



Guidelines

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

Mark D. Russell ¹, Mrinalini Dey², Julia Flint³, Philippa Davie¹, Alexander Allen⁴, Amy Crossley⁵, Margreta Frishman⁶, Mary Gayed⁷, Kenneth Hodson⁸, Munther Khamashta⁹, Louise Moore¹⁰, Sonia Panchal¹¹, Madeleine Piper¹², Clare Reid⁵, Katherine Saxby¹³, Karen Schreiber^{14,15,16}, Naz Senvar¹⁷, Sofia Tosounidou¹⁸, Maud van de Venne¹⁹, Louise Warburton²⁰, David Williams²¹, Chee-Seng Yee ²², Caroline Gordon ²³, Ian Giles^{24,*}; for the BSR Standards, Audit and Guidelines Working Group[†]

¹Centre for Rheumatic Diseases, King's College London, London, UK

²Institute of Life Course and Medical Sciences, University of Liverpool, Liverpool, UK

³Department of Rheumatology, Robert Jones and Agnes Hunt Orthopaedic Hospital NHS Foundation Trust, Shropshire, UK

⁴Clinical Affairs, British Society for Rheumatology, London, UK

⁵Patient Representative, UK

⁶Rheumatology, North Middlesex University Hospital NHS Trust, London, UK

⁷Rheumatology, Sandwell and West Birmingham Hospitals, Birmingham, UK

⁸UK Teratology Information Service, UK

⁹Lupus Research Unit, Division of Women's Health, King's College London, London, UK

¹⁰Rheumatic and Musculoskeletal Disease Unit, Our Lady's Hospice and Care Service, Dublin, Ireland

¹¹Department of Rheumatology, South Warwickshire NHS Foundation Trust, Warwickshire, UK

¹²Royal National Hospital for Rheumatic Diseases, Royal United Hospital, Bath, UK

¹³Pharmacy, University College London Hospitals NHS Foundation Trust, London, UK

¹⁴Thrombosis and Haemostasis, Guy's and St Thomas' NHS Foundation Trust, London, UK

¹⁵Department of Rheumatology, Danish Hospital for Rheumatic Diseases, Sonderborg, Denmark

¹⁶Department of Regional Health Research (IRS), University of Southern Denmark, Odense, Denmark

¹⁷Obstetrics and Gynaecology, St George's University Hospitals NHS Foundation Trust, London, UK

¹⁸Lupus UK Centre of Excellence, Sandwell and West Birmingham Hospitals NHS Trust, Birmingham, UK

¹⁹Obstetrics & Gynaecology, Frimley Park Hospital, Surrey, UK

²⁰Primary Care and Health Sciences, Keele University, Keele, UK

²¹Obstetrics, University College London Hospitals NHS Foundation Trust, London, UK

²²Department of Rheumatology, Doncaster and Bassetlaw Teaching Hospitals NHS Foundation Trust, Doncaster, UK

²³Rheumatology Research Group, Institute of Inflammation and Ageing, University of Birmingham, Birmingham, UK

²⁴Centre for Rheumatology, Division of Medicine, University College London, London, UK



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*Correspondence to: Ian Giles, Centre for Rheumatology, Division of Medicine, University College London, Room 411, Rayne Institute, 5 University Street, London WC1E 6JF, UK. E-mail: i.giles@ucl.ac.uk

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

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Scope and purpose

Background

The rationale behind this update of 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 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). 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 [9].

Need for guideline

There has been an appreciable increase in the number of published pregnancy exposures to biologic DMARDs (bDMARDs), and two of these drugs are now licensed for use in pregnancy. In addition, therapeutic advances in management of various inflammatory rheumatic diseases (IRDs) have led to an expansion of bDMARDs and biosimilars with different modes of action, as well as a new class of targeted synthetic DMARDs (tsDMARDs).

The continuing expansion of existing and novel DMARDs means that uncertainty remains around the use of many of these drugs in pregnancy. This uncertainty may still lead to withdrawal of treatment from pregnant women unnecessarily [10]. Discontinuation of treatment in preparation for or during early pregnancy can increase the risk of disease activity and flares during pregnancy, and are reported following discontinuation of biologics in patients with IRDs [11]. The compatibility of various immunosuppressive and disease-modifying 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 the Faculty of Sexual and Reproductive Healthcare [12, 13].

Objectives of guideline

To update the previous BSR guidelines on prescribing in pregnancy in rheumatic disease of the following drug categories: antimalarials; corticosteroids; conventional synthetic (cs)DMARDs and immunosuppressive therapies; bDMARDs;

and tsDMARDs. The full list of medications is shown in [Supplementary Data S1](#), available at *Rheumatology* online. This revised guideline was produced by systematically reviewing all evidence published since the previous guideline, to answer specific questions in relation to each drug, as follows: Should it be stopped pre-conception? 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 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 specific rheumatic diseases in pregnancy. Other drug categories (pain management; NSAIDs 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 (<https://doi.org/10.1093/rheumatology/keac552>). 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 licensing information or Summary of Product Characteristics for individual medications.

Stakeholder involvement

This guideline was commissioned by the BSR Standards, Guidelines and Audit Working Group. A Guideline Working group (GWG) was created, consisting of a chair (I.G.), alongside representatives from relevant stakeholders shown in [Supplementary Table S1](#), available at *Rheumatology* online. 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 Teratology 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

The 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) [15]. Studies were identified by searching MEDLINE and Embase databases from 1 January 2014 to 31 December 2020 using combinations of the key MESH and free terms: pregnancy; lactation; breastfeeding; paternal exposure; and the name of each drug. The full electronic search strategies for the MEDLINE and Embase databases are shown in [Supplementary Data S2](#), available at *Rheumatology* online. Searches were not limited by disease indication; in addition to IRDs, studies in non-rheumatic diseases, such as psoriasis, inflammatory bowel disease (IBD) and organ transplantation were considered, if relevant. Additional published studies were identified through the Cochrane, LactMed (a National Library of Medicine database on drugs and lactation) and UKTIS databases (weblinks shown in [Supplementary Data S2](#), available at *Rheumatology* online), and checking of reference lists from recently published national and international guidelines and systematic literature reviews. Due to the paucity of data pertaining to the use of non-TNFi biologic drugs and tsDMARDs in pregnancy and breastmilk exposure, relevant pharmaceutical companies were contacted between July and November 2021, and asked for any further available data.

Two independent reviewers screened the titles and abstracts of articles from the searches then reviewed the full texts of relevant studies, selecting articles that met inclusion criteria of: randomized and non-randomized controlled trials; cohort studies; case-control studies; and case series with more than ten participants. For medications with data on fewer than 300 pregnancy exposures, case series with more than five participants were eligible for inclusion. Conference abstracts were eligible for inclusion if they contained sufficient relevant data and there was no corresponding published manuscript. Case reports, and case series with fewer than five participants, were excluded, as were animal studies. Data extraction was performed by two reviewers. Disagreements arising during screening and extraction were resolved by group discussion, with involvement of a third reviewer where necessary.

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

The working group met regularly to formalize the search strategy, review evidence, resolve disagreements and, finally, to determine recommendations. 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 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 revised until all members were satisfied that they would score at least 80 on a scale of 1 (no agreement) to 100 (complete agreement). The 20/24 working group members with full voting rights then scored each recommendation on the same scale, and the average was calculated to generate a strength of agreement (SOA) score. Two patient representatives and data analysts 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 recommendation, 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 the guideline will be updated

The search was conducted in January 2021. Limits were placed for English language and filters as described above. The guideline will be updated in five years.

The guideline

A flow diagram of study selection is shown in [Fig. 1](#), displaying the initial number of articles screened ($n = 27\,908$), the number of articles selected for full-length review ($n = 706$), and the number included in the final analysis from this

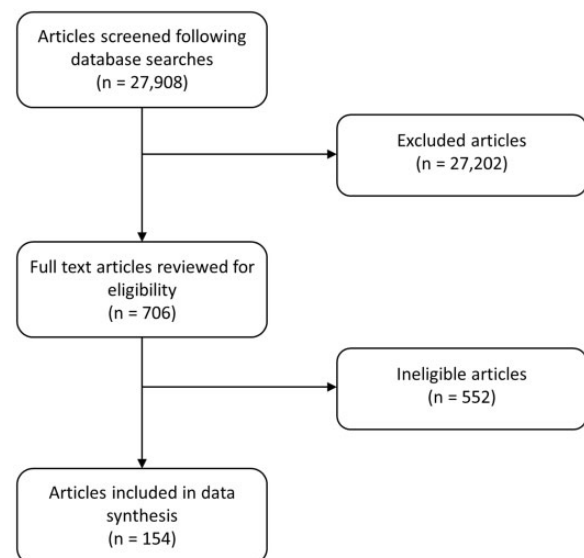


Figure 1. Flow diagram of studies selected for inclusion

updated search ($n = 154$). This information was then merged with the results of the previous guideline's systematic review to give the total exposure data for each drug. The following data were extracted where possible for each medication: number of studies and study type; number of pregnancy exposures; number of live births; pregnancy duration; birth weight; maternal complications; miscarriages; number and type of congenital anomalies (where possible, congenital anomalies described in original publications were classified as major/minor according to European surveillance of congenital anomalies (EUROCAT) definitions [16]); breastmilk exposure; long-term follow-up; and paternal exposure. An overall summary of 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 the text and in Tables 2 and 3, while paternal exposures and recommendations are described separately and shown in Table 4. The data synthesis strategy for Tables 2–4 is shown in Supplementary Data S3, available at *Rheumatology* online. Other relevant papers identified in our search that did not meet the inclusion criteria are discussed in the main text.

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%).
- 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) Immunization 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

HCQ is the antimalarial drug most used to treat rheumatic disease and has been extensively studied in pregnancy. We identified an additional 23 studies [17–39] that, combined with the previous 23 studies [40–62], reported on ($n = 4701$) pregnancy exposures to HCQ, with very limited information on other antimalarials [17, 39, 63, 64]. Many of these studies were confounded by primarily reporting pregnancy outcomes in patients with SLE treated with other immunosuppressive agents, including MMF and corticosteroids, and use in anti-Ro/La positive patients in the prevention of congenital heart block (CHB). Despite these limitations, there were no appreciable adverse effects of HCQ on pregnancy duration or birth weight in the largest studies. In fact, several studies comparing HCQ-treated and untreated cohorts with rheumatic disease (mostly SLE) either found no significant difference between cohorts [17, 19, 21, 24, 28, 34, 36, 37], or significantly longer pregnancy durations and/or higher birth weight in the HCQ-treated pregnancies [18, 20, 22, 25, 27, 29, 30, 32, 33, 35]. The weighted mean for gestation across 15 studies reporting pregnancy duration in HCQ-exposed *vs* HCQ-unexposed pregnancies was 36.4 weeks and 34.7 weeks, respectively [18–21, 24, 27, 28, 30, 32–34, 36, 37, 43, 49]. The weighted mean for birth weight for HCQ-exposed *vs* HCQ-unexposed pregnancies was 2847 and 2733 g, respectively, in 10 studies reporting these outcomes [18, 20, 21, 27, 29, 33, 34, 36, 37, 43]. A total of 60 first trimester miscarriages were reported from 524 HCQ-exposed pregnancies (11.5%) in 10 studies, compared with 117 first trimester miscarriages in 718 HCQ-unexposed pregnancies (16.3%) [18–22, 27, 28, 30, 32, 33]. No specific pattern of congenital malformations was observed in association with HCQ exposure. No increased risk of adverse foetal outcomes was reported in >3229 chloroquine-exposed pregnancies in four studies [17, 39, 63, 64], including two studies where chloroquine was used as malaria prophylaxis during pregnancy; although, in these two studies, higher rates of maternal adverse events were reported, relative to the comparator (sulfadoxine-pyrimethamine). No information was found on mepacrine.

