, 2] was described in detail in the guideline scope [3]. In brief, despite the existence of additional evidence-based guidelines on prescribing/managing rheumatic disease in pregnancy [4–7] the information contained within them requires continual review to include emerging information on the safety of new and existing drugs in pregnancy.

Chronic disease adversely affects pregnancy. Data from Mothers and Babies: Reducing Risk through Audits and Confidential Enquiries across the UK (MBRRACE-UK) reports regularly from a national programme of work conducting surveillance and investigating the causes of maternal deaths, stillbirths and infant deaths [8]. Data from 2017–19 found that 8.8 women per 100 000 died during pregnancy or up to six weeks after childbirth or the end of pregnancy, and most women who died had multiple health problems or other vulnerabilities [8]. In all decisions regarding medication choices and changes, it is also important to consider the potential for deterioration in the mother's wellbeing through side effects or reduced disease control (and its adverse impact on the baby). Therefore, the exposure of the foetus to different drugs when switches are made must be balanced against possible foetal gains and understanding the potential impact of reduced control of the medical disorder on a pregnancy is vital [9].

### Need for guideline

Patients with inflammatory rheumatic disease (IRD) should be counselled to achieve and then maintain remission or low disease activity before/during pregnancy to reduce the risk of adverse pregnancy outcomes [10]. This goal is primarily achieved through adjustment of therapy to ensure disease control with disease modifying anti-rheumatic drugs (DMARDs) and/or immunosuppressive drugs that are compatible with pregnancy. These medications are reviewed in the BSR guideline on prescribing drugs in pregnancy and breastfeeding: immunomodulatory anti-rheumatic drugs and corticosteroids [11]. Many patients with IRD, however, have an additional burden of pain and comorbid illness [12] that require treatment with other medications. The compatibility of various comorbidity medications relevant to rheumatic disease will be covered in this update. This updated information will provide advice for healthcare professionals and patients to ensure more confident prescribing in these scenarios and will highlight any medications that should be stopped and/or avoided in the reproductive age group unless highly effective contraception is used, in line with guidance issued by the Medicines and Healthcare Products Regulatory Agency (MHRA) and Faculty of Sexual and Reproductive Healthcare [13, 14].

### Objectives of guideline

To update the previous BSR guidelines on prescribing in pregnancy in rheumatic disease for the following drug categories: pain management; non-steroidal anti-inflammatory drugs (NSAIDs); low-dose aspirin (LDA); anticoagulants; colchicine; dapsone; bisphosphonates; anti-hypertensives; and pulmonary vasodilators. This revised guideline was produced by consensus review of current evidence to answer specific questions in relation to each drug as follows. Should it be stopped preconception? Is it compatible with pregnancy? Is it compatible with breastmilk exposure? Where possible, recommendations are made regarding compatibility with paternal exposure.

### Target audience

The primary audience consists of health professionals in the UK directly involved in managing patients with rheumatic disease who are (or are planning to become) pregnant and/or breastfeeding, men planning to conceive, and patients who have accidentally conceived while taking these medications. This audience includes rheumatologists, rheumatology nurses/allied health professionals, rheumatology speciality trainees and pharmacists, as well as the patients themselves. The guideline will also be useful to obstetricians, obstetric physicians, renal physicians, dermatologists and general practitioners who may prescribe these medications to patients in pregnancy. This guideline uses the terms 'woman', 'maternal' or 'mother' throughout. These should be taken to include people who do not identify as women but are pregnant or have given birth [15].

### The areas the guideline does not cover

This guideline does not cover the management of infertility or acute pain relief during labour, hence morphine was excluded. Other drug categories: antimalarials; corticosteroids; disease modifying anti-rheumatic and immunosuppressive therapies; and biologic drugs are considered in another guideline [11].

