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Guidelines

Guidelines

Executive Summary: British Society for Rheumatology guideline on prescribing drugs in pregnancy and breastfeeding: immunomodulatory anti-rheumatic drugs and corticosteroids

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This is the executive summary of 'British Society for Rheumatology guideline on prescribing drugs in pregnancy and breastfeeding: immunomodulatory anti-rheumatic drugs and corticosteroids.' For the full guideline, please see https://doi.org/10.1093/rheumatology/keac551

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Scope and purpose

Need for guideline

The rationale behind this update of the 2016 British Society for Rheumatology (BSR) guidelines on prescribing antirheumatic drugs in pregnancy and breastfeeding [1, 2] was previously described [3]. Additional evidence-based guidelines on managing rheumatic disease in pregnancy now exist [4–7]. However, emerging information on pregnancy exposures to biologic DMARDs, biosimilars and targeted synthetic DMARDs requires regular review to assess their safety in pregnancy. Uncertainty around use of these drugs in pregnancy may lead to withdrawal of treatment from women with inflammatory rheumatic diseases (IRDs) unnecessarily [8], which can increase the risk of poor disease control during pregnancy [9].

Data from Mothers and Babies: Reducing Risk through Audits and Confidential Enquiries across the UK (MBRRACE-UK) between 2017 and 2019 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 [10]. In all decisions regarding medication choices and changes, it is 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) [10]. As such, the potential benefit to the foetus from any drug changes in the mother must be balanced against the possible risks to the foetus from loss of disease control in the mother [11].

Objectives of guideline

To update the previous BSR guidelines on prescribing in pregnancy in rheumatic disease of corticosteroids and immunomodulatory drugs (Supplementary Data S1, available at *Rheumatology* online) by systematically reviewing all evidence published since the previous guideline.

This guideline will highlight 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 and the Faculty of Sexual and Reproductive Healthcare [12, 13].

Target audience

This guideline is directed at healthcare professionals in the UK involved in managing patients with rheumatic disease who are (or are planning to become) pregnant and/or breastfeeding, men with rheumatic disease who are planning to conceive, and patients with rheumatic disease who have unintentionally 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, midwives, renal physicians, dermatologists, gastroenterologists, respiratory physicians and general practitioners who prescribe these medications 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 [14]. Where the term 'breastfeeding' is used in this guideline it also refers to infant breastmilk exposure via other methods (e.g. expressed breastmilk, administered via a bottle).

The areas the guideline does not cover

This guideline does not cover the management of infertility or the indications for these drugs in rheumatic diseases in pregnancy. Other drug categories (pain management; non-steroidal anti-inflammatory drugs and low dose aspirin; anticoagulants; bisphosphonates; anti-hypertensives; and pulmonary vasodilators) are considered in the BSR guideline on prescribing drugs in pregnancy and breastfeeding: comorbidity medications used in rheumatology practice [15]. All recommendations in this guideline were formulated by the working group on the basis of published evidence at the time of the systematic literature search, and do not necessarily refer to licencing information or Summary of Product Characteristics for individual medications.

Stakeholder involvement

A guideline working group (GWG), chaired by I.G., consisted of rheumatologists from a range of clinical backgrounds, allied health professionals, other specialists in women's health, lay members, and representatives from the United Kingdom Teratology Information Service (UKTIS), this is shown in Supplementary Table S1, available at *Rheumatology* online.

Rigour of development

Statement of scope of literature search and strategy employed

Evidence used to develop these guidelines was compiled from a systematic literature search conducted according to guidelines of Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) [16]. Studies were identified by searching MEDLINE and Embase databases from 1 January 2014 to 31 December 2020, with additional studies identified through the Cochrane, LactMed and UKTIS databases (Supplementary Data S2, available at *Rheumatology* online). The searches were conducted in January 2021. Limits were placed for English language studies. The searches were not limited by disease indication; studies in non-rheumatic diseases were considered, if relevant. Evidence from the current searches (referred to as 'recent studies' in the text) was combined with data from the previous guideline (referred to as 'previous studies') [1], to inform recommendations. Relevant pharmaceutical companies were also contacted for additional data.

Two independent reviewers screened the titles and abstracts of articles, reviewed the full texts of studies that met inclusion criteria (Supplementary Data S2, available at *Rheumatology* online), and performed data extraction. Any disagreements were resolved by group discussion.

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

This guideline was developed in line with BSR's Guidelines Protocol using Grading of Recommendations, Assessment, Development and Evaluations (GRADE) methodology, to determine quality of evidence and strength of recommendation. Accompanying each recommendation, in brackets, is the strength of recommendation, quality of evidence and strength of agreement (SOA).

Recommendations were categorized as strong (1), when the benefits clearly outweigh the risks (or vice versa), or weak (2),

when the benefits were more closely balanced with the risks or more uncertain. The quality of evidence was determined as high (A), moderate (B) or low/very low (C), reflecting the confidence in the estimates of benefits or harm. The wording of each recommendation was agreed by all members and subjected to a vote for SOA on a scale of 1–100 (no to complete agreement). The guideline will be updated in five years.

The guideline

A flow diagram of study selection is shown in Fig. 1. The findings for all drug exposures, including information from the previous BSR guideline [1], are summarized in the full-length guideline. An overall summary of the compatibility of each drug pre-conception, during pregnancy, with breastmilk exposure, and with paternal exposure is shown in Table 1. For each drug, maternal information is summarized in Tables 2 and 3, while paternal information is summarized in Table 4. The data synthesis strategy for Tables 2–4 is shown in Supplementary Data S3, available at *Rheumatology* online. The list of references included within the evidence tables is shown in Supplementary Data S4, also available at *Rheumatology* online.

Generic recommendations on prescribing immunomodulatory drugs and/or corticosteroids in rheumatic disease in pregnancy

i) Pre-conception counselling should be addressed by all healthcare professionals, with referral to professionals with relevant expertise as appropriate, to optimize disease control before pregnancy; with advice on the timing of pregnancy, and drug therapy before, during and after pregnancy, including contraception (GRADE 1A, SOA 99.5%).
ii) If a woman is planning pregnancy, avoid pregnancy-incompatible drugs (GRADE 1A, SOA 100%).
iii) The risks and benefits to the mother and foetus of drug treatment to control maternal disease should be discussed and clearly documented by all healthcare professionals involved in the patient's care (GRADE 1A, SOA 99.5%).