The findings for HCQ were consistent across all studies apart from a large population-based cohort study comparing HCQ-exposed ($n = 2045$) and HCQ-unexposed ($n = 21\,679$) pregnancies in patients with rheumatic disease, which did not control fully for disease, comorbidity-related pregnancy risk factors, dose of corticosteroids and combination with specific immunosuppressive drugs [23]. This study found a small increase in the risk of congenital malformations associated with first trimester HCQ use, mainly oral clefts, respiratory anomalies and urinary defects, with wide confidence intervals for specific malformations. A statistically significant increase in risk, however, was only found with daily doses of ≥ 400 mg of HCQ. This study concluded that for most patients with

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 (≤ 400 mg/day)	Yes	Yes	Yes	Yes	Yes
Conventional synthetic DMARDs					
Methotrexate (≤ 2.5 mg/week)	Stop ≥ 1 month pre-conception	No	No	No	Yes
Sulfasalazine (with folic acid 5 mg/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 > 12 months, 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 [17–25, 27, 28, 30–39, 44–53] 1 rct [29] 1 nrt [26] 2 cc [42, 43] 3 cs [54–56] 6 cr [57–62] 2 sr [40, 41]	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 [84–86] 3 cc [43, 87, 88] 22 ct [31, 46, 48, 51–53, 71, 73–81, 89–95] 12 cs [55, 72, 96–105] 16 cr [55, 57, 59–61, 96–117] 1 Cochr [82] 1 sr [83]	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 [172, 181] 8 ct [37, 50, 52, 91, 179, 180, 182, 183] 1 cs [173] 5 cr [174–178]	766 (1st trimester ≥239, 2nd/3rd trimester ≥8)	80/479	Insufficient data; only one study reported birthweight in a cohort of $n=23$ [37], with two studies reporting pregnancy duration ($n=43$) [37, 181]	36/265 Individual case reports of MTX embryopathy, but larger studies show limited numbers of cases of foetal 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 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%)

(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 [46, 50, 52] 1 cs [55] 2 cr [62, 193]	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 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%)
LEF	6 ct [50, 91, 194, 199–201] 4 cr [195–198]	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 foetal medicine department considered (GRADE 1B, SOA 99%) iv) LEF is not recommended while breastfeeding (GRADE 1C, SOA 99.5%) i) AZA is compatible throughout pregnancy (GRADE 1B, SOA 100%) ii) AZA is compatible with breastmilk exposure (GRADE 2C, SOA 99.5%)
AZA	5 cc [88, 135, 172, 203, 204] 16 cr [31, 45, 50–52, 78, 90, 92, 93, 95, 205, 206, 212–215] 6 cs [55, 99, 102, 173, 207, 208] 2 cr [61, 107] 1 sr [83]	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	
CsA	4 cc [43, 88, 135, 136] 8 ct [50, 51, 92, 93, 95, 182, 219, 220] 3 cs [54, 101, 165]	401 (1st ≥131, 2nd/3rd ≥136)	9/132	Possible trend towards shorter pregnancy duration [92, 101, 136, 165] and low birth weight [88, 92, 165]	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 [92, 93, 219, 223, 225–231] 1 cs [99] 2 cr [107, 116]	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 [102] 4 cr [106, 111, 167, 168] 1 ct [232]	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 foetal morbidity and mortality without this therapy (GRADE 1B, SOA 99.5%) ii) CYC is not recommended while breastfeeding (GRADE 2C, SOA 100%)
MMF	7 ct [92, 95, 215, 242–245] 3 cs [99, 208, 235] 12 cr [57, 60, 113, 114, 116, 236–241]	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 <i>n</i> = 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 while breastfeeding (GRADE 2C, SOA 99.7%)
IVIg	1 cc [248] 12 ct [48, 49, 74, 79, 127, 128, 133, 249–253] 1 Cochr [82] 1 cs [97] 3 cr [58, 110, 254]	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.
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 [277, 278, 295–298, 301–313, 315–323] 1 cs [279] 4 cc [172, 299, 300, 314]	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	<ul style="list-style-type: none"> 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 [283, 284] 1 cs [285]	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 [50, 260–263, 291–294] 8 cs [173, 264–270] 1 cr [271]	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 [50, 52, 260, 286, 287] 3 cs [100, 266, 272] 4 cr [108, 109, 273, 274] 1 rct [288]	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 [50, 52, 252, 261, 280–282] 5 cs [99, 266, 268–270] 3 cr [271, 275, 276]	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 [289, 290]	166 (NR)	34/166	NR	3/115 Overall, no increase in rate of major malformations attributable to drug	See recommendations above
RTX	5 ct [50, 343, 344, 350, 354] 4 cs [345, 351–353] 4 cr [346–349]	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	<ul style="list-style-type: none"> 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 [358, 359] 2 cs [356, 357]	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	<ul style="list-style-type: none"> 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 [50, 371] 4 cs [367, 369, 370, 372] 1 cr [368]	48 (1st \geq 25, 2nd/3rd \geq 40)	3/43	No significant adverse effect attributable to drug	2/41 (including one resulting in miscarriage at 30 weeks)	<ul style="list-style-type: none"> 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 [369]	8 (all 1st)	1/8	No significant adverse effect noted	0/7	See recommendations above
ABA	1 cs [175] 1 cr [349] 2 ct [375, 376]	99 (1st \geq 145, 2nd/3rd \geq 10)	49/187	No significant adverse effect attributable to drug (data limited by confounding)	10/104 Overall, no pattern of malformations attributable to drug	<ul style="list-style-type: none"> 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 [380]	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	<ul style="list-style-type: none"> 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 [387, 388]	244 (1st ≥161, 2nd/3rd NR)	26/125	No significant adverse effect noted	2/54 Overall, no pattern of malformations attributable to drug	<ul style="list-style-type: none"> 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 [389]	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 [391, 392] 1 cs [393]	517 (1st \geq 31, 2nd/3rd \geq 10)	92/517	No significant adverse effect noted	17/375 Overall, no pattern of malformations attributable to drug	<ul style="list-style-type: none"> 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 [397]	116 (all 1st, 2nd/3rd NR)	15/72	No significant adverse effect noted	2/44 Overall, no pattern of malformations attributable to drug	<ul style="list-style-type: none"> 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 breastmilk, 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.
 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 [52] 1 cs [404]	13	No increase	Paternal exposure to HCQ is compatible with pregnancy (GRADE 2C, SOA 99.3%)
CS	5 ct [52, 405–407, 411] 2 cs [404, 408]	4507	No increase	Paternal exposure to prednisolone is compatible with pregnancy (GRADE 1B, SOA 99.3%)
SSZ	3 ct [52, 407, 412] 1 cc [409]	237	No increase	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 >12 months when stopping SSZ should be considered along with other causes of infertility (GRADE 1C, SOA 99.0%)
LEF	1 ct [52] 1 cr [413]	2	No increase	Paternal exposure to LEF is compatible with pregnancy (GRADE 2C, SOA 99.3%)
AZA	9 ct [52, 185, 187, 216, 405–407, 414, 415] 1 cc [409] 2 cs [404, 408]	3282 ^a	No increase	Paternal exposure to AZA is compatible with pregnancy (GRADE 1B, SOA 99.3%)
MTX	10 ct [52, 184–189, 405, 407] 3 cs [404, 410], 1 cr [428]	2289	No increase	Paternal exposure to low-dose (≤ 25 mg/week) MTX is compatible with pregnancy (GRADE 1B, SOA 99.3%)
CsA	3 ct [185, 406, 416] 2 cs [408, 410]	501 ^a	No increase	Paternal exposure to CsA is compatible with pregnancy (GRADE 1C, SOA 99.3%)
TAC	3 ct [406, 416, 417]	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 [185, 246, 247] 3 cs [406, 416, 426]	292	No increase	Paternal exposure to MMF is compatible with pregnancy (GRADE 2C, SOA 99.3%)
TNFi	13 ct [52, 263, 293, 298, 306, 405, 412, 427, 430–434] 2 cs [404, 410] 2 cr [428, 429] 1 cc [409]	751	No increase	Paternal exposure to TNFi is compatible with pregnancy (GRADE 1C, SOA 99.3%)
RTX	1 ct [343]	11	No increase	Paternal exposure to RTX is compatible with pregnancy (GRADE 2C, SOA 99.3%)
IL-6i	1 ct [359]	15 (TOC)	No increase	Paternal exposure to IL-6i is compatible with pregnancy (GRADE 2C, SOA 99.3%)
IL-1i	1 ct [369]	5 (ANA) 6 (CAN)	No increase	Paternal exposure to IL-1i is compatible with pregnancy (GRADE 2C, SOA 99.3%)
ABA	1 ct [375]	10	No increase	Paternal exposure to ABA is compatible with pregnancy (GRADE 2C, SOA 99.3%)
IL-17i	2 ct [387, 389]	54 (SEC) 34 (IXE)	No increase	Paternal exposure to IL-17i is compatible with pregnancy (GRADE 2C, SOA 99.3%)
JAKi	1 ct [398]	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.

^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.

autoimmune rheumatic disorders, the benefits of treatment during pregnancy will likely outweigh this risk.

Importantly, a more recent study (published after our search date) of pregnant women prospectively enrolled into MotherToBaby/Organisation of Teratology Information Specialists (OTIS) pregnancy studies, compared outcomes for HCQ-exposed pregnancies ($n=279$) with disease-matched ($n=279$) and healthy comparator ($n=279$) HCQ-unexposed groups [65]. Reassuringly, this study found no evidence of an increased risk for structural defects or other adverse outcomes with HCQ at any dose (average 325 mg/day; range 100–800 mg/day), except for an isolated finding of reduced head circumference at birth with HCQ exposure, which was not thought to be of any clinical significance.

Therefore, advice on HCQ dosage in pregnancy relates to general guidance for reducing ophthalmic risk outside of pregnancy to a maximum of 400 mg/day, as pharmacokinetic changes in pregnancy reduce the reliability of weight-based dosing [66]. Ultimately, it is important to maintain HCQ during pregnancy, as discontinuation of this drug in pregnancy may increase risk of disease flares and foetal loss [67]. Disease flares would increase the need for alternative medications with more potential risks for mother or baby in pregnancy.

Previous studies of breastmilk exposure to HCQ were mostly limited to case reports, showing that <1% of the maternal dose of HCQ was found in breastmilk [68]. Three more recent studies of HCQ use ($n=195$) confirmed very low concentrations of HCQ in breastmilk and no adverse effects on breastfed infants [36, 69, 70]. There remain limited studies of long-term outcomes in children, but no adverse immunological or clinical findings have been reported [36, 43].

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 a dose of ≤ 400 mg/day (GRADE 1B, SOA 100%).
- ii) HCQ is compatible with breastmilk exposure (GRADE 1B, SOA 99.5%).

Corticosteroids

Corticosteroids used to treat rheumatic disease (prednisolone, prednisone and methylprednisolone) are metabolized in the placenta, and so 10% or less of the active drug reaches the foetus. Previously, we identified 47 studies on prednisolone and found it to be compatible with pregnancy and breastmilk exposure [1]. Studies of corticosteroid use in pregnancy were confounded by multiple concomitant medications and use in high-risk pregnancies; particularly the fluorinated steroids, which are used to prevent or treat preterm labour and complications such as foetal lung immaturity. Therefore, we searched for further evidence on corticosteroids used to treat rheumatic disease and identified additional studies: 11 on prednisolone with ($n=1218$) pregnancies [31, 71–80] and one on methylprednisolone with ($n=12$) pregnancies [81]. This evidence was combined with the previous studies: 47 on prednisolone ($n=1503$) [43, 46, 48, 51–53, 55, 57, 59–61, 82–117]; 31 on dexamethasone ($n=11\,214$) [48, 54, 88, 97, 118–144]; 27 on betamethasone ($n=27\,746$) [118–120, 125, 126, 128, 130, 131, 140, 143, 145–162]; and 10 on general corticosteroid use ($n=785$) [42, 49, 50, 54, 163–168].