### Stakeholder involvement

This guideline was commissioned by the BSR Standards, Audit and Guidelines Working Group. A Guideline Working group (GWG) was created, consisting of a chair (I.G.), alongside representatives from relevant stakeholders (Table 1). In accordance with BSR policy, all members of the GWG made declarations of interest, available on the BSR website.

### Involvement and affiliations of stakeholder groups involved in guideline development

The GWG consisted of rheumatologists from a range of clinical backgrounds, various allied health professionals, other specialists in women's health, lay members and representatives from the United Kingdom Tetralogy Information Service (UKTIS). All members of the working group contributed to the process for agreeing key questions, guideline content, recommendations and strength of agreement.

## Rigour of development

### Statement of scope of literature search and strategy employed

Most medications covered in this guideline have been comprehensively and systematically reviewed in multiple other documents, since the first BSR guideline on this topic. Therefore, a consensus-based approach was taken to compile and assess most significant evidence published since 2013 to December

**Table 1.** Composition of guideline working group; list of group members and relevant stakeholders

| Tasks | Role | PICO definition | Data search | Data extraction | Voting member | Non-voting member | Manuscript authors |
|---|---|---|---|---|---|---|---|
| Karen Schreiber | Lead author, trainee rheumatologist | x | x | x | x | | x |
| Margreta Frishman | Lead author, trainee obstetrician | x | x | x | x | | x |
| Mark Russell | Trainee rheumatologist | x | | | x | | |
| Mrinalini Dey | Trainee rheumatologist | x | | | x | | |
| Julia Flint | Trainee rheumatologist | x | | | x | | |
| Alexander Allen | Data analyst | x | x | | | x | |
| Amy Crossley | Patient representative | | | | | x | |
| Mary Gayed | Consultant rheumatologist | x | | | x | | |
| Kenneth Hodson | Head of UK Tetralogy Information Service & consultant obstetrician | x | | | x | | |
| Munther Khamashta | Consultant rheumatologist | x | | | x | | |
| Louise Moore | Clinical nurse specialist | x | | | x | | |
| Sonia Panchal | Consultant rheumatologist | x | | | x | | |
| Madeleine Piper | Consultant rheumatologist | x | | | x | | |
| Clare Reid | Patient representative | x | | | | x | |
| Katherine Saxby | Pharmacist | x | | | x | | |
| Naz Senvar | Trainee obstetrician | x | | | x | | |
| Sofia Tosounidou | Consultant rheumatologist | x | | | x | | |
| Maud van de Venne | Consultant obstetrician | x | | | x | | |
| Louise Warburton | General practitioner | x | | | x | | |
| David Williams | Consultant obstetric physician | x | | | x | | |
| Chee-Seng Yee | Consultant rheumatologist | x | | | x | | |
| Caroline Gordon | Consultant rheumatologist | x | | | x | | |
| Ian Giles | Chair of working group & consultant rheumatologist | x | x | x | x | | x |

All members were involved in data review, formulation of recommendations and editing of the manuscript.

2020 through a comprehensive search of MEDLINE, PubMed and EMBASE databases with specific search terms (Supplementary Table S1, available at *Rheumatology* online). Filters were applied to capture National Institute for Health and Care Excellence (NICE) guidance, international guidelines, systematic reviews, cohort studies or case-series. Information was preferentially selected from NICE guidance and/or largest/most recent systematic reviews and where lacking was extracted from largest cohort, case-series or abstract. Findings were cross-referenced with the previous BSR guideline [2], as well as the Cochrane, Lactmed (a National Library of Medicine database on drugs and lactation) and UKTIS databases.

Two independent reviewers screened the title and abstract of 2997 articles, identified 130 and selected the most recent/largest systematic reviews or largest cohort study or case-series as well any NICE guidance and international guidelines. Thirty-six studies (Fig. 1) met the inclusion criteria and relevant information was extracted into data-extraction tables.