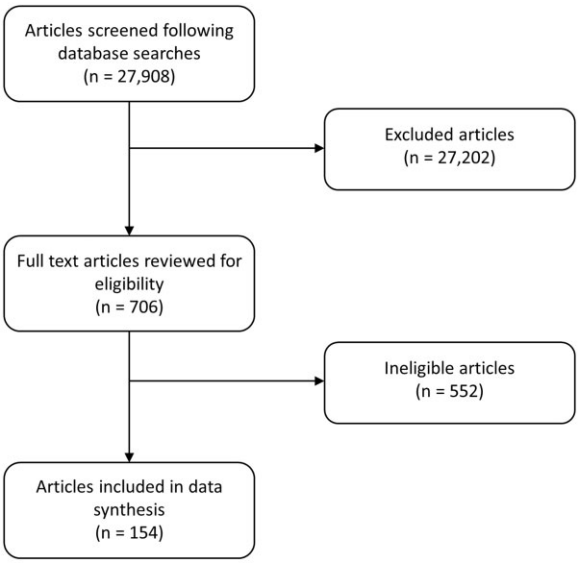

Figure 1. Flow diagram of studies selected for inclusion

iv) Immunomodulatory drugs that are contraindicated in pregnancy should be switched to a pregnancy-compatible alternative in advance of conception to ensure maintenance of disease control on the new medication (GRADE 1A, SOA 100%).
v) When no pregnancy-compatible drugs are suitable, control of severe/life-threatening maternal disease should take priority over concerns for potential foetal outcomes (GRADE 1B, SOA 99.0%).
vi) All biologic DMARDs may be continued throughout pregnancy if required to control active/severe maternal disease (GRADE 1B, SOA 98.5%).
vii) Immunisation schedules in infants after in-utero exposure to biologic DMARDs will depend on timing of exposure, bioavailability and persistence of the drug, mechanism of action of the drug, and live vaccines (GRADE 1C, SOA 99.5%).
viii) Where possible, the minimum effective dose of immunomodulatory drug or corticosteroid should be used to maintain maternal disease suppression, and stopping the drug during pregnancy may be considered in women at low risk of disease flare on withdrawal of therapy (GRADE 1B, SOA 100%).
ix) Some drugs may reduce male fertility, but paternal drug exposure in humans has not convincingly been associated with adverse foetal development or pregnancy outcome. Although the evidence is weak, men who take rheumatological medicines should be reassured about the safety of conceiving (GRADE 2C, SOA 98.4%).

Antimalarials

Recommendations were based on 23 studies of HCQ identified in the current literature search and 23 studies identified in the previous guideline's literature search, in addition to four studies of chloroquine and no studies of mepacrine. Three recent and one previous study of breastmilk exposure to HCQ were identified.

Recommendations for hydroxychloroquine in pregnancy and breastmilk exposure

i) HCQ remains the antimalarial of choice in women planning a pregnancy with rheumatic disease in need of treatment, and should be continued during pregnancy at dose of $\leq$400 mg/day (GRADE 1B, SOA 100%).
ii) HCQ is compatible with breastmilk exposure (GRADE 1B, SOA 99.5%).

Corticosteroids

Recommendations were based on 11 recent studies of prednisolone, one study of methylprednisolone, and previous studies: 47 on prednisolone; 31 on dexamethasone; 27 on betamethasone; and 10 on general corticosteroid use.

Recommendations for corticosteroids in pregnancy and breastmilk exposure

i) Prednisolone is compatible with pregnancy and is the preferred corticosteroid in the treatment of maternal rheumatological disease in pregnancy and requires shared care with obstetric teams to monitor maternal blood pressure and blood glucose (GRADE 1B, SOA 100%).

Table 1. Summary of drug compatibility in pregnancy and breastmilk exposure

	Peri-conception	First trimester	Second/third trimester	Breastfeeding	Paternal exposure
Corticosteroids					
Prednisolone	Yes	Yes	Yes	Yes	Yes
Antimalarials					
Hydroxychloroquine (≤400mg/day)	Yes	Yes	Yes	Yes	Yes
Conventional synthetic DMARDs					
Methotrexate (≤25 mg/week)	Stop ≥1 month pre-conception	No	No	No	Yes
Sulfasalazine (with folic acid 5mg/day in first trimester)	Yes	Yes	Yes	Yes[a]	Yes[b]
Leflunomide	No: Cholestyramine washout	No	No	No	Yes
Azathioprine	Yes	Yes	Yes	Yes	Yes
Ciclosporin	Yes	Yes[c]	Yes[c]	Yes	Yes
Tacrolimus	Yes	Yes[c]	Yes[c]	Yes	Yes
Cyclophosphamide	Exceptional circumstances[d]	Exceptional circumstances[d]	Exceptional circumstances[d]	No	No
Mycophenolate mofetil	Stop ≥6 weeks pre-conception	No	No	No	Yes
Intravenous immunoglobulin	Yes	Yes	Yes	Yes	Yes
Anti-TNFα medications					
Infliximab	Yes	Yes	Yes[e]	Yes	Yes
Etanercept	Yes	Yes	Yes[f]	Yes	Yes
Adalimumab	Yes	Yes	Yes[g]	Yes	Yes
Certolizumab	Yes	Yes	Yes	Yes	Yes
Golimumab	Yes	Yes	Yes[g]	Yes	Yes
Other biologic DMARDs					
Rituximab	Consider stopping at conception[h]	Severe disease if no alternatives[h]	Severe disease if no alternatives[i]	Yes[j]	Yes[j]
IL-6 inhibitors	Consider stopping at conception[h]	Severe disease if no alternatives[h]	Severe disease if no alternatives[i]	Yes[j]	Yes[j]
IL-1 inhibitors	Consider stopping at conception[h]	Severe disease if no alternatives[h]	Severe disease if no alternatives[i]	Yes[j]	Yes[j]
Abatacept	Consider stopping at conception[h]	Severe disease if no alternatives[h]	Severe disease if no alternatives[i]	Yes[j]	Yes[j]
Belimumab	Consider stopping at conception[h]	Severe disease if no alternatives[h]	Severe disease if no alternatives[i]	Yes[j]	Yes[j]
IL-17 inhibitors	Consider stopping at conception[h]	Severe disease if no alternatives[h]	Severe disease if no alternatives[i]	Yes[j]	Yes[j]
IL-12/23 inhibitors	Consider stopping at conception[h]	Severe disease if no alternatives[h]	Severe disease if no alternatives[i]	Yes[j]	Yes[j]
Targeted synthetic DMARDs					
JAK-inhibitors	Stop ≥2 weeks pre-conception	No	No	No	Yes[j]

For further information and caveats, see relevant recommendations and main text in the executive summary and full guideline.

[a] In the healthy, full-term infant only.

[b] If conception is delayed by >12months, consider stopping sulfasalazine alongside investigation of other causes of infertility.

[c] Suggested monitoring of maternal blood pressure, renal function, blood glucose and drug levels.

[d] Only in cases of severe (life or organ-threatening) maternal disease.

[e] If low risk of disease flare and stopped by 20 weeks, full term infant can have a normal vaccination schedule.

[f] If low risk of disease flare and stopped by 32 weeks, full term infant can have a normal vaccination schedule.

[g] If low risk of disease flare and stopped by 28 weeks, full term infant can have a normal vaccination schedule.

[h] May be considered to manage severe maternal disease if no other pregnancy-compatible drugs are suitable.

[i] If used in third trimester, avoid live vaccinations in infant vaccination schedule until 6 months of age.

[j] Limited evidence.