Studies on the use of methylprednisolone in pregnancy were not specifically sought in the previous guideline because it is generally used as rescue therapy for severe disease. Compared with prednisolone, parenteral administration of methylprednisolone has a prolonged duration of action with similar rates of placental transfer to prednisolone [169].

Previously, we found that following prednisolone (or unspecified corticosteroid) exposure, average pregnancy duration in the majority of randomized controlled trial (RCT), case-control, cohort and case-series studies (where reported) was usually term, at ≥ 37 weeks [43, 51, 84, 85, 88, 92, 94, 96, 101, 102, 104, 105]. Other studies reporting ≤ 37 -week delivery were confounded by factors such as maternal disease and concomitant medications [46, 57, 59, 60, 86, 87, 99, 106, 113, 117, 163, 165]. Birth weights followed a similar pattern and were affected by preterm deliveries and confounding factors, as described above. For instance, prednisolone exposure in those RCTs, cohorts, case-control studies and case series which reported average gestations of ≥ 37 weeks, average birth weights ranged from 2.6–3.4 kg [43, 46, 51, 85, 88, 92, 94, 96, 101, 104, 105]. Overall, prednisolone itself was not felt to have contributed to low birth weight (LBW) in any study [1].

High rates of maternal complications compatible with underlying disease were previously reported for prednisolone and dexamethasone, but none were specifically attributed to these medications [1]. The major congenital malformations observed with prednisolone were frequently confounded by concomitant teratogenic drug exposure, such as MMF [116], and the overall incidence was not significantly higher than in drug-free controls. Studies reporting major malformations with fluorinated steroid exposure [e.g. patent ductus arteriosus (PDA), blindness and deafness [126, 145]] did not attribute them to steroid therapy. Furthermore, in the majority of cases, the steroids were used for treatment of underlying conditions such as preterm delivery [126], where steroids were found to be beneficial in improving outcomes, or treatment of maternal autoantibody-mediated cardiomyopathy [133]. A large study analysing 832 636 live births did not show an increased risk of orofacial cleft palate with the use of corticosteroids in pregnancy [164]. foetal loss in studies of prednisolone and fluorinated steroids was attributed to underlying disease rather than steroid therapy, such as in APS [105] and complete atrio-ventricular block [170].

Most (8/11) of the additional studies on maternal prednisolone exposure that we found in our updated search did not identify any adverse effects of prednisolone use on pregnancy outcomes [31, 72–74, 76–79]. In contrast, a population-based study from Norway exploring the associations between disease activity and medications with offspring birth weight, pre-eclampsia and preterm birth in SLE found prednisolone use to be significantly associated with lower birth weight, increased risk of pre-eclampsia, and a 3-fold increase in preterm birth [71]. A conference abstract reported that continuation of high-dose glucocorticoids during 164 pregnancies increased the risks of preterm birth, low birth weight and preterm premature rupture of membranes (PPROM) at prednisolone cut-off doses of 7.5 mg, 6.7 mg, 5.0 mg per day, respectively [75]. In contrast, another conference abstract of 143 SLE pregnancies found that foetal complications were associated with prednisone >25 mg, and that low (10 mg/day) to moderate (10–24 mg/day) doses of prednisone during pregnancy were not associated with adverse foetal outcomes [77]. Similarly, the largest prospective study of SLE pregnancy outcomes did

not identify prednisolone ≤ 20 mg/day as a risk factor for adverse pregnancy outcomes [31].

UKTIS notes that many of the studies reporting pregnancy outcomes following gestational exposure to systemic corticosteroids are limited by a lack of stratification to account for differing doses, treatment duration and steroid potencies, as well as confounding by maternal disease [171]. It concludes that pre-term delivery may be associated with gestational exposure to systemic corticosteroids, and further well-controlled studies are required to address this question. Therefore, an increased risk of adverse foetal effects following use of high-dose/potency corticosteroids, or use for extended periods, cannot be ruled out.

Based on limited evidence, prednisone, prednisolone and methylprednisolone are considered compatible with breastmilk exposure [1]. There remain few breastmilk exposure studies. One study, comprising 19 pregnancy and breastmilk exposures, found that prednisone and prednisolone exhibit dose- and concentration-dependent pharmacokinetics during pregnancy, and infant exposure to these agents via breastmilk is minimal [76]. Another study of 12 patients with multiple sclerosis found the transfer of methylprednisolone into breastmilk to be low even when maternal serum concentration levels were highest at the end of an infusion, and although these levels were not considered to pose a threat to the infant, they state that mothers may choose to wait two to four to further limit an infant's exposure [81].

Previously, long-term follow-up studies had not reported any adverse events after prednisolone exposure in pregnancy [1]. Two additional studies did not report any adverse events from 9–12 months of post-partum follow-up of 227 non-rheumatic disease pregnancies exposed to prednisolone [78, 79].

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%).
- 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 and immunosuppressive therapies

Methotrexate

MTX is contraindicated in pregnancy and was previously recommended to be stopped at least three months in advance of conception [68]. UKTIS considers MTX risk in pregnancy to be dependent on its use at high (> 25 mg per week) or low (≤ 25 mg per week) dosages [171]. Rheumatology usage of MTX to treat inflammatory arthritis falls into the low-dose category and is far removed from the high doses used as a

chemotherapeutic agent in the treatment of various cancers (e.g. > 500 mg/m²) or as an abortifacient at 50 mg/m². UKTIS concludes that exposure to high-dose MTX in early pregnancy confers a risk of severe embryopathy (including craniofacial defects, malformations of the digits and defects of the spine and ribs) in the foetus, and the option of termination of pregnancy should be discussed with the patient. In contrast, for exposure to lower doses of MTX prior to conception, additional foetal monitoring is advised, as well as counselling of women and their partners about the lack of available data to facilitate quantification of risk of adverse pregnancy outcomes.

Previously, we identified a high proportion of major anomalies following MTX (and other DMARD) exposure, predominantly during the first trimester of pregnancy, in 27 pregnancies from 10 studies [50, 52, 91, 172–178]. An additional 12 studies of MTX exposure in 2765 pregnancies were identified: six maternal studies [37, 179–183] and six paternal studies [184–189].

Several studies reported on the risks of pre-conceptual and pregnancy exposure to MTX. Data from the National Birth Defects Prevention Study, a US case-control study of major birth defects, reported that 4/10 113 (0.04%) mothers of foetus/infants without major birth defects (controls) had been exposed to MTX, compared with 16/27 623 (0.06%) mothers of live-born infants with a major birth defect (cases) who had been exposed to MTX [181]. The dose of MTX was not reported, but indications included a neoplasm of endocrine glands and so was presumably of high dose in at least one case. Of the 16 cases with major birth defects, 15 were exposed from three months pre-conception to the end of the first trimester.

A cohort study of 240 SLE pregnancies in whom 36.8% were exposed to MTX before and during the first trimester reported an increased risk of foetal complications [182]. A large prospective observational multicentre cohort study of 324 pregnancies exposed to MTX found an increase in the cumulative incidence of spontaneous miscarriage (42.5%) and major congenital anomalies (6.6%) among pregnancies ($n = 188$) exposed to a median dose of 10 mg/week of MTX after a median of 4.3 weeks post-conception [179]. This difference reached statistical significance when compared with a cohort of women without autoimmune diseases, but not when compared with a disease-matched cohort. No increased risk of miscarriage or major congenital anomaly was found in pregnancies ($n = 136$) exposed to a median dose of 15 mg/week of MTX that was stopped three months pre-conception.

Not all studies reported increased risks with MTX exposure. A study of pre-conception use of MTX on miscarriage rates in 114 RA pregnancies, compared with 48 MTX-unexposed RA pregnancies, did not find a statistically significant association between miscarriage and MTX use [180]. An analysis of 18 pregnancies exposed to MTX (≤ 20 mg/week) from up to one year pre-conception and in the first trimester found a high percentage of live-born children with no malformations [183]. Analysis of 23 first trimester exposures to low-dose MTX, identified from three United States health plan databases, did not reveal a significant increase in the risk of congenital malformations, foetal death or neonatal complications in women with chronic autoimmune disease, compared with those who received MTX before, but not during, pregnancy [37].

These studies provide some evidence that a 3-month MTX-free interval prior to conception might not be required. Therefore, unintentional exposure to low-dose MTX during the peri-conceptional period confers minimal risk in unintended pregnancy exposures, and so termination of pregnancy is not routinely recommended for MTX exposure unless it is maternally requested due to unplanned pregnancy [37, 180, 183].

Studies of MTX in breastfeeding remain very limited. Although they did not meet our inclusion criteria, we identified two case reports that found low levels of MTX in breastmilk and no adverse effects on the breastfed infants [190, 191]. LactMed describes low levels of MTX in breastmilk and conflicting expert opinion on whether it can safely be used during breastfeeding [192]. It states that withholding breastfeeding for 24 h after a weekly low-dose of MTX may decrease the infant's dose by 40%, and that if breastfeeding is undertaken during long-term, low-dose MTX use, monitoring of the infant's complete blood count and differential could be considered.

Post-partum follow-up of up to 14 months after first trimester MTX exposure was reported in three infants with long-term complications of foetal MTX syndrome, including semi lobar holoprosencephaly, cardiac abnormalities, tracheostomy and requirement for antiepileptic therapy [176, 177].

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

Previously, we recommended that SSZ is compatible with pregnancy and breastmilk exposure and can be continued with adequate folic acid supplementation (5 mg/day) [1]. This recommendation was based on six publications reporting SSZ exposure in 178 pregnancies in patients with RA, osteoporosis and ankylosing spondylitis (AS) [46, 50, 52, 55, 62, 193]. These studies contained limited information relating to miscarriage rate, pregnancy duration, birth weight or malformation rate; overall, however, there were no significant adverse effects highlighted that were considered to be directly attributable to SSZ. We did not identify any additional studies on the use of SSZ in pregnancy, breastmilk exposure or paternal exposure.

UKTIS does not identify any specific risks with SSZ exposure. It comments that although high-dose folic acid (5 mg/day) is generally recommended, no studies have investigated

whether there is increased benefit of this higher dose of folic acid compared with a standard dose of 400 micrograms/day.

Minimal amounts of SSZ are expressed in breastmilk, and it can be used during breastfeeding if the infant is full term and healthy, although it should be avoided in ill, stressed or premature infants, and in infants with hyperbilirubinaemia or glucose-6-phosphate dehydrogenase deficiency [68].

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

Based upon limited evidence, we previously found that LEF may not be a human teratogen, but there was insufficient evidence to support its compatibility in human pregnancy, so our recommendation was that LEF is not the DMARD of choice in women planning pregnancy [1]. This recommendation was based on data from seven studies [50, 91, 194–198] reporting on 111 pregnancies exposed to LEF (discontinued in almost all cases in the first trimester, and frequently followed by a cholestyramine washout). Overall, the findings were largely reassuring, with no direct evidence of human teratogenicity.