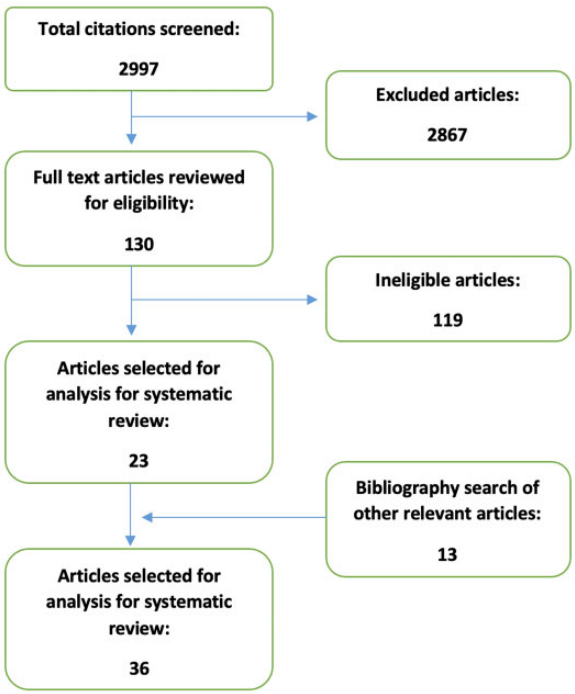


**Figure 1.** Flow diagram of study selection

## Statement of methods used to formulate the recommendations (levels of evidence)

The working group met regularly to formalise search strategy, review evidence, resolve disagreements and finally to determine recommendations. This guideline was developed in line with BSR's Guideline Protocol using Grading of Recommendations, Assessment, Development and Evaluations (GRADE) methodology to determine quality of evidence and strength of recommendation. Accompanying each recommendation in this guideline, in brackets, is the strength of recommendation, quality of evidence and strength of agreement (SOA).

## Strength of recommendation

Using GRADE, recommendations were categorized as either strong (denoted by 1) or weak (denoted by 2), according to the balance between benefits and risks. A strong recommendation was made when the benefits clearly outweigh the risks (or vice versa). A weak recommendation denotes that the benefits are more closely balanced with the risk or more uncertain.

### Quality of evidence

Using the GRADE approach, the quality of evidence was determined as either high (A), moderate (B) or low/very low (C) reflecting the confidence in the estimates of benefits or harm.

### Strength of agreement

The wording of each recommendation was discussed until all members were satisfied they would score at least 80 on a scale of 1 (no agreement) to 100 (complete agreement) and then 20/23 members with full voting rights scored each recommendation on the same scale and the average was calculated to generate a strength of agreement (SOA) score. Two patient representatives and a data-analyst expressed concern that they did not have sufficient medical knowledge of all drugs reviewed to score all recommendations, so while they fully agreed with each, they did not wish to score each one and did not contribute to the final SOA score.

### Statement of any limits of search and when guideline will be updated

The search was conducted in December 2020. Limits were placed for English language and filters as described above. The guideline will be updated in five years.

## The guideline

Drugs are considered in the following categories: pain management; NSAIDs and low-dose aspirin in the management of multisystem rheumatic disease; anticoagulants; bisphosphonates; anti-hypertensive medication in the management of multisystem rheumatic disease; and pulmonary vasodilators. The overall findings for maternal and foetal breastmilk exposures to each drug, including information and key references from the previous BSR guideline [2] are summarised in the full-length guideline and updated recommendations listed below. Paternal exposures and recommendations are described separately after maternal data. An overall summary of compatibility of each drug pre-conception, during pregnancy, breastmilk exposure and paternal exposure is shown in Table 2. Generic recommendations were developed based on evidence as shown in Supplementary Table S2, available at *Rheumatology* online.