Table 2. Summary of maternal exposure to conventional synthetic DMARDs, antimalarials and corticosteroids

Drug	Studies (type and number)	Pregnancy exposures (exposures per trimester)	Foetal losses/ total pregnancy outcomes	Pregnancy duration and birth weight	Malformations/total births	Recommendation (GRADE/Strength of agreement)
HCQ	31 ct [1–31] 1 rct [32] 1 nrt [33] 2 cc [34, 35] 3 cs [36–38] 6 cr [39–44] 2 sr [45, 46]	4701 (1st ≥3075, 2nd/ 3rd ≥583)	95/936	No significant adverse effect noted	162/3126 Overall, no increase in rate of major malformations attributable to drug	i) HCQ remains the antimalarial of choice in women planning a pregnancy with rheumatic disease in need of treatment, and should be continued during pregnancy at dose of ≤400 mg/day (GRADE 1B, SOA 100%) ii) HCQ is compatible with breastmilk exposure (GRADE 1B, SOA 99.5%)
Pred / MP	3 rct [47–49] 3 cc [35, 50, 51] 22 ct [13, 24, 26, 29–31, 52–68] 12 cs [37, 69–79] 16 cr [37, 39, 41–43, 69–78, 80–91] 1 Cochr [92] 1 sr [93]	2733 (1st ≥995, 2nd/3rd ≥637)	70/518	No significant adverse effect attributable to drug	63/697 No increase in rate of major malformations attributable to drug	i) Prednisolone is compatible with pregnancy and is the preferred corticosteroid in the treatment of maternal rheumatological disease in pregnancy and requires shared care with obstetric teams to monitor maternal blood pressure and blood glucose (GRADE 1B, SOA 100%) ii) Where possible, the dose of prednisolone should be <20 mg/day and tapered to the minimum effective dose to control maternal disease, in conjunction with steroid-sparing drugs compatible with pregnancy (GRADE 1C, SOA 99.5%) iii) Prednisolone is compatible with breastmilk exposure (GRADE 1B, SOA 100%) iv) Methylprednisolone has similar rates of placental transfer to prednisolone and would therefore be expected to be compatible with pregnancy and breastmilk exposure (GRADE 2C, SOA 99%)
MTX	2 cc [94, 95] 8 ct [19, 28, 30, 63, 96–99] 1 cs [100] 5 cr [101–105]	766 (1st trimester ≥239, 2nd/3rd trimester ≥8)	80/479	Insufficient data; only one study reported birthweight in a cohort of $n = 23$ [19], with two studies reporting pregnancy duration ($n = 43$) [19, 95]	36/265 Individual case reports of MTX embryopathy, but larger studies show limited numbers of cases of fetal malformation	i) MTX at any dose should be avoided in pregnancy and stopped at least one month in advance of planned conception, when it should be switched to another pregnancy-compatible drug to ensure maintenance of maternal disease suppression (GRADE 1A, SOA 98%) ii) In women treated with low-dose (≤25 mg/week) MTX within one month prior to conception, folic acid supplementation (5 mg/day) should be continued up to 12 weeks of pregnancy (GRADE 1B, SOA 99.5%) iii) In unintended pregnancy on low-dose MTX (≤25 mg/week), there is minimal risk to the fetus; the drug should be stopped immediately, folic acid supplementation (5 mg/day) continued, and a careful evaluation of fetal risk with early referral to a fetal medicine department considered (GRADE 1C, SOA 100%) iv) Although only minute amounts of MTX are excreted into breast milk, MTX cannot be recommended in breastfeeding because of theoretical risks and insufficient data on outcomes (GRADE 2C, SOA 99%)

(continued)

Table 2. (continued)

Drug	Studies (type and number)	Pregnancy exposures (exposures per trimester)	Foetal losses/ total pregnancy outcomes	Pregnancy duration and birth weight	Malformations/total births	Recommendation (GRADE/Strength of agreement)
SSZ	3 ct [24, 28, 30] 1 cs [37] 2 cr [44, 106]	178 (NR)	NR	No significant adverse effect noted	Rate not specifically quantified in the majority of papers. Overall, no increase in rate of major malformations attributable to drug	i) SSZ is compatible throughout pregnancy, with folic acid 5mg/day recommended in the periconception period and during the first trimester (GRADE 1B, SOA 100%) ii) SSZ is compatible with breastmilk exposure in healthy, full-term infants (GRADE 1C, SOA 99.5%)
LEF	6 ct [28, 63, 107–110] 4 cr [111–114]	814 (1st ≥156, 2nd/3rd ≥24)	138/811	No significant adverse effect noted	42/525 Overall, no increase in rate of major malformations attributable to drug, but most cases stopped in 1st trimester and received cholestyramine washout	i) LEF may not be a human teratogen but there remains insufficient evidence to support use at the time of conception or during pregnancy (GRADE 1B, SOA 98%) ii) Women on LEF considering pregnancy should stop and undergo a standard cholestyramine washout procedure, and switch to alternative medication compatible with pregnancy (GRADE 1B, SOA 98.8%) iii) If unintended conception occurs on LEF, the drug should be stopped immediately and a standard cholestyramine washout procedure given, with early referral to a fetal medicine department considered (GRADE 1B, SOA 99%) iv) LEF is not recommended whilst breastfeeding (GRADE 1C, SOA 99.5%)
AZA	5 cc [51, 94, 115–117] 16 ct [13, 23, 28–30, 58, 62, 64, 65, 67, 118–123] 6 cs [37, 72, 75, 100, 124, 125] 2 cr [43, 81] 1 sr [93]	1757 (1st ≥1254, 2nd/3rd ≥580)	130/642	No significant adverse effect noted	18/487 Overall, no increase in rate of major malformations attributable to drug	i) AZA is compatible throughout pregnancy (GRADE 1B, SOA 100%) ii) AZA is compatible with breastmilk exposure (GRADE 2C, SOA 99.5%)
CsA	4 cc [35, 51, 116, 126] 8 ct [28, 29, 64, 65, 67, 98, 127, 128] 3 cs [36, 74, 129]	401 (1st ≥131, 2nd/3rd ≥136)	9/132	Possible trend towards shorter pregnancy duration [64, 74, 126, 129] and low birth weight [51] [64] [129]	2/26 Data confounded by concomitant AZA / MMF exposure	i) CsA is compatible throughout pregnancy with monitoring of maternal blood pressure, renal function, blood glucose and drug levels (GRADE 1B, SOA 100%) ii) CsA is compatible with breastmilk exposure (GRADE 2C, SOA 99.7%)
TAC	1 ct [64, 65, 127, 130–137] 1 cs [72] 2 cr [81, 90]	515 (1st ≥302, 2nd/3rd ≥135)	108/451	Insufficient data to confirm lack of a significant adverse effect	12/270 Overall, insufficient data, mainly in organ transplant cohorts	i) TAC is compatible throughout pregnancy with monitoring of maternal blood pressure, renal function, blood glucose and drug levels (GRADE 2B, SOA 100%) ii) TAC is compatible with breastmilk exposure (GRADE 2C, SOA 99.8%)

(continued)

Table 2. (continued)