We identified three additional studies of 703 pregnancies exposed to LEF at various stages of pregnancy, with varying exposure to washout and/or plasma testing of LEF metabolites, which did not find an increased risk of adverse pregnancy outcomes compared with the general population [199–201]. Although it was not included within our systematic review, pregnancy outcomes have been reported for teriflunomide—the principal active metabolite responsible for leflunomide's activity *in vivo*—which, at recommended doses, results in a similar range of plasma concentrations to leflunomide [202]. The known outcomes from 222 pregnancy exposures to teriflunomide for relapsing forms of multiple sclerosis also found outcomes consistent with the general population [202]. Overall, these findings do not indicate a teratogenic risk of LEF in human pregnancies. The practicality of previous recommendations regarding the testing of plasma levels of teriflunomide has been questioned [199], and testing is not currently routinely available in the UK.

We did not identify any data on breastmilk exposure to LEF, and no information is available in LactMed [192].

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

Previously, we recommended that AZA is compatible with pregnancy at doses ≤ 2 mg/kg, with breastmilk exposure and with paternal exposure [1]. These recommendations were based on 28 studies [45, 50–52, 55, 61, 83, 88, 90, 92, 93, 95, 99, 101, 102, 107, 135, 172, 173, 203–211] in 738 AZA-exposed pregnancies, which included a wide range of diagnoses and concomitant medications, compared with 1121 disease-matched and 667 healthy controls. These data did not demonstrate an increased risk of miscarriage, preterm birth, low birth weight or congenital malformation due to AZA exposure in pregnancy.

We identified an additional nine studies of 3699 pregnancy exposures to AZA: six maternal studies [31, 78, 212–215] and three paternal studies [185, 187, 216]. Overall, the findings from maternal exposures ($n=1019$) to AZA did not identify any adverse pregnancy outcomes. One study, reporting on AZA metabolism in 30 IBD pregnancies, measured active metabolites and found only 6-thioguanine nucleotide (6-TGN) but not 6-mercaptopurine (6-MP) in umbilical cord blood at delivery; no major teratogenicity was observed, although 60% of the infants had anaemia, which was suspected to be due to maternal thiopurine use [214]. Two of these studies extended follow-up to 3 months and nearly 10 years, without any adverse effects being reported. The majority of studies did not specify the mean/median dose of AZA utilized in the study populations, and there is no clear evidence regarding a dose limit. Use of AZA at an effective dose should be supported by monitoring of blood tests, following local guidelines.

Based on our previous evidence from 26 infants breastfed by mothers on AZA or 6-MP, minimal amounts of AZA were detected in breastmilk, and no adverse effects were identified [101, 209–211]. We did not identify any new studies of breastmilk exposure to AZA. LactMed states that avoiding breastfeeding for 4 h after maternal ingestion of AZA should markedly reduce the dose received by the infant in breastmilk [192]. In routine clinical practice, there is no concern in the management of solid organ transplant patients who breastfeed on this drug [217].

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

An earlier consensus document reviewed evidence from >800 human pregnancies exposed to ciclosporin (CsA) [68]. Our previous search from 2005 onwards identified a further 13 studies/reports [43, 50, 51, 54, 88, 92, 93, 95, 101, 135, 136, 165, 218] of 98 pregnancies in patients with a variety of diseases and multiple concomitant medications who had been exposed to CsA at 2–6 mg/kg during pregnancy. Reports of increased rates of preterm delivery and low birth weight were

confounded by maternal disease and concomitant medications, and there was no evidence of an increased malformation risk [1]. Comorbidities, such as hypertension, pre-eclampsia and gestational diabetes mellitus, were reported at higher incidences than the general population. Based upon this evidence, CsA was considered compatible with pregnancy at the lowest effective dose, with monitoring of blood pressure, blood glucose and renal function [68]. UKTIS draws a similar conclusion [171].

We identified an additional five studies of 550 pregnancy exposures [182, 185, 219–221]. Three studies reported on maternal exposure [182, 219, 220]. A cohort study of 240 SLE pregnancies, in whom 50% were exposed to CsA before and during the first trimester, increased the risk of pancytopenia and/or pre-eclampsia in maternal outcomes [182]. A single-centre experience of outcomes of pregnancy ($n=117$) following liver transplantation did not find any difference between those on CsA ($n=34$) compared with tacrolimus ($n=81$), and so did not attribute these outcomes to medication [219]. A study of the efficacy and safety of CsA in 29 pregnancies of patients with systemic autoimmune diseases did not find an increased risk of maternal–foetal complications, and stated that it should be continued in patients who benefit from therapy [220].

Previously identified studies described small amounts of CsA in breastmilk and almost universally undetectable blood levels in infants [68, 218], without any adverse effects reported during breastmilk exposure. We found a further study that reported low transfer of CsA and its metabolites into the breastmilk of seven post-transplant mothers in the first two days post-partum, although this study was not designed to make a corresponding assessment of drug safety [221]. LactMed recommends that breastfed infants should be monitored if CsA is used during lactation, possibly with measurement of serum levels if there is a concern for toxicity [192]. In routine clinical practice, there is no concern in the management of solid organ transplant patients who breastfeed on this drug [217].

No additional studies of long-term follow-up were identified to those found previously on 10 infants exposed to CsA *in utero*, which reported no complications at 11–14 months [43, 54, 135].

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

Based upon previous consensus [68, 222] and our previous review of six studies [92, 93, 99, 107, 116, 223] of 26 pregnancies exposed to tacrolimus and two breastmilk exposure studies [223, 224], tacrolimus was considered compatible with pregnancy and breastmilk exposure. There were complex confounding issues in many of these studies and, overall, no adverse outcomes were considered to be directly attributable to tacrolimus [1].

We found additional evidence from eight studies of 489 pregnancy exposures to tacrolimus [219, 225–231]. Studies

of maternal outcomes, mostly from solid organ transplant recipients, reported varying incidences of adverse maternal-foetal outcomes, but these outcomes were confounded by transplant-associated comorbidities and concomitant immunosuppression, particularly MMF [219, 225, 227–231].

UKTIS concludes that the available data do not suggest an association between spontaneous miscarriage, congenital malformation or intrauterine death and exposure to tacrolimus during pregnancy, but data are limited and potentially confounded; therefore, an increased risk of these outcomes cannot be excluded [171].

Previously, we found studies reporting low levels of tacrolimus in umbilical cord blood and breastmilk in small numbers of breastfed infants without any adverse effects [223, 224]. These findings were confirmed in an additional study of 13 breastfed infants of mothers with SLE [225]. This study found concentrations of tacrolimus in the umbilical cord blood were lower than those in the maternal blood; the relative infant dose in breastfed infants of tacrolimus was <1%, and the level of tacrolimus in infant blood was below detectable limits. LactMed suggests that exclusively breastfed infants should be monitored [192]. In routine clinical practice, there is no concern in the management of solid organ transplant patients who breastfeed on this drug [217].

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

CYC is a known human teratogen and is gonadotoxic in men and women [68]. Our previous findings from reports of predominantly first trimester use of CYC in nine pregnancies, revealed multiple adverse outcomes in mothers with severe maternal disease and multiple concomitant medications [102, 106, 111, 167, 168]. No maternal complications of CYC were reported. The nine pregnancies ended in two first trimester miscarriages, six healthy infants and one major congenital anomaly (Klippel–Feil syndrome). Follow-up to 87–90 months in four live births reported normal development in three children [102] and the single case of Klippel–Feil syndrome [111].

We found an additional study of pregnancies ($n=11$) in women with multiple sclerosis who had been exposed to CYC prior to conception [232]; 10 women had a successful delivery [five preterm delivery and one small for gestational age (SGA)], while one underwent elective termination. It should be noted, however, that the time between the last dose of CYC and conception in this study was an average of 3.7 ± 1.5 years (range 0.33–5.9 years).

Although it did not meet our inclusion criteria, one case report analysed breastmilk levels of CYC in a woman with multiple sclerosis [233]. CYC levels in breastmilk samples were measured after IV CYC at a dose of 2.8 g, with relatively low levels identified in the milk. The authors reported an average relative infant dose for a period of four days that varied from 4.7% at day 1 to 0.9% at day 4.

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

MMF is a known teratogen and is recommended to be stopped at least 6 weeks before a planned pregnancy [68, 222]. It is rapidly absorbed following oral administration and hydrolysed to form the active ingredient, mycophenolic acid (MPA). This active metabolite has a mean apparent half-life of 17 h after a 1 g oral dose of MMF, and undergoes enterohepatic circulation, with a secondary plasma peak at 6–12 h after an oral or intravenous dose [234].

We previously reviewed data from 16 studies/reports [57, 60, 92, 95, 99, 113, 114, 116, 208, 235–241] of 90 pregnancies exposed to MMF, mostly from renal transplant patients in whom there was concomitant exposure to prednisolone and tacrolimus. Increased rates of premature delivery, low birth weight and major congenital malformations were reported, including malformations typical for the previously described MMF embryopathy (including cleft lip and/or palate, microtia with aural atresia, micrognathia and ocular anomalies) [1].

Our updated search found eight further studies of 934 pregnancy exposures to MMF: five maternal exposure studies [215, 242–245] and three paternal exposure studies [185, 246, 247]. The five studies of maternal exposure in pregnancies ($n=714$) all reported increased risks of miscarriage and birth defects, with 351 foetal losses, eight stillbirths and 38 cases of congenital malformation [215, 242–245]. These studies were mostly of first trimester exposure, with three including second and third trimester exposures. One study, however, found that following discontinuation of MMF within 6 weeks of conception, outcomes including the rates of birth defects and miscarriages were similar to pregnancies not exposed to MMF [245].

UKTIS describes the increased risks of first trimester pregnancy loss, as well as major congenital anomalies, and states that women of childbearing potential who are prescribed MMF or MPA should be informed of the associated risks to the foetus and, therefore, the importance of adequate contraception. It notes that European Medicines Agency guidelines for male and female patients, published in October 2015 following a periodic safety update review, recommend additional measures to prevent foetal exposure to MMF and should be read prior to prescribing MMF [171].

As in our previous search, we did not identify any data on breastmilk exposure. Similarly, LactMed reports that no information is available on the excretion of MMF into breastmilk, and that a few infants have reportedly been breastfed during MMF therapy with no adverse effects reported [192].

We did not identify any additional long-term follow-up data to that previously found of one case of ‘small for age’ with otherwise normal development [57], and another study

reporting on 3/6 exposed children (one with normal development, one who required hearing aids, and one who had motor and speech delay) [99].

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

IVIG is considered to be compatible with pregnancy and breastmilk exposure [68, 222]. Our previous review of data found 16 studies/reports [48, 49, 58, 82, 97, 110, 127, 128, 133, 248–254] of 336 pregnancies in which IVIG was used, mostly in APS or in the prevention of CHB in anti-Ro/La positive mothers. The studies identified were focused on therapeutic efficacy rather than the safety of IVIG; hence, all outcomes were confounded by use in patients with high-risk pregnancies and multiple concomitant medications. Overall, the number and type of maternal and foetal complications observed were compatible with known effects of the underlying maternal disease on pregnancy, rather than being specific to IVIG. The studies reviewed did not raise any new concerns to question the accepted safety of IVIG in pregnancy [1].

We identified two further studies of 67 exposures to IVIG to treat immune thrombocytopenia (ITP) in pregnancy [74, 79]. One study found that glucocorticoids increased the risk of maternal hypertension, while the addition of IVIG to corticosteroid regimes did not adversely affect pregnancy outcomes [79]. The other study found comparable benefits of IVIG compared with corticosteroids in treating ITP in pregnancy, compared with no treatment, and similar neonatal outcomes between the treatment groups [74]. UKTIS does not report on IVIG.