### Generic recommendations on prescribing in rheumatic disease in pregnancy

i) Pre-conception counselling should be addressed by all healthcare professionals, with referral to professionals with relevant experience as appropriate to optimise all therapy, including non-pharmacological options for chronic pain management during pregnancy (GRADE 1A, SOA 99.5).
ii) The risks and benefits of drug treatment to mother and foetus should be discussed and clearly documented by all healthcare professionals involved in the patient's care (GRADE 1A, SOA 99).
iii) The cause of pain and other symptoms should be assessed and managed appropriately (GRADE 1B, SOA 98.5).
iv) The requirement for analgesia should be assessed and minimum effective dose should be prescribed and titrated according to response (GRADE 1B, SOA 100).
v) Tricyclic antidepressants are preferred over other antidepressant medications to manage chronic pain (GRADE 1B, SOA 98.1).
vi) Cessation of anti-depressant therapy that is being used as chronic pain medication in the post-natal period is not recommended, due to the risk of adverse impact on mood (GRADE 1C, SOA 96).
vii) LDA (≤150 mg/day) is recommended in all patients at high risk for pre-eclampsia (GRADE 1A, SOA 99.5).
viii) Low molecular weight heparin is the preferred anticoagulant (GRADE 1A, SOA 100).
ix) Nifedipine is the preferred vasodilator (GRADE 1B, SOA 98.5).
x) Paternal drug exposure may reduce male fertility but has not been associated with adverse foetal development or pregnancy outcome. Although evidence is weak, we recommend that men are reassured about the safety of fathering a pregnancy whilst taking medicines to manage comorbidities as described in this guideline (GRADE 1C, SOA 98).

### Pain management: conventional analgesics Paracetamol

Recommendations were based on two systematic reviews [16, 17], UKTIS [18], Royal College of Obstetricians (RCOG) guidance [19] and LactMed [20], as shown in Supplementary Table S3, available at *Rheumatology* online.

#### Recommendations for paracetamol in pregnancy and breastfeeding

i) Paracetamol is the analgesic of choice and compatible peri-conception and throughout pregnancy (GRADE 1B, SOA 99).
ii) LactMed describes paracetamol as a good choice for analgesia and fever reduction in breastfeeding mothers (GRADE 2C, SOA 99.5).

### Codeine

Recommendations were based on a systematic review [16] (including a large Norwegian population-based cohort study [21], a large case-control study [22] and a case-control study [23]), UKTIS [18], breastfeeding exposures from references [24–26] and LactMed [20], as shown in Supplementary Table S3, available at *Rheumatology* online.

#### Recommendations for codeine in pregnancy and breastfeeding

i) Codeine is compatible peri-conception and throughout pregnancy, although long-term use should be avoided. There is no consistent evidence to recommend a dose reduction pre-delivery but neonatologists should be aware of maternal use (GRADE 1B, SOA 97.8).
ii) Caution is advised with use of codeine in breastfeeding, due to the risk of CNS depression resulting from unpredictable metabolism of codeine to morphine (GRADE 1C, SOA 98).

### Tramadol

Recommendations were based on a systematic review [16] (including a large prospective cohort study of over 1.6 million women [27]), UKTIS [18] (including case reports [28]),