Drug	Studies (type and number)	Pregnancy exposures (exposures per trimester)	Foetal losses/ total pregnancy outcomes	Pregnancy duration and birth weight	Malformations/total births	Recommendation (GRADE/Strength of agreement)
CYC	1 cs [75] 4 cr [80, 85, 138, 139] 1 ct [140]	20 (1st ≥6, 2nd/3rd ≥2)	2/16	Insufficient data	0/13 Few data, from individual case reports or case series, available	i) CYC is a known teratogen and gonadotoxic, and therefore should only be considered in pregnancy in cases of severe life/organ-threatening maternal disease when there is appreciable risk of maternal and fetal morbidity and mortality without this therapy (GRADE 1B, SOA 99.5%) ii) CYC is not recommended whilst breastfeeding (GRADE 2C, SOA 100%)
MMF	7 ct [64, 67, 123, 141–144] 3 cs [72, 125, 145] 12 cr [39, 42, 87, 88, 90, 146–151]	804 (1st ≥796, 2nd/3rd ≥320)	371/753	Evidence of reduced pregnancy duration and birth weight	47/316 Data mainly from organ transplant cohorts, including one cohort of n=221 demonstrating both reduced gestation and birth weight	i) MMF remains contraindicated during pregnancy, and should be avoided in women planning pregnancy or switched to a pregnancy-compatible alternative at least 6 weeks before attempting to conceive (GRADE 1B, SOA 100%) ii) In cases of unintended conception, switch MMF to a pregnancy-compatible alternative and refer to local experts for further advice and risk assessment (GRADE 1B, SOA 100%) iii) MMF is not recommended whilst breastfeeding (GRADE 2C, SOA 99.7%)
IVIG	1 cc [152] 12 ct [26, 27, 54, 59, 153–160] 1 Cochr [92] 1 cs [70] 3 cr [40, 84, 161]	403 (1st ≥13, 2nd/3rd ≥77)	10/178	No significant adverse effect noted	22/121 Overall, no increase in rate of major malformations attributable to drug, albeit limited data available	i) IVIG is compatible with pregnancy (GRADE 1B, SOA 99.5%) ii) IVIG is compatible with breastmilk exposure (GRADE 2C, SOA 100%)

All studies that provided quantitative and/or qualitative information on the safety of the relevant drug in pregnancy were included; however, numerical outcome data could only be collated from papers where the relevant outcome was clearly quantified. Details of how numerical data in this table were derived are shown in Supplementary Data S3, available at *Rheumatology* online. References shown in the table are included within Supplementary Data S4, available at *Rheumatology* online.

cc: case control; Cochr: Cochrane review; cr: case report; cs: case series; CsA: ciclosporin; ct: cohort; MP: methylprednisolone; NR: not reported; nrt: non-randomized trial; Pred: prednisolone; rct: randomised controlled trial; SOA: strength of agreement; sr: systematic review; TAC: tacrolimus.

Table 3. Summary of maternal exposure to biological DMARDs and targeted synthetic DMARDs

Drug	Studies (type and number)	Pregnancy exposures (exposures per trimester)	Foetal losses/ total pregnancy outcomes	Pregnancy duration and birth weight	Malformations/total births	Recommendation (GRADE/Strength of agreement)
TNFi (combined data for all licenced drugs)	See individual drugs below, plus: 28 ct [162–189] 1 cs [190] 4 cc [94, 191–193]	7787 (1st ≥2929, 2nd/3rd ≥2150)	886/4192	No significant adverse effect noted overall	214/5157 Overall, no increase in rate of major malformations attributable to drug	i) Women with no/low disease activity established on a tumour necrosis factor inhibitor (TNFi) with known placental transfer (INF, ADA, GOL) do not need to be switched to an alternative TNFi with established minimal placental transfer (CZP) either before or during pregnancy (GRADE 1B, SOA 100%) ii) CZP is compatible with all three trimesters of pregnancy, has no to minimal placental transfer compared with other TNFi, and does not require any alteration to the infant vaccination schedule (GRADE 1B, SOA 100%) iii) Women considered to have low risk of disease flare on withdrawal of TNFi in pregnancy could stop INF at 20 weeks, ADA and GOL at 28 weeks, and ETA at 32 weeks so that a full-term infant can have a normal vaccination schedule, with rotavirus vaccination at 8 weeks as per the UK schedule (GRADE 1B, SOA 99.5%) iv) INF, ADA, ETA or GOL may be continued throughout pregnancy to maintain maternal disease control; in these circumstances, live vaccines should be avoided in infants until they are 6 months of age (GRADE 1B, SOA 100%) v) If a TNFi is stopped in pregnancy, it can be restarted as soon as practical post-partum in the absence of infections or surgical complications, regardless of breastfeeding status, to ensure control of maternal disease (GRADE 1C, SOA 100%) vi) TNFi are compatible with breastmilk exposure (GRADE 1C, SOA 100%)
CZP	2 ct [194, 195] 1 cs [196]	567 (1st ≥371, 2nd/3rd ≥335)	52/567	No significant adverse effect noted overall	9/488 Overall, no increase in rate of major malformations attributable to drug	See recommendations above
INF	9 ct [28, 197–204] 8 cs [100, 205–211] 1 cr [212]	2645 (1st ≥1301, 2nd/3rd ≥92)	255/2484	No significant adverse effect noted overall	56/2090 Overall, no increase in rate of major malformations attributable to drug	See recommendations above
ETA	5 ct [28, 30, 197, 213, 214] 3 cs [73, 207, 215] 4 cr [82, 83, 216, 217] 1 rct [218]	821 (1st ≥475, 2nd/3rd ≥207)	73/383	No significant adverse effect noted overall	47/676 Overall, no increase in rate of major malformations attributable to drug	See recommendations above

(continued)

Table 3. (continued)

Drug	Studies (type and number)	Pregnancy exposures (exposures per trimester)	Foetal losses/ total pregnancy outcomes	Pregnancy duration and birth weight	Malformations/total births	Recommendation (GRADE/Strength of agreement)
ADA	7 ct [28, 30, 159, 198, 219–221] 5 cs [72, 207, 209–211] 3 cr [212, 222, 223]	473 (1st ≥425, 2nd/3rd ≥298)	33/371	No significant adverse effect noted overall	30/397 Overall, no increase in rate of major malformations attributable to drug	See recommendations above
GOL	2 ct [224, 225]	166 (NR)	34/166	NR	3/115 Overall, no increase in rate of major malformations attributable to drug	See recommendations above
RTX	5 ct [28, 226–229] 4 cs [230–233] 4 cr [234–237]	316 (1st ≥13, 2nd/3rd ≥1)	68/293	No significant adverse effect noted	6/170 Overall, no increase in rate of major malformations attributable to drug	i) Limited evidence has not shown RTX to be teratogenic; however, there remains insufficient evidence to be confident that it is compatible with pregnancy. Consider stopping the drug at conception (GRADE 2C, SOA 99.3%) ii) RTX may be considered to manage severe maternal disease in pregnancy if no other pregnancy-compatible drugs are suitable (GRADE 2C, SOA 99.7%) iii) If RTX is used to treat severe maternal disease in the third trimester, it is currently recommended to avoid all live vaccines in the infant vaccination schedule until 6 months of age (GRADE 2C, SOA 98.7%) iv) Based on limited evidence, maternal treatment with RTX is compatible with breastmilk exposure (GRADE 2C, SOA 99.5%)
TOC	2 ct [238, 239] 2 cs [240, 241]	365 (1st ≥46, 2nd/3rd ≥2)	84/354	No significant adverse effect attributable to drug (data limited by confounding)	8/211 Overall, no increase in rate of major malformations attributable to drug	i) Limited evidence has not shown IL-6i to be teratogenic; however, there remains insufficient evidence to be confident that they are compatible with pregnancy. Consider stopping the drug at conception. Any exposure, however, during pregnancy is unlikely to be harmful (GRADE 2C, SOA 99.7%) ii) IL-6i may be considered to manage severe maternal disease in pregnancy if no other pregnancy-compatible drugs are suitable (GRADE 2C, SOA 100%) iii) If IL-6i are used to treat severe maternal disease in the third trimester, it is currently recommended to avoid all live vaccines in the infant vaccination schedule until 6 months of age (GRADE 2C, SOA 99.3%) iv) Based on limited evidence, maternal treatment with IL-6i is compatible with breastmilk exposure (GRADE 2C, SOA 100%)