None of the studies we previously or recently identified addressed the use of IVIG in breastmilk exposure or with paternal exposure. LactMed states that immunoglobulin is a normal component of breastmilk, and data from two mothers indicate that IgG concentrations in milk are normal or higher, and IgM levels in milk are normal or lower, during IVIG therapy [192].

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

Biological therapies are commonly used as second-line agents to treat various forms of IRDs. They are recombinant proteins, most commonly monoclonal IgG1 antibodies directed against specific targets, or fusion proteins containing the Fc portion of IgG1 joined to receptor-blocking proteins. The presence of the Fc region of IgG1 in most of these biologic drugs is required for their active placental transfer, which accelerates by active transport from the second trimester onwards. Biologic drugs are often given alongside other DMARDs, and decisions regarding continuation of treatment should be taken for each drug independently. Although the evidence base for biosimilar use in pregnancy and breastmilk exposure is more limited than for originator biologics, they would be expected to have comparable effects. Therefore, for pragmatic reasons, our recommendations are applicable to equivalent licensed biosimilars.

Five studies were identified that assessed the impact of biologic drugs as a whole on pregnancy outcomes [255–259]. These studies included a total of 379 pregnancies in women with autoimmune disease on predominantly anti-TNF α drugs, but also rituximab (RTX), abatacept (ABA), tocilizumab (TCZ), ustekinumab (UST) and anakinra. Separate birth outcomes for specific medications were not reported. Overall, the authors of these studies found no increased risk of miscarriage, stillbirth or congenital anomalies in biologic-exposed patients. One study that reported outcomes for 120 pregnancies in women with autoimmune diseases (predominantly RA and IBD) found a slightly increased risk of prematurity and a trend towards low birth weight in the biologic-exposed group compared with those not exposed [257]. However, once statistical modelling had been performed to correct for confounding by indication and proxies of unmeasured confounders, no association was found between biologic exposure and birth weight or gestational age. In addition, the same authors found that biologic use was not associated with an increased risk of serious infections in mothers, during postpartum, or in infants during the first year of life [256].

Anti-TNF α drugs

Five biologic agents that inhibit TNF α (TNFi) are currently licensed to treat IRDs: etanercept (ETA), infliximab (INF), adalimumab (ADA), golimumab (GOL) and certolizumab pegol (CZP). Three of these drugs (INF, ADA and GOL) are monoclonal IgG1 directed against TNF α , one (ETA) is a fusion protein of the TNF receptor joined to the Fc region of IgG1, while CZP is an antigen-binding fragment (Fab') of a monoclonal anti-TNF α antibody which lacks the Fc region of IgG1 and has been conjugated with polyethylene glycol (PEG). These drugs have different half-lives, bioavailability and rates of placental transfer, which are relevant when considering their potential use in pregnancy.

Initial 2006/8 consensus recommendations advised avoidance of ETA, INF and ADA in pregnancy and breastfeeding due to a lack of evidence rather than evidence of harm [68, 222]. Previously, we reviewed outcome data from TNFi-exposed pregnancies ($n=706$) of patients with predominantly IBD but also rheumatic disease and non-autoimmune-mediated recurrent spontaneous miscarriage, compared with ($n=399$) disease and ($n=170$) healthy control pregnancies [50, 52, 99, 100, 108, 109, 172, 173, 252, 260–279]. There were multiple confounders of concomitant therapies (including MTX, LEF

and MMF) and active inflammatory disease. Overall, these studies did not describe an increased incidence of adverse effects upon miscarriage rates, pregnancy duration, birth weight, foetal death or congenital malformation that was attributable to ETA, INF, ADA or CZP. At that time, there was limited information on placental transfer, and no published studies of GOL in human pregnancy or breastmilk exposure.

TNFi exposure in pregnancy and with breastmilk exposure has been extensively studied since our last search. We identified an additional 50 studies, reporting 12 491 pregnancy exposures to TNFi, including INF ($n \geq 5377$), ADA ($n \geq 2797$), ETA ($n \geq 2210$), CZP ($n \geq 776$) and GOL ($n \geq 196$) [37, 255–259, 280–323]. Many studies reported combined outcomes for exposure to different TNFi agents. The majority of studies of maternal exposure did not report an increased risk of preterm birth, miscarriage, low birth weight or congenital malformations [37, 255, 257–259, 280–286, 288–291, 294, 296, 298–302, 304–308, 314, 316–318, 320–323].

Different adverse outcomes were reported in some studies, however. A study of ETA found that the proportion of infants with major birth defects was higher (9.4% *vs* 3.5%, respectively) in ETA-exposed pregnancies ($n = 370$) than in pregnancies of disease-matched, non-exposed women ($n = 164$) [287]; however, the lack of a specific pattern of birth defects and the expected minimal placental transfer of ETA in early pregnancy did not support the biologic plausibility of a drug-related effect. A study reporting a lower live birth rate in INF-exposed pregnancies ($n = 99$) in women with Crohn's disease considered their findings to be confounded by more severe disease in those patients exposed to INF and increased exposure to other immunosuppressive agents [293]. A population-based study of TNFi-exposed pregnancies ($n = 1027$) found increased risks of preterm birth, caesarean section and SGA babies in comparison with TNFi-unexposed pregnancies ($n = 9399$) [295]; however, the authors noted that these associations may have been related to underlying disease activity rather than agent-specific effects, due to diverse findings across disease groups.

A retrospective cohort study of TNFi-exposed pregnancies ($n = 1457$) in women with IBD found TNFi exposure to be an independent risk factor for maternal complications and infections when compared with TNFi-unexposed pregnancies ($n = 9818$) [303]. In this study, TNFi exposure did not associate with congenital malformations or an increased risk of infection in children during the first year of life. Furthermore, there was no difference in the risk of complications in women exposed to TNFi during the third trimester, relative to cessation before week 24, although disease relapses were more common in those stopping TNFi prior to the third trimester. A study of 4961 pregnant women with autoimmune inflammatory conditions found similar risks of serious infections in women taking steroids, csDMARDs or TNFi during pregnancy, but found that higher doses of steroids were an independent risk factor for serious infections in pregnancy [323].

A registry-based study from Denmark and Sweden reported a non-statistically significant higher risk of having children with birth defects in women with RA, AS, psoriatic arthritis (PsA), IBD or psoriasis who had received TNFi during pregnancy ($n = 683$), relative to women with chronic inflammatory disease but without TNFi exposure ($n = 21 549$) [310]; however, the heterogeneity of observed birth defects went against a common aetiology. A prospective cohort study of TNFi pregnancy exposures ($n = 495$) in women with chronic

inflammatory disease (RA, AS, PsA, psoriasis and IBD) found prenatal TNFi exposure to be associated with an increased risk of birth defects without a distinct pattern of malformations, when compared with non-disease-matched, TNFi-unexposed controls ($n = 1532$) [312]. An increased risk of preterm births and reduced birth weight, but not spontaneous miscarriage, was also noted. The authors concluded that, although TNFi may carry a risk of adverse pregnancy outcomes of moderate clinical relevance, they may remain a treatment option, considering the impact of inadequately controlled disease on the mother and unborn child.

A small number of studies specifically compared risks between TNFi agents. In one study, INF was found to be associated with a greater risk for preterm births relative to ETA, and a higher prevalence of severely SGA babies relative to ETA and ADA, in pregnant women with RA, AS, PsA or psoriasis. In IBD, however, the risk of preterm births and SGA babies did not differ between INF and ADA [295]. In a study of individual safety reports in pregnant IBD patients exposed to TNFi ($n = 783$), the odds for maternal or foetal adverse events were found to be lower for CZP monotherapy, but not for INF or ADA monotherapy, when compared with an aminosalicylate monotherapy comparator in multi-level regression models [316]. In another study, the risk of birth defects did not differ significantly between ADA, INF or ETA-exposed women with chronic inflammatory diseases [310].

Several studies specifically compared outcomes for pregnancies exposed to TNFi during late *vs* early trimesters [37, 280–282, 284, 289, 291, 292, 295–297, 303, 305, 308, 309, 317], the majority of which reported no significant concerns with late trimester exposure. In a study of INF-exposed pregnancies ($n = 1850$) in women with IBD, RA, AS, PsA and psoriasis, frequencies of congenital abnormalities and other adverse birth and infant outcomes (including neonatal infections) were similar when comparing first and third trimester exposure [291]. In a study comparing early discontinuation of INF (>90 days before delivery; $n = 68$) to late discontinuation (<90 days before delivery; $n = 318$) in pregnancies of women with IBD, early discontinuation was associated with increased disease flares, more steroid usage and more preterm births than late discontinuation [292]. Rates of other adverse outcomes, including congenital malformations and infant respiratory infections, were similar between these groups. A further study of TNFi-exposed pregnancies ($n = 153$) in women with IBD reported that continuation of TNFi after gestational week 30, relative to cessation before week 30, was independently associated with modestly lower birth weights in multivariate regression models after adjustment for disease activity, but not other adverse infant outcomes [297].

Different rates of placental transfer of TNFi and timing of drug exposure in the second and/or third trimester of pregnancy influenced previous advice regarding avoidance of live vaccines in the first 7 months of life. Previously, a small cohort study found CZP (a PEGylated Fab' fragment, lacking the Fc region) to have minimal rates of placental transfer compared with INF and ADA [270], and two case reports demonstrated very low rates of placental transfer of ETA administered throughout pregnancy [108, 274]. Therefore, previous recommendations described discontinuation of ADA and ETA at the end of the second trimester to ensure negligible or no drug is detectable in cord blood at delivery. For INF, due to its prolonged bioavailability and higher rate of placental transfer, it

was recommended to be stopped earlier in pregnancy (at 16 weeks) for it to be undetectable in cord blood at delivery.

Since the last guideline, we found increased data demonstrating different rates of placental transfer of TNFi [283, 285, 302, 308, 309]. In a study of pregnant women with IBD exposed to INF ($n=44$) or ADA ($n=36$), the median time to drug clearance was 4 months for ADA and 7 months for INF [308]. In this study, continuation of TNFi in the third trimester did not increase the risk of childhood infection, relative to discontinuation before the third trimester. In a prospective study of ADA ($n=58$) and INF-exposed pregnancies ($n=73$) in women with IBD, cord blood samples showed significantly higher levels of INF than ADA at birth [302]. In this study, placental transfer of INF increased exponentially over the third trimester, while ADA transportation was limited and increased in a linear fashion. Maternal and birth outcomes were comparable between these groups, as were one-year infant health outcomes, including infection and adverse reactions to vaccinations. A study of infants ($n=14$) with third trimester maternal exposure to CZP found minimal rates of placental transfer, supporting continuation of this treatment during pregnancy [283]. Recent data, published after our literature search and highlighted by UCB Pharma during public consultation, reported no signal for adverse pregnancy outcomes following maternal CZP exposure in a large ($n=1425$) cohort [324].

UKTIS reports that studies that investigate the use of TNFi (ADA, CZP, ETA and INF only) during pregnancy have not found an overall increased risk of congenital malformation for these therapies as a class; there is also no compelling evidence of an increased risk for spontaneous miscarriage, intrauterine death or adverse neurodevelopmental outcomes; however, data are currently too limited to exclude adverse effects on the foetus. LBW and preterm birth have been associated with *in-utero* TNFi exposure in some studies but are confounded by maternal disease. UKTIS also states that there are theoretical concerns that the use of immunosuppressant antibodies, which actively cross the placenta, may result in neonatal or infant immunosuppression and increase the risk of infection; therefore, a delay is advised in administration of live vaccines to infants of: 5 months after last dose of ADA; 16 weeks after last dose of ETA; and until 6 months of age after *in-utero* INF. In contrast, as CZP is minimally transferred across the placenta, it is unlikely that infants born to women who used CZP in pregnancy would experience sufficient levels of TNF α inhibition to significantly inhibit their immune response [171].