**Table 2.** Summary of drug compatibility in pregnancy and breastfeeding

| | Compatible peri-conception | Compatible with 1st trimester | Compatible with 2nd/3rd trimester | Compatible with breastfeeding | Compatible with paternal exposure |
|---|---|---|---|---|---|
| **Conventional painkillers** | | | | | |
| Paracetamol | Yes | Yes[a] | Yes[a] | Yes | Yes[b] |
| Codeine | Yes | Yes | Yes | Yes[a] | Yes[b] |
| Tramadol | No | No | Yes[a] | Yes[c] | Yes[b] |
| **Other chronic pain treatments** | | | | | |
| Amitriptyline | Yes | Yes | Yes | Yes | Yes[b] |
| Gabapentin | Yes | Yes[d] | Yes[d] | Yes | Yes[b] |
| Pregabalin | Yes | Yes[d] | Yes[d] | Yes | Yes[b] |
| Venlafaxine | Yes | Yes | Yes | Yes[e] | Yes[b] |
| Fluoxetine | Yes | Yes | Yes | Yes[c,e] | Yes[b] |
| Paroxetine | Yes | Yes | Yes | Yes[c,e] | Yes[b] |
| Sertraline | Yes | Yes | Yes | Yes[c,e] | Yes[b] |
| Duloxetine | Yes | Yes | Yes | Yes[e] | Yes[b] |
| **NSAIDS** | | | | | |
| NSAIDs | Yes | Yes[a,f] | Stop by week 30 | Yes | Yes |
| Cox-2 inhibitors | No | No | No | No | Yes[b] |
| **Other drugs** | | | | | |
| Colchicine | Yes | Yes | Yes | Yes | Yes[b] |
| Dapsone | Yes | Yes | Yes | Yes | Yes[b] |
| **Anti-platelet agents** | | | | | |
| Low dose aspirin | Yes | Yes | Yes | Yes | Yes [b] |
| Clopidogrel | Yes[c] | Yes[c] | Yes[c] | Yes[c] | Yes[b] |
| **Anticoagulants** | | | | | |
| Warfarin | No | No | Exceptional circumstances only | Yes | Yes[b] |
| LMWH | Yes | Yes | Yes | Yes | Yes[b] |
| DOACs | No | No | No | Rivaroxaban only | Yes[b] |
| Fondaparinux | Yes[c] | Yes | Yes | Yes | Yes[b] |
| **Bisphosphonates** | | | | | |
| Bisphosphonates | Stop 3 months in advance | No | No | No data | Yes[b] |
| **Antihypertensives** | | | | | |
| ACEi/ARBs | Stop when pregnancy confirmed | | Exceptional circumstances only | Yes (enalapril)[c] | Yes[b] |
| Nifedipine | Yes | Yes <90 mg/day | Yes <90 mg/day | Yes | Yes[b] |
| Amlodipine | Yes[c] | Yes[c] | Yes[c] | Yes[c] | Yes[b] |
| Labetalol* | Yes | Yes | Yes | Yes | Yes[b] |
| Methyldopa* | Yes | Yes | Yes | Yes | Yes[b] |
| **Pulmonary vasodilators** | | | | | |
| Sildenafil | Multi-disciplinary Team assessment | | | No data | Yes[b] |
| Bosentan | Multi-disciplinary Team assessment | | | No data | Yes[b] |
| Prostacyclines | Multi-disciplinary Team assessment | | | No data | Yes[b] |

For further information and caveats, see relevant recommendations and main text in the Executive Summary and full Guideline.
[a] Intermittent use advised—see main text for details.
[b] Based on limited data and no association with adverse foetal development or pregnancy outcome, therefore unlikely to be harmful.
[c] Limited evidence, but unlikely to be harmful.
[d] Limited evidence regarding use for treatment of chronic pain in pregnancy. High dose folic acid (5 mg/day) recommended.
[e] Cessation of anti-depressant therapy in post-natal period is not recommended.
[f] Possible association with miscarriage and malformation.
* Drugs not included in systematic search, but added because of their relevance.

LactMed [20] (including [29]) and RCOG guidance [19], as shown in Supplementary Table S3, available at *Rheumatology* online.

### Recommendations for tramadol in pregnancy and breastfeeding

i) Avoid tramadol peri-conception and in first trimester and only consider in second/third trimester if no alternative analgesia (GRADE 2B, SOA 97.8).
ii) Based on limited data, tramadol may be compatible with short-term use in breastfeeding (GRADE 2C, SOA 94.8).

## Other treatments for chronic pain

### Amitriptyline

Recommendations were based on NICE guidance [30], a systematic review [16], UKTIS [18] and LactMed [20], as shown in Supplementary Table S4, available at *Rheumatology* online.

### Recommendations for amitriptyline in pregnancy and breastfeeding

i) Amitriptyline is compatible with pregnancy. There is no evidence of adverse effect on IQ or developmental outcomes (GRADE 1C, SOA 100).
ii) Because very little amitriptyline is found in breastmilk with antidepressant doses and it is used at lower doses

for chronic pain, it is unlikely to cause adverse effects in breastfed infants (GRADE 1C, SOA 100).