(continued)

Table 3. (continued)

Drug	Studies (type and number)	Pregnancy exposures (exposures per trimester)	Foetal losses/ total pregnancy outcomes	Pregnancy duration and birth weight	Malformations/total births	Recommendation (GRADE/Strength of agreement)
ANA	2 ct [28, 242] 4 cs [243–246] 1 cr [247]	48 (1st ≥25, 2nd/3rd ≥40)	3/43	No significant adverse effect attributable to drug	2/41 (including one resulting in miscarriage at 30 weeks)	i) Limited evidence has not shown IL-1i to be teratogenic; however, there remains insufficient evidence to be confident that they are compatible with pregnancy. Consider stopping the drug at conception. Any exposure, however, during pregnancy is unlikely to be harmful (GRADE 2C, SOA 99.8%) ii) IL-1i may be considered to manage severe maternal disease in pregnancy if no other pregnancy-compatible drugs are suitable (GRADE 2C, SOA 100%) iii) If IL-1i are used to treat severe maternal disease in the third trimester, it is currently recommended to avoid all live vaccines in the infant vaccination schedule until 6 months of age (GRADE 2C, SOA 99.3%) iv) Based on limited evidence, maternal treatment with IL-1i is compatible with breastmilk exposure (GRADE 2C, SOA 100%)
CAN	1 cs [244]	8 (all 1st)	1/8	No significant adverse effect noted	0/7	See recommendations above
ABA	1 cs [102] 1 cr [237] 2 ct [248, 249]	99 (1st ≥145, 2nd/3rd ≥10)	49/187	No significant adverse effect attributable to drug (data limited by confounding)	10/104 Overall, no pattern of malformations attributable to drug	i) Limited evidence has not shown ABA to be teratogenic; however, there remains insufficient evidence to be confident that it is compatible with pregnancy. Consider stopping the drug at conception. Any exposure, however, during pregnancy is unlikely to be harmful (GRADE 2C, SOA 99.3%) ii) ABA may be considered to manage severe maternal disease in pregnancy if no other pregnancy-compatible drugs are suitable (GRADE 2C, SOA 99.3%) iii) If ABA is used to treat severe maternal disease in the third trimester, it is currently recommended to avoid all live vaccines in the infant vaccination schedule until 6 months of age (GRADE 2C, SOA 99.3%) iv) Based on limited evidence, maternal treatment with ABA is compatible with breastmilk exposure (GRADE 2C, SOA 99.5%)

(continued)

Table 3. (continued)

Drug	Studies (type and number)	Pregnancy exposures (exposures per trimester)	Foetal losses/ total pregnancy outcomes	Pregnancy duration and birth weight	Malformations/total births	Recommendation (GRADE/Strength of agreement)
BEL	1 ct [250]	66 (NR)	18/66	No significant adverse effect attributable to drug (data limited by confounding)	3/33 Overall, no pattern of malformations attributable to drug	i) Limited evidence has not shown BEL to be teratogenic; however, there remains insufficient evidence to be confident that it is compatible with pregnancy. Consider stopping the drug at conception. Any exposure, however, during pregnancy is unlikely to be harmful (GRADE 2C, SOA 99.3%) ii) BEL may be considered to manage severe maternal disease in pregnancy if no other pregnancy-compatible drugs are suitable (GRADE 2C, SOA 99.5%) iii) If BEL is used to treat severe maternal disease in the third trimester, it is currently recommended to avoid all live vaccines in the infant vaccination schedule until 6 months of age (GRADE 2C, SOA 98.8%) iv) Based on limited evidence, maternal treatment with BEL is compatible with breastmilk exposure (GRADE 2C, SOA 99.5%)
SEC	2 ct [251, 252]	244 (1st ≥161, 2nd/3rd NR)	26/125	No significant adverse effect noted	2/54 Overall, no pattern of malformations attributable to drug	i) Limited evidence has not shown IL-17i to be teratogenic; however, there remains insufficient evidence to be confident that they are compatible with pregnancy. Consider stopping the drug at conception. Any exposure, however, during pregnancy is unlikely to be harmful (GRADE 2C, SOA 99.3%) ii) IL-17i may be considered to manage severe maternal disease in pregnancy if no other pregnancy-compatible drugs are suitable (GRADE 2C, SOA 99%) iii) If IL-17i are used to treat severe maternal disease in the third trimester, it is currently recommended to avoid all live vaccines in the infant vaccination schedule until 6 months of age (GRADE 2C, SOA 99.3%) iv) Based on limited evidence, maternal treatment with IL-17i is compatible with breastmilk exposure (GRADE 2C, SOA 99.5%)
IXE	1 ct [253]	18 (NR)	5/18 (spontaneous and induced)	No significant adverse effect noted	0/8 Overall, no pattern of malformations attributable to drug	See recommendations above

(continued)

Table 3. (continued)

Drug	Studies (type and number)	Pregnancy exposures (exposures per trimester)	Foetal losses/ total pregnancy outcomes	Pregnancy duration and birth weight	Malformations/total births	Recommendation (GRADE/Strength of agreement)
UST	2 ct [254, 255] 1 cs [256]	517 (1st ≥31, 2nd/3rd ≥10)	92/517	No significant adverse effect noted	17/375 Overall, no pattern of malformations attributable to drug	i) Limited evidence has not shown UST to be teratogenic; however, there remains insufficient evidence to be confident that it is compatible with pregnancy. Consider stopping the drug at conception. Any exposure, however, during pregnancy is unlikely to be harmful (GRADE 2C, SOA 99.3%) ii) UST may be considered to manage severe maternal disease in pregnancy if no other pregnancy-compatible drugs are suitable (GRADE 2C, SOA 98.8%) iii) If UST is used to treat severe maternal disease in the third trimester, it is currently recommended to avoid all live vaccines in the infant vaccination schedule until 6 months of age (GRADE 2C, SOA 99.3%) iv) Based on limited evidence, maternal treatment with UST is compatible with breastmilk exposure (GRADE 2C, SOA 99.5%)
TOF	1 ct [257]	116 (all 1st, 2nd/3rd NR)	15/72	No significant adverse effect noted	2/44 Overall, no pattern of malformations attributable to drug	i) There are insufficient data to make a recommendation on JAKi use during pregnancy and they should be stopped at least two weeks before planned conception (GRADE 2C, SOA 99.5%) ii) There are insufficient data to recommend JAKi in breastfeeding and, given they are likely to transfer into breast milk, they should be avoided (GRADE 2C, SOA 99.5%)

All studies that provided quantitative and/or qualitative information on the safety of the relevant drug in pregnancy were included; however, numerical outcome data could only be collated from papers where the relevant outcome was clearly quantified. Details of how numerical data in this table were derived are shown in Supplementary Data S3, available at *Rheumatology* online. References shown in the table are included within Supplementary Data S4, available at *Rheumatology* online.