Previously, we found case reports and case series reporting detection of ADA in breastmilk but not in infant serum [269], and detection of ETA and INF in breastmilk in some [108, 267, 273, 274] but not all studies [265], with no adverse effects detectable in any of these breastfed infants. We found nine additional studies of TNFi reporting on 133 breastmilk exposures [283, 285, 300, 307, 308, 317, 319, 325, 326]. Overall, these studies did not find any adverse effects of TNFi. A study of mothers ($n=17$) breastfeeding while taking CZP found minimal transfer of this drug into breastmilk [325]. Another study reported low or undetectable concentrations of INF, ADA, CZP, GOL and UST in 72 breastmilk samples [326]. In this study, breastfed infants on biologics ($n=243$), thiopurines ($n=102$) or combination therapy ($n=67$) were found to have similar risks of infection and rates of milestone achievement compared with infants

unexposed to these drugs via breastmilk or not breastfed. LactMed states that: CZP is excreted into breastmilk in some, but not all, women in small amounts; INF is usually either not detectable in breastmilk or detectable at very low levels; ETA, ADA and GOL are minimally excreted into breastmilk, with all TNFi being predicted to be poorly absorbed by the infant due to large molecular weight of each drug [192]. While some evidence suggests that IgG antibodies may not be digested by the gut in the early neonatal period [327, 328], other studies demonstrate marked digestion of IgG by the infant gut [329, 330].

Previously, we found long-term follow-up data in children exposed *in utero* to ETA [108, 266, 270, 272–274], ADA [269] and CZP [270]. We found an additional 16 studies reporting long-term follow-up data after exposure to TNFi [256, 291, 292, 299–303, 307–309, 317, 319–322]. In one study, 196 children with intrauterine exposure to TNFi (ADA, $n=81$; INF, $n=115$) for maternal IBD were followed up for 5 years, finding no association with long-term adverse health outcomes (including childhood infections and vaccination adverse reactions) when compared with TNFi-unexposed controls [296]. This study included women continuing TNFi during the third trimester, where no increased risk of infection was noted in their offspring. In a retrospective cohort study of children ($n=388$) exposed to TNFi (ADA, $n=164$; INF, $n=223$; CZP, $n=1$) *in utero* for maternal IBD, the incidence of severe infections was similar to TNFi-unexposed children of IBD mothers after median follow-up of 5 years [301]. Similarly, in another study, the risk of serious or opportunistic infections during the first year of life in live-born infants ($n=229$) exposed to ADA during pregnancy in women with RA or IBD was not significantly different to disease-matched, non-exposed controls and healthy controls [281]. In this study, the risk of infection remained similar when restricting to infants exposed to ADA during the third trimester. Two additional studies, which were not included in our final analysis because they did not report primarily on pregnancy or breastmilk exposure outcomes, described infections in the first 3 years of life in children after *in-utero* exposure to TNFi (predominantly ETA, ADA and INF) and/or csDMARDs for IRDs, psoriasis and IBD. One study of 493 children exposed *in utero* to TNFi reported an increased risk of some site-specific infections but not other adverse outcomes within the first year of life only [331]. The other study of 1027 children demonstrated a slightly increased risk of paediatric infections associated with both TNFi and csDMARDs in the first and second year after birth; however, the authors noted that this association was present regardless of third trimester exposure and could also have been confounded by disease severity [332].

Studies of vaccine safety and efficacy were not specifically sought through our systematic literature search but are relevant to consider, because most guidance recommends avoidance of live vaccines up to 6–12 months post-partum in infants exposed to bDMARDs in the second/third trimester [1, 333]. This advice is heavily influenced by the finding that placental transfer of bDMARDs can lead to persistence of drug levels by up to 12 months following *in-utero* exposure, with a median clearance time of 6 months and longest clearance times for INF. In addition, a fatal case of disseminated TB-like disease had been reported in a 4-month-old infant who had received Bacille Calmette et Guerin (BCG) vaccination following *in-utero* exposure to INF [334]. This guidance

impacts on rotavirus vaccination and, if indicated, the BCG vaccine, while the measles, mumps and rubella (MMR) vaccine (typically given at 12 months) is not affected. These restrictions significantly impact on rotavirus only, since the BCG vaccine may easily be deferred to be given later in life, while the rotavirus course of vaccination must be completed by 24 weeks of age due to risk of intussusception [335]. Currently, the restrictions may be avoided by discontinuing TNFi in the second or early third trimester, several half-lives prior to delivery.

Rotavirus continues to be a major cause of acute gastroenteritis in young children and has been estimated to result in >500 000 deaths and 2.4 million hospital admissions worldwide [336]. The rotavirus vaccine is over 85% effective at protecting against severe rotavirus gastroenteritis in the first two years of life [335]. Although current UK guidance recommends avoidance of rotavirus vaccination in infants of mothers exposed to biologics during pregnancy [337], it refers readers to the green book [335]. This text states that, although the vaccine is a live attenuated virus, with the exception of severe combined immunodeficiency (SCID), the benefit from vaccination may exceed risk in other forms of immunosuppression [335].

There are increasing reports of the safe use of rotavirus vaccination in infants following perinatal exposure to bDMARDs, including INF. A systematic review described cohort studies and case reports of infants ($n=54$) of mothers who received antenatal bDMARDs (mostly TNFi, including INF) who then received rotavirus vaccine without significant adverse effects [336]. The authors of that review recommended that otherwise healthy newborns with a history of perinatal exposure to bDMARDs should receive rotavirus vaccinations as per the recommended schedule, while the BCG vaccine should be withheld in the first year of life. Not all consensus review articles have reached the same conclusion, however, with some recommending avoidance of both rotavirus and BCG vaccinations in infants exposed to bDMARDs *in utero* in the first 6 months of life unless levels of biological drugs are undetectable [338], or avoidance of live vaccines until 6–12 months of age in infants exposed to biologics that may cross the placenta at clinically significant levels [339].

A systematic review published in abstract form after our search date evaluated vaccine safety in infants exposed to bDMARDs or tsDMARDs in pregnancy [340]. It identified *in-utero* exposures to ADA ($n=326$), CZP ($n=18$), ETA ($n=1$), INF ($n=408$), GOL ($n=1$), RTX ($n=1$), TCZ ($n=3$), UST ($n=1$) and no tsDMARD exposures in mostly IBD ($n=849$) pregnancies. Infant vaccination included: BCG ($n=111$) and/or rotavirus ($n=48$) in the first year of life (many <6 months); and MMR at 12 months ($n=590$), 6–9 months ($n=12$) and at 1, 2 or 4 months ($n=3$). Adverse events with BCG vaccination included one death, two large local skin reactions, and one infant with axillary lymphadenopathy. A freedom of information request to the MHRA revealed four further suspected fatal BCG infections in infants exposed to TNFi *in utero* (INF, $n=2$; ADA, $n=1$; and unspecified TNFi, $n=1$). Adverse effects noted in infants given rotavirus vaccination were mild and at similar frequency to those in biologic-unexposed infants. No complications were reported with MMR vaccination. Overall, the most evidence of clinically harmful effects was found after administration of BCG to infants <3 months of age and after *in-utero* exposure

to INF. In contrast, outcomes following rotavirus (mostly <6 months) and MMR (mostly at a year) vaccinations were reassuring. Notably, disseminated rotavirus infection has not been reported.

Other systematic reviews have also evaluated vaccine efficacy, and report adequate vaccination response (measured by antibody levels) following non-live vaccination in infants exposed to TNFi [336], although there are conflicting reports, with low antibody responses to the Haemophilus influenzae type-B vaccine reported in some infants exposed to INF or ADA [338].

Although our literature search did not assess evidence relating to the peri-operative use of TNFi or other bDMARDs (for example, in the context of caesarean sections), relevant guidance can be found in other BSR guidelines [341].

Recommendations for anti-TNF α medications in pregnancy and breastmilk exposure

- i) Women with no/low disease activity established on a 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%).

Other biologic DMARDs (non-TNFi)

Data relating to non-TNFi biologic use in pregnancy remain scarce, and in this guideline updated case reports and small case series were excluded for consistency. A recent systematic review summarized all available data (including case reports) on non-TNFi bDMARDs and tsDMARDs and did not identify any adverse safety signals [342].

Rituximab

Previously, we found insufficient evidence to be confident that RTX is compatible with pregnancy and recommended it should be stopped 6 months before conception, although there were no direct reports of teratogenicity and only second/third trimester exposure was associated with neonatal B-cell

depletion. RTX is a monoclonal IgG1 that actively crosses the placenta from 16 weeks of pregnancy onwards. Previously, we found eight studies [50, 343–349] on 173 RTX-exposed pregnancies that met our inclusion criteria. Overall, these studies reported reassuring pregnancy outcomes, but found low B cells at birth in infants exposed to RTX in the second/third trimester, no human breastmilk exposure studies were identified [1].

We identified five further studies of 143 RTX pregnancy exposures [350–354] in addition to eight exposures in studies that reported on combined outcomes of multiple biologic-exposed pregnancies (see ‘Biologic DMARDs’ above). Four studies ($n = 135$) of mostly pre-conception or first trimester maternal exposure did not report an increased risk of preterm birth, miscarriage, LBW or congenital anomaly [350–352, 354]. An additional cohort study of eight mothers treated with one to four cycles of RTX during pregnancy ($n = 6$ for diffuse large B-cell lymphoma; $n = 2$ for SLE) found a high rate of preterm birth and intrauterine infections, but noted the potential for confounding by the underlying disease and concomitant medications [353].

UKTIS reports that there is insufficient evidence to assess whether the risk for spontaneous miscarriage, congenital malformation, birth weight, intrauterine death or adverse neurodevelopmental outcomes is increased following exposure to RTX *in utero*. Due to a lack of data on the effects of RTX on the neonatal/infant immune system, it recommends delaying administration of live vaccines following *in-utero* exposure to RTX, although no specific timescale is given [171].

There were three studies of breastmilk exposure ($n = 23$) to RTX [352, 354, 355]. One study detected minimal transfer of RTX into the breastmilk of nine breastfeeding mothers, with a relative infant dose of rituximab well below theoretically acceptable levels ($<0.4\%$) [355]. No adverse effects attributable to RTX exposure were reported in the breastfed infants, and the drug was considered to have an acceptable benefit-to-risk ratio, supporting both maternal treatment and breastmilk exposure. LactMed states that the amount of RTX in breastmilk is very low and absorption is unlikely because it is a protein with a high molecular weight that is likely to be partially destroyed in the infant’s gastrointestinal tract; thus, absorption by the infant is probably minimal [192].

Vaccine efficacy after prenatal exposure to RTX is much less studied, and systematic reviews have identified adequate non-live vaccination outcomes from 5/6 RTX-exposed infants, with low immunity to diphtheria detected in one 11-month-old infant exposed to RTX at conception [336, 338].

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

Tocilizumab

Due to insufficient data, we previously recommended that TCZ be stopped at least three months pre-conception, but that unintentional exposure early in the first trimester is unlikely to be harmful due to its IgG1 structure. This limited data came from outcomes of 33 pregnancies in 32 patients, published in abstract form [356]. We identified three further studies of 365 pregnancy exposures to TCZ [357–359] in addition to four exposures in the papers described above which reported combined outcomes of multiple biologic-exposed pregnancies (see ‘DMARDs’ above). These studies of mainly first trimester exposure did not find increased rates of congenital abnormalities in patients with rheumatic disease. Two studies commented on a higher than background rate of spontaneous miscarriage [357, 359], and could not exclude an effect on birth weight and risk of prematurity, while acknowledging potential confounding factors. For example, stopping effective treatment early in pregnancy could destabilize the rheumatic disease, with adverse consequences for the pregnancy.