## Gabapentin and pregabalin

Recommendations were based on [16, 18, 19, 31–35] and [20], as shown in Supplementary Table S4, available at *Rheumatology* online.

### Recommendations for gabapentin and pregabalin in pregnancy and breastfeeding

i) Gabapentin at lowest effective dose may be considered in pregnancy with folic acid supplementation if no alternative analgesic suitable (GRADE 1B, SOA 95).
ii) Gabapentin may be considered in breastfeeding if no alternative analgesic is suitable (GRADE 2C, SOA 96).
iii) Pregabalin may be considered in pregnancy (with folic acid supplementation) and during breastfeeding (GRADE 2C, SOA 95.3).

## Serotonin–norepinephrine reuptake inhibitors (SNRIs)

Recommendations were based on NICE guidance [30], two systematic reviews [16, 33], UKTIS [18] and LactMed [20], as shown in Supplementary Table S4, available at *Rheumatology* online.

### Recommendations for SNRIs in pregnancy and breastfeeding

i) Venlafaxine is compatible at conception and throughout pregnancy. There may be an increased risk of neonatal abstinence syndrome/short-term behavioural effects, but larger studies are needed to evaluate this finding (GRADE 2C, SOA 95.8).
ii) Duloxetine may be considered in pregnancy and breastfeeding but there are fewer data than for venlafaxine (GRADE 2C, SOA 95.3).
iii) Venlafaxine and duloxetine may be considered in breastfeeding if there is no alternative chronic pain medication (GRADE 2C, SOA 95.8).

## Selective serotonin reuptake inhibitors (SSRIs)

Recommendations were based on [16, 18, 30, 36–39] and [20], as shown in Supplementary Table S4, available at *Rheumatology* online.

### Recommendations for SSRIs in pregnancy and breastfeeding

i) Fluoxetine, paroxetine and sertraline are compatible with pregnancy (GRADE 1B, SOA 98.8).
ii) Based on limited evidence, SSRIs are compatible with breastfeeding (GRADE 2C, SOA 98.3).

## NSAIDs and anti-platelet drugs

Recommendations were based on NICE guidance [40], four systematic reviews [16, 41–43], a case report/review [44], UKTIS [18], LactMed [20] and United States Food and Drug Administration (FDA) guidance [45], as shown in Supplementary Tables S5 and S6, available at *Rheumatology* online.

### Recommendations for NSAIDs and COX-2 inhibitors in pregnancy and breastfeeding

i) Discordant findings from retrospective, large studies with population controls on the use of NSAIDs in the first trimester of pregnancy raise the possibility of a low risk of miscarriage and malformation. Therefore, these drugs should only be used intermittently in the first trimester of pregnancy (GRADE 1B, SOA 97.3).
ii) Intermittent rather than regular use of all non-selective NSAIDs except LDA is recommended throughout pregnancy and weaned from end of second trimester (26 weeks) to stop by gestational week 30 to avoid premature closure of the ductus arteriosus (GRADE 1B, SOA 98).
iii) At present there are limited data on selective COX-2 inhibitors; they should therefore be avoided during pregnancy (GRADE 2C, SOA 98.5).
iv) Non-selective NSAIDs (especially ibuprofen) are compatible with breastfeeding (GRADE 1C, SOA 98.8).

### Recommendations for low-dose aspirin and clopidogrel in pregnancy and breastfeeding

i) LDA of ≤150 mg/day may be continued throughout pregnancy and NICE guidelines (2019) for hypertension in pregnancy advise treatment with LDA (for prophylaxis of pre-eclampsia) until delivery (GRADE 1B, SOA 99.0).
ii) LDA is compatible with breastfeeding (GRADE 2C, SOA 99.8).
iii) There are limited data on clopidogrel but it may be considered where alternative drugs are not suitable in pregnancy and breastfeeding (GRADE 2C, SOA 96.3).