ABA: abatacept; ADA: adalimumab; ANA: anakinra; BEL: belimumab; CAN: canakinumab; cc: case control; cr: case report; cs: case series; ct: cohort; CZP: certolizumab; ETA: etanercept; GOL: golimumab; IL-1i: IL-1 inhibitors; IL-6i: IL-6 inhibitors; IL-17i: IL-17 inhibitors; INF: infliximab; IXE: ixekizumab; JAKi: Janus kinase inhibitor; NR: not reported; rct: randomized controlled trial; RTX: rituximab; SEC: secukinumab; SOA: strength of agreement; TNFi: TNF-alpha inhibitor; TOC: tocilizumab; TOF: tofacitinib; UST: ustekinumab.

Table 4. Summary of pregnancy outcomes after paternal exposure

Drug	Studies included (type and number)	Pregnancy exposures	Adverse pregnancy outcomes (foetal losses or malformations)	Recommendation (GRADE / Strength of agreement)
HCQ	1 ct [30] 1 cs [258]	13	No increase	Paternal exposure to HCQ is compatible with pregnancy (GRADE 2C, SOA 99.3%)
CS	5 ct [30, 259–262] 2 cs [258, 263]	4507	No increase	Paternal exposure to prednisolone is compatible with pregnancy (GRADE 1B, SOA 99.3%)
SSZ	3 ct [30, 261, 264] 1 cc [265]	237	No increase	Men who take SSZ may have reduced fertility. There is little evidence to suggest that SSZ should be stopped preconception, unless conception is delayed by more than 12 months when stopping SSZ should be considered along with other causes of infertility (GRADE 1C, SOA 99.0%)
LEF	1 ct [30] 1 cr [266]	2	No increase	Paternal exposure to LEF is compatible with pregnancy (GRADE 2C, SOA 99.3%)
AZA	9 ct [30, 259–261, 267–271] 1 cc [265] 2 cs [258, 263]	3282[a]	No increase	Paternal exposure to AZA is compatible with pregnancy (GRADE 1B, SOA 99.3%)
MTX	10 ct [30, 259, 261, 267, 268, 272–275] 3 cs [258, 276] 1 cr [277]	2289	No increase	Paternal exposure to low-dose (≤25 mg/week) MTX is compatible with pregnancy (GRADE 1B, SOA 99.3%)
CsA	3 ct [260, 267, 278] 2 cs [263, 276]	501[a]	No increase	Paternal exposure to CsA is compatible with pregnancy (GRADE 1C, SOA 99.3%)
TAC	3 ct [260, 278, 279]	41[a]	No increase	Paternal exposure to TAC is compatible with pregnancy (GRADE 2C, SOA 99.3%)
CYC	No data meeting inclusion criteria		Known to affect male fertility; evidence of an adverse impact on germ cell development and male-mediated teratogenicity from animal studies	Due to the adverse effect of CYC on male fertility, semen cryopreservation is recommended for men prior to paternal exposure (GRADE 1C, SOA 99.5%)
MMF	3 ct [267, 280, 281] 3 cs [260, 278, 282]	292	No increase	Paternal exposure to MMF is compatible with pregnancy (GRADE 2C, SOA 99.3%)
TNFi	13 ct [30, 165, 171, 200, 203, 259, 264, 283–288] 2 cs [258, 276] 2 cr [277, 289] 1 cc [265]	751	No increase	Paternal exposure to TNFi is compatible with pregnancy (GRADE 1C, SOA 99.3%)
RTX	1 ct [228]	11	No increase	Paternal exposure to RTX is compatible with pregnancy (GRADE 2C, SOA 99.3%)
IL-6i	1 ct [238]	15 (TOC)	No increase	Paternal exposure to IL-6i is compatible with pregnancy (GRADE 2C, SOA 99.3%)
IL-1i	1 ct [244]	5 (ANA) 6 (CAN)	No increase	Paternal exposure to IL-1i is compatible with pregnancy (GRADE 2C, SOA 99.3%)
ABA	1 ct [249]	10	No increase	Paternal exposure to ABA is compatible with pregnancy (GRADE 2C, SOA 99.3%)
IL-17i	2 ct [251, 253]	54 (SEC) 34 (IXE)	No increase	Paternal exposure to IL-17i is compatible with pregnancy (GRADE 2C, SOA 99.3%)
JAKi	1 ct [290]	87 (TOF)	No increase	Paternal exposure to JAKi is compatible with pregnancy (GRADE 2C, SOA 99.3%)

All studies that provided quantitative and/or qualitative information on the safety of the relevant drug following paternal exposure were included. Details of how numerical data in this table were derived are shown in Supplementary Data S3, available at *Rheumatology* online. References shown in the table are included within Supplementary Data S4, available at *Rheumatology* online.

[a] Minimum number of pregnancy exposures to drug; additional exposures were described in some studies but could not be separated from grouped study data.

ABA: abatacept; ANA: anakinra; BEL: belimumab; CAN: canakinumab; cc: case control; cr: case report; cs: case series; CS: corticosteroids; CsA: ciclosporin; ct: cohort; IL-1i: IL-1 inhibitors; IL-6i: IL-6 inhibitors; IL-17i: IL-17 inhibitors; IXE: ixekizumab; JAKi: Janus kinase inhibitors; NR: not reported; RTX: rituximab; SEC: secukinumab; SOA: strength of agreement; TAC: tacrolimus; TNFi: TNF-alpha inhibitor; TOC: tocilizumab; TOF: tofacitinib; UST: ustekinumab.

ii) Where possible, the dose of prednisolone should be <20 mg/day and tapered to the minimum effective dose to control maternal disease, in conjunction with steroid-sparing drugs compatible with pregnancy (GRADE 1C, SOA 99.5%).
iii) Prednisolone is compatible with breastmilk exposure (GRADE 1B, SOA 100%).
iv) Methylprednisolone has similar rates of placental transfer to prednisolone and would therefore be expected to be compatible with pregnancy and breastmilk exposure (GRADE 2C, SOA 99%).

Conventional synthetic DMARDs

Methotrexate

Recommendations were based on 12 recent and 10 previous studies of MTX.

Recommendations for methotrexate in pregnancy and breastmilk exposure

i) MTX at any dose should be avoided in pregnancy and stopped at least one month in advance of planned conception, when it should be switched to another pregnancy-compatible drug to ensure maintenance of maternal disease suppression (GRADE 1A, SOA 98%).
ii) In women treated with low-dose (≤25 mg/week) MTX within one month prior to conception, folic acid supplementation (5 mg/day) should be continued up to 12 weeks of pregnancy (GRADE 1B, SOA 99.5%).
iii) In unintended pregnancy on low-dose (≤25 mg/week) MTX, there is minimal risk to the foetus; the drug should be stopped immediately, folic acid supplementation (5 mg/day) continued, and a careful evaluation of foetal risk with early referral to a foetal medicine department considered (GRADE 1C, SOA 100%).
iv) Although only minute amounts of MTX are excreted into breastmilk, MTX cannot be recommended in breastfeeding because of theoretical risks and insufficient data on outcomes (GRADE 2C, SOA 99%).

Sulfasalazine

Recommendations were based on six studies of SSZ identified in the previous guideline.

Recommendations for sulfasalazine in pregnancy and breastmilk exposure

i) SSZ is compatible throughout pregnancy, with folic acid 5 mg/day recommended in the periconception period and during the first trimester (GRADE 1B, SOA 100%).
ii) SSZ is compatible with breastmilk exposure in healthy, full-term infants (GRADE 1C, SOA 99.5%).