UKTIS notes a small number of studies lacking comparator groups that are confounded by maternal disease, and states that there is currently no compelling evidence that TCZ is teratogenic or fetotoxic. Due to lack of data on effects on the neonatal/infant immune system, it recommends that live vaccines are avoided until the infant is 6 months of age [171].

One study of $n = 2$ breastmilk exposure to TCZ did not report any adverse effects attributable to the drug [360]. Saito *et al.* have described a total of four cases of babies exposed to TCZ via breastmilk with no complications in the infants (three publications which did not meet our inclusion criteria) [360–362]. Concentrations of TCZ were measured in the breastmilk in these studies and two additional cases reports, with no clinical adverse effects reported [363, 364]. Levels in the breastmilk were found to peak on day three following the infusion [362], but were significantly lower than the corresponding maternal serum concentrations in all of these cases, ranging from 11% in colostrum [364], down to as low as 1:2000 [360, 363].

Sarilumab

No papers were found that met our inclusion criteria. Sanofi provided data on 13 patients who became pregnant in the sarilumab and DMARD long-term safety population, of whom seven had a miscarriage [365]. In addition, two male patients fathered two healthy children.

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

Anakinra

Anakinra is a recombinant form of human interleukin-1 receptor antagonist (IL-1Ra) with a high molecular weight which was not found to cross *ex-vivo* full-term human placenta [366]. Previously, there was insufficient information evidence on which to base a recommendation for anakinra in pregnancy, but unintentional exposure in the first trimester was considered unlikely to be harmful [1]. This limited evidence came from reports on five pregnancies in three studies/reports, with no evidence of harm [50, 367, 368].

Subsequently, we identified four studies of 43 pregnancy exposures to anakinra [369–372], in addition to one exposure in the papers described above which reported combined outcomes of multiple biologic-exposed pregnancies (see ‘Biologic DMARDs’ above). These exposures were mostly in patients with periodic fevers and severe maternal disease. Overall, outcomes were reassuring, although two congenital renal anomalies and two cases of oligohydramnios (which can be linked to foetal renal anomalies) were reported [369, 371, 372]. It was unclear, however, whether the renal abnormalities were associated with antenatal anakinra use or maternal hyperthermia or both. Given the significant beneficial effects of anakinra in suppressing maternal disease with limited pregnancy-compatible options, it was considered a safe alternative in managing disease in women with periodic fever in pregnancy. UKTIS does not report on anakinra.

Two studies of $n = 12$ breastmilk exposures to anakinra did not report any adverse effects attributable to the drug [369, 371]. LactMed states that IL-1Ra is a normal component of human milk, possibly as an anti-inflammatory agent, and that several infants have been breastfed during maternal anakinra therapy with no obvious adverse effects. If anakinra is required by the mother, it is not a reason to discontinue breastfeeding [192].

Canakinumab

Canakinumab is a human monoclonal antibody to IL-1. There is, therefore, the potential for active transport across the placenta from the second trimester onwards.

One paper reporting canakinumab use from pre-conception in eight pregnancies (stopped during first trimester in 5/8 pregnancies) met our inclusion criteria [369]. There were seven live births, all of whom were healthy, full term and normal birth weight. One mother with refractory Cogan syndrome had an early miscarriage at 6 weeks (after a miscarriage the previous year while on anakinra).

In addition, Novartis supplied information from analyses of the Novartis Global Safety Database, which included 76 maternal and nine paternal exposures [373]. There were 47 known pregnancy outcomes, with 27 healthy newborns, one preterm birth (with meconium staining not thought likely to be related to canakinumab exposure), nine spontaneous miscarriages (including two miscarriages related to paternal exposure in one father) and three elective terminations. Seven

other adverse events were reported: one case of congenital pylodilatation following paternal exposure to canakinumab; one case of congenital musculoskeletal abnormality following maternal exposure, with insufficient data on other contributory factors; one case of inherited genetic disease with neonatal RSV infection and pyrexia following infant vaccinations; and four adverse events very unlikely to relate to canakinumab exposure (one newborn non-serious hypotension and three cases of likely inherited disease: Muckle–Wells syndrome and CAPS).

One cohort study reported breastmilk exposure in four infants whose mothers were prescribed regular canakinumab, with no reported serious infections or developmental abnormalities [369].

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

ABA is a fusion protein containing the Fc region of IgG1 fused to the extracellular domain of CTLA-4; therefore, it is able to cross the placental barrier from approximately week 16. Previously, there was insufficient data to recommend ABA in pregnancy, but unintentional exposure early in the first trimester was considered unlikely to be harmful [1]. This conclusion was based on reports from 11 pregnancy exposures (and a further eight exposures reported in abstract form only), many of which were confounded by concomitant MTX [175, 349, 374].

We identified two further studies of at least 196 pregnancy exposures to ABA (with some overlap of data) [375, 376], in addition to three exposures in the papers described above which reported combined outcomes of multiple biologic-exposed pregnancies (see ‘Biologic DMARDs’ above). The data from these studies did not suggest an increased risk of adverse pregnancy outcomes with ABA, and many of the congenital abnormalities were considered by the authors to be associated with concomitant use of other teratogenic DMARDs. The apparently high rate of spontaneous miscarriage (total $\geq 48/184$) is difficult to interpret due to confounding by indication and other medications such as MTX, as well as detection bias of early miscarriages during the close monitoring of clinical trials [375]. The authors concluded that ABA should only be used during pregnancy if the benefit to the mother justifies potential risk to the foetus. UKTIS does not report on ABA.

Although it did not meet our inclusion criteria, we identified one case report of breastmilk exposure to ABA, with no adverse effects, in which ABA was secreted into breastmilk at levels 1/200–1/300 of those in serum [377]. LactMed describes one case report that reported concentrations of ABA in milk were very low and did not appear to affect the breastfed infant, concluding that if ABA is required by the mother, it is not a reason to discontinue breastfeeding, although alternative drugs may be preferred [192].

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

Belimumab (BEL) is a fully humanized monoclonal IgG1 that inhibits B-cell activating factor. Previously, our systematic search did not identify any publications that met our search criteria on use of BEL in human pregnancy, although we found reference to pregnancy outcomes from placebo-controlled, phase 2 and 3 studies in 83 SLE pregnancies [378], and BEL pregnancy registry data describing known outcomes from 118 SLE pregnancies [379]. Overall, these studies did not identify any pattern of adverse effects in pregnancy directly attributable to BEL.

We subsequently identified one study of 66 BEL pregnancy exposures [380]. Total foetal losses in BEL-treated subjects were similar to background estimates in SLE patients (~25%), although data remain limited. Another six studies, which did not meet our search criteria [381–386], reported an additional 124 pregnancies exposed to BEL. There was only one reported congenital abnormality: a case report of mild Ebstein's anomaly in a baby following successful control of SLE (with previous lupus nephritis and APS, previously only controlled on MMF) [381]. Two case series (26 pregnancy exposures) reported preterm delivery in 12/22 live births, with six babies being SGA [385, 386]. However, these cohorts included patients with complex rheumatic disease (SLE and APS), including some patients with previous lupus nephritis and active disease at conception [385], and a high average maternal age and rate of previous pregnancy losses [386]. Both authors concluded that, while careful consideration and further research is required, BEL could be a reasonable treatment option for patients with SLE requiring treatment in pregnancy. UKTIS does not report on BEL.

Although they did not meet our inclusion criteria, we identified two cases of breastmilk exposure while on BEL [381,

382]. No neonatal outcomes, adverse or otherwise, were reported in one case [381]. In the other case, there were no adverse effects, and BEL was secreted into breastmilk at levels 1/200–1/500 of those in serum [382]. LactMed states that, based on preliminary information that BEL levels in breastmilk are very low and infant absorption is probably minimal, if BEL is required by the mother, it is not a reason to discontinue breastfeeding, although caution is required, especially while nursing a newborn or preterm infant [192].

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

Interleukin-17 inhibitors (IL-17i) were not in general use and so not considered in our previous search. Secukinumab has an IgG1 structure, which may theoretically suggest increased transplacental transfer compared with the IgG4 structure of ixekizumab.

We found three studies of mostly first trimester pregnancy exposures to secukinumab ($n=244$) and ixekizumab ($n=18$) [387–389]. The authors did not report any increased incidence of adverse outcomes directly attributable to the drugs, although information, particularly for ixekizumab, remains very limited.

In addition, Novartis provided data from a search of their Global Safety Database, relating to 298 reports of maternal pregnancy exposures and 90 paternal exposures to secukinumab, mostly during the first trimester [390]. No outcome data were provided, but analysis within Novartis did not reveal any new safety information. UKTIS does not report on these drugs.

There were no data on breastmilk exposure to IL-17i identified in our search or in LactMed. Data provided from the Novartis Global Safety Database identified six breastmilk exposures to secukinumab, including one report of newborn pyrexia during breastfeeding [390]. The data in all cases were too limited to draw conclusions, but no new safety concerns were inferred.

Recommendations for interleukin-17 inhibitors in pregnancy and breastmilk exposure

- 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%).

Interleukin-12/23 inhibitors

UST is an interleukin-12/23 inhibitor (IL-12/23i) with an IgG1 structure. UST was not in general use and not considered in our previous search. We found three studies of mostly first and second trimester pregnancy exposures to UST ($n = 517$) for maternal psoriasis, PsA and IBD [391–393]. Overall, these data showed that the rates of live births, spontaneous miscarriages and congenital anomalies were consistent with the general population and TNFi-exposed pregnancies.

Similarly, UKTIS did not identify any specific drug-related risk but was unable to provide a reliable evidence-based evaluation of risk due to limited information [171].

Although they did not meet our inclusion criteria, we identified two reports of exposure to UST during breastmilk exposure [326, 394]. In one case report, the trough level of UST in breastmilk after restarting this drug post-partum in a Crohn's disease patient was initially in the same range as the corresponding serum trough level, and then decreased during maintenance therapy [394]. In another study assessing breastfeeding mothers taking a range of biologic medication for IBD, UST was detected at low levels in 4/6 mothers taking this medication [326]. Overall, in this study, breastfed infants of mothers on biologics were found to have similar risks of infection and rates of milestone achievement compared with non-breastfed infants or infants unexposed to these drugs. LactMed states that UST is either not detectable or found at very low levels in breastmilk and infant absorption is probably minimal; as such, if UST is required by the mother, it is not a reason to discontinue breastfeeding, although caution is required especially while nursing a newborn or preterm infant [192].

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 is a fully human, IgG1 κ monoclonal antibody to type I interferon receptor subunit 1. Although it is not currently licensed for use in the UK, anifrolumab is approved for use in other countries, including FDA approval to treat moderate-to-severe SLE in the USA [395]. Although there is no published evidence on the use of this drug in pregnancy, breastmilk or paternal exposure, further information was provided by AstraZeneca on data from completed trials. Despite the mandatory contraception use in anifrolumab clinical trials, pregnancies have been reported in 20 SLE patients receiving anifrolumab in studies completed by December 2021. Patients who became pregnant during studies had to immediately discontinue the investigational product. No anifrolumab-associated congenital abnormalities or anifrolumab-associated adverse events have been observed in the clinical trials. Current data on anifrolumab pregnancy exposure are insufficient to inform about potential drug-related risks and therefore post-authorisation pregnancy studies are planned.