## Colchicine and dapsone

Recommendations were based on [18, 46–50] and [20], as shown in Supplementary Table S5, available at *Rheumatology* online.

### Recommendations for colchicine and dapsone in pregnancy and breastfeeding

i) Colchicine therapy may be considered during pregnancy (GRADE 1B, SOA 99.5).
ii) Dapsone may be used in pregnancy (GRADE 2C, SOA 95.0).
iii) Colchicine may be used in breastfeeding (GRADE 2C, SOA 98.3).
iv) Dapsone may be used in breastfeeding and due to the risk of haemolytic anaemia it is advised to monitor the infant for signs of haemolysis, especially in newborn or premature breastfed infants (GRADE 2C, SOA 90.7).

## Anticoagulants in rheumatic disease

Recommendations were based on [18, 41, 51–58] and [20], as shown in Supplementary Table S6, available at *Rheumatology* online.

**Recommendations for anticoagulants in pregnancy and breastfeeding**

i) Low molecular weight heparin (LMWH) is compatible throughout pregnancy (GRADE 1A, SOA 100).
ii) LMWH is compatible with breastfeeding (GRADE 1C, SOA 100).
iii) The use of warfarin in pregnancy is associated with increased foetal risk throughout pregnancy and has limited indications, therefore should only be considered in exceptional circumstances (GRADE 1B, SOA 98.8).
iv) Warfarin is compatible with breastfeeding (GRADE 1A, SOA 100).
v) Direct oral anticoagulants (DOACs) cannot be recommended in pregnancy (GRADE 1C, SOA 97.9)
vi) Rivaroxaban may be considered in breastfeeding (GRADE 2C, SOA 95.3)
vii) Other DOACs are not recommended in breastfeeding due to lack to human data and concerns from animal studies (GRADE 1C, SOA 97.4)
viii) Fondaparinux may be considered in pregnancy and breastfeeding if there is an allergy or adverse response to LMWH (GRADE 2C, SOA 95.5)

## Bisphosphonates

Recommendations were based on [18, 59, 60] and [20], as shown in Supplementary Table S7, available at *Rheumatology* online.

**Recommendations for bisphosphonates in pregnancy and breastfeeding**

i) There is insufficient data upon which to recommend bisphosphonates in pregnancy or to advise a specific time for them to be stopped pre-conception. Given their biological half-life in bone of up to 10 years and no evidence of harm from limited reports of their use in pregnancy, a pragmatic recommendation is that they should be stopped 3 months in advance of pregnancy (GRADE 2C, SOA 96.8).
ii) There are no data on which to base a recommendation for the use of bisphosphonates during breastfeeding (GRADE 2C, SOA 98.5).

## Antihypertensive medication in rheumatic disease

Recommendations were based on [18, 40, 61–64] and [40], as shown in Supplementary Table S8, available at *Rheumatology* online.

**Recommendations for angiotensin-converting enzyme inhibitors (ACEis)/angiotensin receptor blockers (ARBs) in pregnancy and breastfeeding**

i) ACEi and ARBs should be stopped as soon as possible when pregnancy is confirmed in the first trimester and if necessary an alternative antihypertensive compatible with pregnancy given (GRADE 1A, SOA 100).
ii) ACEis/ARBs should be avoided in the second and third trimester but may be considered under specialist advice in certain circumstances (GRADE 1C, SOA 98.5).
iii) Based on limited evidence, enalapril is compatible with breastfeeding (GRADE 2C, SOA 98.5).

## Calcium channel blockers

Recommendations were based on [18, 20, 40], as shown in Supplementary Table S8, available at *Rheumatology* online.