Leflunomide

Recommendations were based on three recent and seven previous studies of LEF.

Recommendations for leflunomide in pregnancy and breastmilk exposure

i) LEF may not be a human teratogen but there remains insufficient evidence to support use at the time of conception or during pregnancy (GRADE 1B, SOA 98%).
ii) Women on LEF considering pregnancy should stop and undergo a standard cholestyramine washout procedure, and switch to alternative medication compatible with pregnancy (GRADE 1B, SOA 98.8%).
iii) If unintended conception occurs on LEF, the drug should be stopped immediately and a standard cholestyramine washout procedure given, with early referral to a foetal medicine department considered (GRADE 1B, SOA 99%).
iv) LEF is not recommended while breastfeeding (GRADE 1C, SOA 99.5%).

Azathioprine

Recommendations were based on nine recent and 28 previous studies of AZA.

Recommendations for azathioprine in pregnancy and breastmilk exposure

i) AZA is compatible throughout pregnancy (GRADE 1B, SOA 100%).
ii) AZA is compatible with breastmilk exposure (GRADE 2C, SOA 99.5%).

Ciclosporin

Recommendations were based on five recent and 13 previous studies of ciclosporin (CsA).

Recommendations for ciclosporin in pregnancy and breastmilk exposure

i) CsA is compatible throughout pregnancy with monitoring of maternal blood pressure, renal function, blood glucose and drug levels (GRADE 1B, SOA 100%).
ii) CsA is compatible with breastmilk exposure (GRADE 2C, SOA 99.7%).

Tacrolimus

Recommendations were based on eight recent and seven previous studies of tacrolimus.

Recommendations for tacrolimus in pregnancy and breastmilk exposure

i) Tacrolimus is compatible throughout pregnancy with monitoring of maternal blood pressure, renal function, blood glucose and drug levels (GRADE 2B, SOA 100%).
ii) Tacrolimus is compatible with breastmilk exposure (GRADE 2C, SOA 99.8%).

Cyclophosphamide

Recommendations were based on one recent and five previous studies of CYC.

Recommendations for cyclophosphamide in pregnancy and breastmilk exposure

i) CYC is a known teratogen and gonadotoxic, and therefore should only be considered in pregnancy in cases of severe life/organ-threatening maternal disease when there is appreciable risk of maternal and foetal morbidity and mortality without this therapy (GRADE 1B, SOA 99.5%).
ii) CYC is not recommended while breastfeeding (GRADE 2C, SOA 100%).

Mycophenolate mofetil

Recommendations were based on eight recent and 16 previous studies of MMF.

Recommendations for mycophenolate mofetil in pregnancy and breastmilk exposure

i) MMF remains contraindicated during pregnancy, and should be avoided in women planning pregnancy or switched to a pregnancy-compatible alternative at least 6 weeks before attempting to conceive (GRADE 1B, SOA 100%).

ii) In cases of unintended conception, switch MMF to a pregnancy-compatible alternative and refer to local experts for further advice and risk assessment (GRADE 1B, SOA 100%).
iii) MMF is not recommended while breastfeeding (GRADE 2C, SOA 99.7%).

Intravenous immunoglobulin

Two recent and 16 previous studies of IVIG were identified.

Recommendations for intravenous immunoglobulin in pregnancy and breastmilk exposure

i) IVIG is compatible with pregnancy (GRADE 1B, SOA 99.5%).
ii) IVIG is compatible with breastmilk exposure (GRADE 2C, SOA 100%).

Biologic DMARDs

Anti-TNFα drugs

Recommendations were based on 50 recent studies, two breastmilk transfer studies, and 29 previous studies of tumour necrosis factor-α inhibitors (TNFi).

Recommendations for anti-TNFα medications in pregnancy and breastmilk exposure

i) Women with no/low disease activity established on a TNFi with known placental transfer [infliximab (INF), adalimumab (ADA), golimumab (GOL)] do not need to be switched to an alternative TNFi with established minimal placental transfer [certolizumab pegol (CZP)] either before or during pregnancy (GRADE 1B, SOA 100%).
ii) CZP is compatible with all three trimesters of pregnancy, has no to minimal placental transfer compared with other TNFi, and does not require any alteration to the infant vaccination schedule (GRADE 1B, SOA 100%).
iii) Women considered to have low risk of disease flare on withdrawal of TNFi in pregnancy could stop INF at 20 weeks, ADA and GOL at 28 weeks, and ETA at 32 weeks so that a full-term infant can have a normal vaccination schedule, with rotavirus vaccination at 8 weeks as per the UK schedule (GRADE 1B, SOA 99.5%).
iv) INF, ADA, ETA or GOL may be continued throughout pregnancy to maintain maternal disease control; in these circumstances, live vaccines should be avoided in infants until they are 6 months of age (GRADE 1B, SOA 100%).
v) If a TNFi is stopped in pregnancy, it can be restarted as soon as practical post-partum in the absence of infections or surgical complications, regardless of breastfeeding status, to ensure control of maternal disease (GRADE 1C, SOA 100%).
vi) TNFi are compatible with breastmilk exposure (GRADE 1C, SOA 100%).

Rituximab

Recommendations were based on five recent studies, a breastmilk transfer study, and eight previous studies of rituximab (RTX).

Recommendations for rituximab in pregnancy and breastmilk exposure

i) Limited evidence has not shown RTX to be teratogenic; however, there remains insufficient evidence to be confident that it is compatible with pregnancy. Consider stopping the drug at conception (GRADE 2C, SOA 99.3%).
ii) RTX may be considered to manage severe maternal disease in pregnancy if no other pregnancy-compatible drugs are suitable (GRADE 2C, SOA 99.7%).
iii) If RTX is used to treat severe maternal disease in the third trimester, it is currently recommended to avoid all live vaccines in the infant vaccination schedule until 6 months of age (GRADE 2C, SOA 98.7%).
iv) Based on limited evidence, maternal treatment with RTX is compatible with breastmilk exposure (GRADE 2C, SOA 99.5%).

Interleukin-6 inhibitors

We identified three recent studies and one previous study of tocilizumab (TCZ). No studies of sarilumab were identified.

Recommendations for IL-6 inhibitors in pregnancy and breastmilk exposure

i) Limited evidence has not shown IL-6 inhibitors (IL-6i) to be teratogenic; however, there remains insufficient evidence to be confident that they are compatible with pregnancy. Consider stopping the drug at conception. Any exposure, however, during pregnancy is unlikely to be harmful (GRADE 2C, SOA 99.7%).
ii) IL-6i may be considered to manage severe maternal disease in pregnancy if no other pregnancy-compatible drugs are suitable (GRADE 2C, SOA 100%).
iii) If IL-6i are used to treat severe maternal disease in the third trimester, it is currently recommended to avoid all live vaccines in the infant vaccination schedule until 6 months of age (GRADE 2C, SOA 99.3%).
iv) Based on limited evidence, maternal treatment with IL-6i is compatible with breastmilk exposure (GRADE 2C, SOA 100%).

Interleukin-1 inhibitors

We identified four recent and three previous studies of anakinra and one study of canakinumab.