UKTIS does not report on anifrolumab. Although there is no information regarding breastmilk exposure to anifrolumab, LactMed states that due to its large molecular weight, the amount in milk is likely to be very low, and it is also likely to be partially destroyed in the infant's gastrointestinal tract with minimal absorption by the infant [192]. Based on this limited evidence, we have not made any recommendations on this drug.

Targeted synthetic DMARDs

Data relating to tsDMARD use in pregnancy remain scarce, and in this guideline, updated case reports and small case series were excluded for consistency. A recent systematic review summarized all available data including case reports and raised no additional safety concerns [342]. No studies were found relating to apremilast use in pregnancy, and therefore we were unable to make any recommendations.

JAK inhibitors

Tofacitinib (TOF), baricitinib (BAR) and upadacitinib (UPA) are oral Janus kinase inhibitors (JAKi) which were not in general use and so not considered in our previous search. They are small molecule inhibitors of low molecular weight which could theoretically cross the placenta.

JAKi have a short half-life (~3 h for TOF), although biological changes can persist for longer (for example, dose-dependent reductions in NK cells and CRP do not appear to reverse before 2 weeks after discontinuation) [396].

We identified three published reports of pregnancies during RCTs and post-marketing surveillance reports for TOF, but due to probable overlap, only the later 2018 paper was included (further updates were published in abstract form in 2020) [397–399]. This included 116 pregnancy exposures to TOF, with the known reported outcomes including 15/72 first trimester miscarriages, and major malformations in 2/44 live births (one pulmonary valve stenosis and one ventricular septal defect), which was in line with background risks in the general population [397].

Pfizer medical information supplied further details on pregnancies reported during the TOF clinical trials programmes

[400]. The RA and psoriasis trials included a total of 60 maternal exposures during the first trimester with 51 known outcomes, with concomitant MTX use either before or during pregnancy in at least 19 of these cases [399]. There were 28 healthy newborns, two premature infants, and one congenital malformation where the mother was also taking losartan. In these trials, there were nine spontaneous miscarriages, nine medical terminations, and one elective termination. In the ulcerative colitis (UC) clinical trial programmes, there were 15 maternal exposures with 13 known outcomes (nine healthy newborns, two spontaneous miscarriages and two medical terminations) [397, 398]. In the PsA programmes, there were a further four maternal and three paternal exposures with six known outcomes (three healthy newborns, two spontaneous miscarriages and one medical termination) [397]. Post-marketing reports up to 2017 were included in the analysis by Mahadevan *et al.* with 42 (predominantly first trimester) maternal exposures and three paternal exposures, with only 12 known outcomes (seven healthy newborns, one congenital malformation, three spontaneous miscarriages and one medical termination) [397].

Although not eligible for inclusion, we found one case report of an RA pregnancy exposed to BAR from pre-conception up to 17 weeks gestation, with a healthy infant delivered at 38 weeks gestation by caesarean section [401]. In addition, Eli Lilly provided data on 36 maternal pregnancies during the BAR clinical trials programme, with 25 known outcomes (trimester and duration unspecified) [402]. Many were taking concomitant medications, including MTX ($n = 14$). Outcomes included 13 healthy newborns (including three born preterm), seven spontaneous miscarriages (with MTX exposure in six of these), and five elective terminations. In addition, there have been 22 post-marketing reports of pregnancy exposures to BAR, with four known outcomes as of January 2021, including three healthy newborns (including one preterm), and one spontaneous miscarriage at 13 weeks in a 36-year-old mother (early first trimester exposure to BAR with concomitant medications for RA including HCQ, GOL, prednisolone, MTX, folic acid and ibuprofen) [402].

UKTIS does not reported on JAKi. We found no evidence relating to breastmilk exposure to JAKi. Given that they are small molecules and likely to transfer into breastmilk, they should be avoided. LactMed states that no information is available on the use of TOF or BAR during breastmilk exposure, and alternate drugs are preferred, especially while nursing a newborn or preterm infant [192].

There were no studies identified that met our inclusion criteria for UPA. Data provided by AbbVie included 54 maternal pregnancies inadvertently exposed to UPA in the month prior to conception or during the first trimester of pregnancy during the clinical trials programme [403]. The 41 known outcomes included 17 healthy live births (including two premature deliveries), 14 spontaneous miscarriages (10 of whom were on concomitant MTX), nine elective terminations (all with no reported foetal defects) and one ectopic pregnancy. Filgotinib was NICE-approved after our search window, and so was not included in our search.

Recommendations for JAK inhibitors in pregnancy and breastmilk exposure

- 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 breastmilk, they should be avoided (GRADE 2C, SOA 99.5%).

Paternal exposure

Hydroxychloroquine

For HCQ, no additional paternal exposures were identified to the previously identified cohort study [52] and case series [404] of 13 pregnancies after paternal exposure to HCQ, which did not find any increased risk of adverse foetal outcomes.

Corticosteroids

Previously, four cohort studies [52, 405–407] and two case series [404, 408] reported on outcomes from ≥ 2127 pregnancies after paternal exposure to prednisolone, and a case-control study [409] and a case series [410] reported on outcomes from ($n = 4$) pregnancies after paternal exposure to methylprednisolone. Overall, the quality of these studies was low, but reassuringly they did not identify an increased risk of adverse foetal outcomes. Since then, an additional study of 2380 paternal exposures to corticosteroids did not identify any statistically significant increase in adverse birth outcomes [411].

Methotrexate

Previous low-quality evidence from outcomes of pregnancies after paternal exposure ($n = 263$) to predominantly low-dose MTX did not find any adverse effects [1]. We identified an additional six studies of paternal exposures to MTX ($n = 2026$) within three months of conception that similarly found no increased risk of adverse foetal outcomes when compared with MTX-unexposed controls ($n = 4\ 700\ 599$) [184–189]. An additional study examined foetal outcomes with paternal MTX (and other DMARD) use compared with abatacept; however, outcomes for individual drugs were not reported [375].

Sulfasalazine

Our previous review of three cohort [52, 407, 412] and one case-control study [409] reporting on 237 pregnancies after paternal exposure to SSZ did not find an increased risk of adverse foetal outcomes, although the quality of evidence was low. SSZ may also affect male fertility, with oligospermia, reduced sperm motility and increased proportions of abnormal sperm previously reported [1]. No further studies of paternal SSZ exposure were identified in our search.

Leflunomide

Previously, we identified a cohort study [52] and case report [413] describing outcomes from ($n = 2$) pregnancies after paternal exposure to LEF within three months of conception, and subsequent pregnancy exposure (with intercourse without a condom) in at least one case with no reported washout. No adverse foetal outcomes were observed. An additional study was identified examining foetal outcomes with paternal leflunomide (and other DMARD) use compared with abatacept; however, outcomes for individual drugs were not reported [375].

Azathioprine

In addition to the previous 602 paternal exposures [52, 404–409, 414, 415], we identified three studies of $n = 2680$ pregnancies after paternal exposure to AZA [185, 187, 216]. Overall, no increased risk of adverse foetal outcomes was observed.

Ciclosporin

In addition to previous studies [406, 408, 410, 416] on outcomes from pregnancies ($n \geq 254$) after paternal exposure to CsA, we found a Danish population-based cohort study of birth outcomes in 247 children fathered by men treated with CsA before conception [185]. Overall, these studies did not identify an increased risk of adverse foetal outcomes with paternal exposure to CsA.

Tacrolimus

No additional paternal studies were found to complement previous findings reporting outcomes from pregnancies ($n \geq 120$) after paternal exposure to tacrolimus, which did not identify an increased risk of adverse foetal outcomes [406, 416, 417].

Cyclophosphamide

No new studies of paternal exposure to CYC were identified. In addition to a potential long-term impact on spermatogenesis (and hence fertility) in men [418], there is evidence of an adverse impact on germ cell development and male-mediated teratogenicity from animal studies [419–422], although this has not been proven in humans [423–425].

Mycophenolate mofetil

In addition to the three previous studies [406, 416, 426] of paternal exposures to MMF ($n \geq 72$), we found three additional studies of pregnancies ($n = 220$) after paternal exposure [185, 246, 247]. Overall, the quality of these studies was low, but they did not identify an increased risk of adverse foetal outcomes.

Intravenous immunoglobulin

There is no evidence relating to paternal exposure but based on maternal compatibility it is unlikely to be harmful.

Anti-TNF α drugs

Previously, we found five cohort studies [52, 263, 405, 412, 427], two case series [404, 410], two case reports [428, 429] and a case-control study [409] that reported on outcomes from pregnancies ($n = 131$) after paternal exposure to INF, ETA and ADA. Overall, the quality of these studies was deemed to be low, but they did not identify an increased risk of adverse foetal outcomes. We identified an additional eight cohort studies reporting outcomes from 620 pregnancies after paternal exposure to TNFi [293, 298, 306, 430–434], with no significant findings to suggest adverse foetal outcomes were more likely after TNFi exposure.

Rituximab

We did not identify any further paternal exposures to the 11 found previously [343], which did not identify any problems in relation to paternal exposure to RTX.

IL-6 Inhibitors

Two studies of $n = 15$ paternal exposures to TCZ did not find any drug-related effects [357, 359].

IL-1 Inhibitors

One study of $n = 5$ paternal exposures to anakinra did not find any drug-related effects [369]. Youngstein *et al.* reported on five healthy pregnancies to three fathers on long-term canakinumab treatment [369].

Abatacept

In addition to the previous case of one healthy pregnancy following paternal ABA exposure [374], a study of clinical trial and post-marketing data submitted to the manufacturer (up to 2014) reported 10 paternal ABA exposures, resulting in nine healthy live births with one elective termination [375].

IL-17 inhibitors

Two studies of paternal exposure to secukinumab ($n = 54$) and ixekizumab ($n = 34$) did not report any adverse drug-related effects [387, 389].

JAK-inhibitors

There were 87 paternal exposures to TOF in a study included in our search [397]. Further details provided by Pfizer reported paternal exposures to TOF in the PsA clinical trials ($n = 3$) and post-marketing reports ($n = 3$), described above. During the RA and psoriasis clinical trials programmes, 66 men were exposed to TOF with 45 known outcomes, including 37 normal healthy newborns, two premature deliveries (with one subsequent neonatal death) and six spontaneous miscarriages [400]. In the UC clinical trial programmes, there were 19 paternal exposures with 17 known outcomes (15 healthy newborns including one healthy preterm delivery at 34 weeks, and two spontaneous miscarriages) [398]. Data provided by Eli Lilly included eight paternal exposures to BAR in the clinical trials programmes, and outcomes included six full-term healthy newborns and two spontaneous miscarriages [402].

No data were found relating to paternal exposure to BEL, IL-12/23i or anifrolumab.

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) MTX, AZA (GRADE 1B); TNFi, cyclosporin (GRADE 1C); HCQ, LEF, tacrolimus, MMF, IVIG, RTX, IL-6i, IL-1i, ABA, BEL, IL-17i, UST and JAKi (GRADE 2C, SOA 99.3%).

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

Ideally, patients with rheumatic disease should receive tailored pre-pregnancy counselling and then be reviewed during pregnancy and the four-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 therapy. These data would also be used to answer specific questions such as the most suitable time to stop MTX pre-conception. Data relating to the impact of paternal exposure to these drugs (both fertility and male-mediated teratogenicity), as well as breastmilk exposure, are particularly limited, and further research in these areas is urgently required. Other research questions include: should bDMARDs with known placental transfer be stopped or switched before/during pregnancy; are tsDMARDs compatible with pregnancy; is it safe to give certain live vaccines to infants ≤ 6 months after *in-utero* exposure to bDMARDs with known placental transfer in the third trimester of pregnancy?

Mechanism for audit of the guideline

An audit pro forma to assess compliance with these guidelines is shown in the audit tool 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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