**Recommendations for calcium channel blockers in pregnancy and breastfeeding**

i) Nifedipine is compatible with pregnancy with no direct evidence of harm at doses up to 90 mg/day (GRADE 1A, SOA 99.0).
ii) Nifedipine is compatible with breastfeeding (GRADE 1B, SOA 100).
iii) Amlodipine can be considered in pregnancy and breastfeeding as there is no evidence of harm (GRADE 1C, SOA 97.9).

## Pulmonary vasodilators

Recommendations were based on [2, 18, 20, 65–69] and [20], as shown in Supplementary Table S7, available at *Rheumatology* online.

**Recommendations for pulmonary vasodilators in pregnancy and breastfeeding**

i) Established moderate-to-severe pulmonary hypertension (PHT) remains a contraindication to pregnancy. If pregnancy occurs, the use of these pulmonary vasodilator drugs in pregnancy should be considered only as part of a multidisciplinary team assessment (GRADE 1C, SOA 99.5).
ii) Limited evidence supports the use of prostacyclines to treat PHT during pregnancy (GRADE 2C, SOA 98.0).
iii) Limited evidence supports the use of sildenafil to treat PHT during pregnancy (GRADE 2C, SOA 98.0).
iv) Bosentan is teratogenic in animals and although there is no evidence of harm from human pregnancy, the evidence is insufficient to recommend in pregnancy (GRADE 1C, SOA 98.8).
v) There are no data relating to breastfeeding exposure to pulmonary vasodilators on which to base a recommendation (GRADE 2C, SOA 98.8).

## Paternal exposures

Recommendations were based on [70–76] and [77], as shown in Supplementary Table S9, available at *Rheumatology* online.

**Recommendations for paternal exposure**

i) Paracetamol is compatible with paternal exposure (GRADE 1B, SOA 98.5).
ii) Amitriptyline, SNRIs and SSRIs are compatible with paternal exposure (GRADE 1B, SOA 98.5).
iii) Non-selective NSAIDs are compatible with paternal exposure (GRADE 1C, SOA 98.4).
iv) Based on limited or no data and no association with adverse foetal development or pregnancy outcome, paternal exposure to all other drugs described in this guideline is unlikely to be harmful (GRADE 2C, SOA 97.3).

## Applicability and utility

### Implementation

Awareness of these guidelines will aid clinical practitioners and patients in decision making and will be raised through presentation at local, regional and national meetings. No barriers to implementation of these guidelines are anticipated.

### Key standards of care

Patients with rheumatic disease should receive tailored pre-pregnancy counselling and then be reviewed during pregnancy and the 4-month post-partum period by clinical practitioners with expertise in the management of rheumatic disease in pregnancy, in addition to their routine obstetric care. They should have access to written information on relevant medications in pregnancy and breastfeeding that is accurate and allows them to make informed decisions regarding compatibility of certain drugs in pregnancy.

### Future research agenda

The limitation of current evidence highlights the need for a national pregnancy registry for patients with rheumatic disease, as currently exists for women with epilepsy. All women with rheumatic disease who become pregnant would be eligible to register, whether or not they are on anti-rheumatic treatment. The prospective pregnancy outcome data would then be published to display information on outcomes such as miscarriage and congenital anomalies in patients treated with anti-rheumatic and other drug therapy. These data would also be used to answer specific questions where data is currently lacking. Data relating to the impact of paternal exposure to these drugs (both fertility and male-mediated teratogenicity), as well as breastfeeding exposure is particularly limited, and further research in these areas is urgently required.

### Mechanism for audit of the guideline

An audit pro forma to assess compliance with these guidelines is shown in Supplementary Data S1, available at *Rheumatology* online.

The full guideline is available at *Rheumatology* online.

## Supplementary data

Supplementary data are available at *Rheumatology* online.

## Data availability statement

All relevant data produced during the guideline development process are presented in the guideline or in the accompanying supplementary material.

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A full list of Standards, Audit and Guidelines Working Group members can be found in Supplementary Data S2, available at *Rheumatology* online. All contributing members are named in the authorship list.

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