Recommendations for IL-1 inhibitors in pregnancy and breastmilk exposure

i) Limited evidence has not shown IL-1 inhibitors (IL-1i) to be teratogenic; however, there remains insufficient evidence to be confident that they are compatible with pregnancy. Consider stopping the drug at conception. Any exposure, however, during pregnancy is unlikely to be harmful (GRADE 2C, SOA 99.8%).
ii) IL-1i may be considered to manage severe maternal disease in pregnancy if no other pregnancy-compatible drugs are suitable (GRADE 2C, SOA 100%).
iii) If IL-1i are used to treat severe maternal disease in the third trimester, it is currently recommended to avoid all

live vaccines in the infant vaccination schedule until 6 months of age (GRADE 2C, SOA 99.3%).
iv) Based on limited evidence, maternal treatment with IL-1i is compatible with breastmilk exposure (GRADE 2C, SOA 100%).

Abatacept

We identified two recent and three previous studies of abatacept (ABA).

Recommendations for abatacept in pregnancy and breastmilk exposure

i) Limited evidence has not shown ABA to be teratogenic; however, there remains insufficient evidence to be confident that it is compatible with pregnancy. Consider stopping the drug at conception. Any exposure, however, during pregnancy is unlikely to be harmful (GRADE 2C, SOA 99.3%).
ii) ABA may be considered to manage severe maternal disease in pregnancy if no other pregnancy-compatible drugs are suitable (GRADE 2C, SOA 99.3%).
iii) If ABA is used to treat severe maternal disease in the third trimester, it is currently recommended to avoid all live vaccines in the infant vaccination schedule until 6 months of age (GRADE 2C, SOA 99.3%).
iv) Based on limited evidence, maternal treatment with ABA is compatible with breastmilk exposure (GRADE 2C, SOA 99.5%).

Belimumab

We identified one recent and two previous studies of belimumab (BEL).

Recommendations for belimumab in pregnancy and breastmilk exposure

i) Limited evidence has not shown BEL to be teratogenic; however, there remains insufficient evidence to be confident that it is compatible with pregnancy. Consider stopping the drug at conception. Any exposure, however, during pregnancy is unlikely to be harmful (GRADE 2C, SOA 99.3%).
ii) BEL may be considered to manage severe maternal disease in pregnancy if no other pregnancy-compatible drugs are suitable (GRADE 2C, SOA 99.5%).
iii) If BEL is used to treat severe maternal disease in the third trimester, it is currently recommended to avoid all live vaccines in the infant vaccination schedule until 6 months of age (GRADE 2C, SOA 98.8%).
iv) Based on limited evidence, maternal treatment with BEL is compatible with breastmilk exposure (GRADE 2C, SOA 99.5%).

Interleukin-17 inhibitors

We identified three studies of secukinumab and ixekizumab.

Recommendations for interleukin-17 inhibitors in pregnancy and breastmilk exposure

i) Limited evidence has not shown interleukin-17 inhibitors (IL-17i) to be teratogenic; however, there remains insufficient evidence to be confident that they are compatible with pregnancy. Consider stopping the drug at conception. Any exposure, however, during pregnancy is unlikely to be harmful (GRADE 2C, SOA 99.3%).
ii) IL-17i may be considered to manage severe maternal disease in pregnancy if no other pregnancy-compatible drugs are suitable (GRADE 2C, SOA 99%).
iii) If IL-17i are used to treat severe maternal disease in the third trimester, it is currently recommended to avoid all live vaccines in the infant vaccination schedule until 6 months of age (GRADE 2C, SOA 99.3%).
iv) Based on limited evidence, maternal treatment with IL-17i is compatible with breastmilk exposure (GRADE 2C, SOA 99.5%).

Interleukin-12/23 inhibitors

We identified three studies of ustekinumab (UST).

Recommendations for interleukin-12/23 inhibitors in pregnancy and breastmilk exposure

i) Limited evidence has not shown UST to be teratogenic; however, there remains insufficient evidence to be confident that it is compatible with pregnancy. Consider stopping the drug at conception. Any exposure, however, during pregnancy is unlikely to be harmful (GRADE 2C, SOA 99.3%).
ii) UST may be considered to manage severe maternal disease in pregnancy if no other pregnancy-compatible drugs are suitable (GRADE 2C, SOA 98.8%).
iii) If UST is used to treat severe maternal disease in the third trimester, it is currently recommended to avoid all live vaccines in the infant vaccination schedule until 6 months of age (GRADE 2C, SOA 99.3%).
iv) Based on limited evidence, maternal treatment with UST is compatible with breastmilk exposure (GRADE 2C, SOA 99.5%).

Anifrolumab

Anifrolumab was not NICE approved at the time of our literature search, and so was not included in the search.

Targeted synthetic DMARDs

Apremilast

No studies relating to apremilast use in pregnancy were found.

JAK inhibitors

We identified three studies of tofacitinib (TOF) and no studies of baricitinib or upadacitinib. Filgotinib was NICE approved after our search, and so was not included.

Recommendations for JAK inhibitors in pregnancy and breastmilk exposure

i) There are insufficient data to make a recommendation on Janus kinase inhibitor (JAKi) use during pregnancy and they should be stopped at least two weeks before planned conception (GRADE 2C, SOA 99.5%).
ii) There are insufficient data to recommend JAKi in breastfeeding and, given they are likely to transfer into breastmilk, they should be avoided (GRADE 2C, SOA 99.5%).

Paternal exposure

Recommendations for paternal exposure to immunomodulatory drugs

i) Due to the adverse effect of CYC on male fertility, semen cryopreservation is recommended for men prior to paternal exposure (GRADE 1C, SOA 99.5%).
ii) Men who take SSZ may have reduced fertility. There is little evidence to suggest that SSZ should be stopped pre-conception, unless conception is delayed by more than 12 months when stopping SSZ should be considered along with other causes of infertility (GRADE 1C, SOA 99.0%).
iii) Paternal exposure to the following anti-rheumatic medication is compatible with pregnancy: prednisolone, low-dose (≤25 mg/week) methotrexate, azathioprine (GRADE 1B); TNFi, cyclosporin (GRADE 1C); hydroxychloroquine, leflunomide, tacrolimus, mycophenolate mofetil, intravenous immunoglobulin, rituximab, interleukin-6 inhibitors, interleukin-1 inhibitors, abatacept, belimumab, interleukin-17 inhibitors, ustekinumab and JAKi (GRADE 2C, SOA 99.3%).

Applicability and utility

Implementation

Awareness of these guidelines will aid clinical practitioners and patients in decision making. No barriers to implementation of these guidelines are anticipated.

Key standards of care

Patients with rheumatic disease should receive pre-pregnancy counselling and regular review during pregnancy and for 6 months post-partum by clinical practitioners with expertise in the management of rheumatic disease in pregnancy. They should have access to information on relevant medications in pregnancy and breastfeeding, enabling them to make informed decisions on drug use in pregnancy.

Future research agenda

Research questions include: should biologic DMARDs with known placental transfer be stopped or switched before/during pregnancy; are targeted synthetic DMARDs compatible with pregnancy; is it safe to give certain live vaccines to infants ≤6 months of age after third trimester exposure to biologic DMARDs with high placental transfer?

Mechanism for audit of the guideline

An audit tool to assess compliance with these guidelines is shown in Supplementary Data S5, 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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