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BSR and BHPR guideline on prescribing drugs in pregnancy and breastfeeding—Part I: standard and biologic disease-modifying anti-rheumatic drugs and corticosteroids

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Key words: rheumatic disease, pregnancy, breastfeeding, prescribing, corticosteroids, hydroxychloroquine, DMARDs, biologics

GUIDELINES

Full guideline

Scope and Purpose

Background

Prescribing of anti-rheumatic and immunosuppressive drugs in women with rheumatic disease is often required to ensure adequate control of maternal disease activity and satisfactory pregnancy outcome. These drugs may also be required to control disease activity in men with rheumatic disease wishing to father a child. However, prescription of many of these drugs is complicated by concerns regarding their safety. These concerns arise from safety information based mainly on experimental and animal studies. Human data are limited to inadvertent exposure described in case reports/series and population

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registries. This *ad hoc* system of reporting has identified obvious risks with some anti-rheumatic drugs and led to uncertainty and theoretical concerns for others, such as LEF and biologics. Consequently, withdrawal or denial of disease-ameliorating therapies often occurs because of a perceived rather than proven risk of their lack of safety in pregnancy. It is important to avoid this situation, because active rheumatic disease is associated with adverse pregnancy outcomes [1], and there is growing evidence of drug safety in pregnancy.

Need for guidelines

A previous survey based on a consensus workshop of international experts discussing the effects of anti-inflammatory, immunosuppressive and biologic drugs during pregnancy and breastfeeding has made recommendations for drug treatment during pregnancy and breastfeeding [2]. These recommendations were made by analysing information published prior to 2006 and updated for biologics with information published in 2006–7 [3]. However, formal guidelines are currently lacking on this topic and the question of whether biologics are safe to prescribe in pregnancy and/or breastfeeding is increasingly being asked. Therefore, guidelines are urgently required for medical professionals across the country to have a consistent approach to prescribing anti-rheumatic drugs before/during pregnancy and breastfeeding.

Objectives of the guideline

To expand and update the previous consensus recommendations (2006–8) and systematically review all current evidence 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 breastfeeding? Where possible, recommendations are made regarding compatibility with paternal exposure.

Target audience

The primary audience consists of health professionals in the UK directly involved in managing patients with rheumatic disease who are (or are planning to become) pregnant and/or breastfeeding, men planning to conceive and patients who have accidentally conceived while taking these medications. This audience includes rheumatologists, rheumatology nurses/allied health professionals, rheumatology speciality trainees and pharmacists, as well as the patients themselves. The guideline will also be useful to obstetricians, obstetric physicians, renal physicians and general practitioners who prescribe these medications in pregnancy.

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. Gold and penicillamine were not included in the search, as these drugs are rarely used in rheumatology practice and thus do not tend to be encountered in patients of childbearing age.

Stakeholder Involvement

Names and affiliations of representatives on the multidisciplinary working group

Coordination team

The chair of the team was Dr Ian Giles, consultant rheumatologist, University College London Hospital, London. Data collection, compilation and analysis was carried out by Dr Ian Giles, Dr Julia Flint, specialist trainee in rheumatology, London Deanery and Dr Sonia Panchal, specialist trainee in rheumatology, University Hospitals of Leicester.

Members of the data collection team

Dr Alice Hurrell and Dr Joel Cunningham, obstetric trainees; Dr Lucy Flanders, core medical trainee; and Dr David Williams, consultant obstetric physician, University College London Hospital, London.

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Allied health care professional, general practice and patient representatives

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Amisha Desai, pharmacist, University Hospital Birmingham NHS Foundation Trust, Birmingham.

Involvement and affiliations of stakeholder groups involved in guideline development

The guidelines working group consisted of rheumatologists from a range of clinical backgrounds, allied health professionals, other specialists in women's health and a lay member. All members of the working group contributed to the process for agreeing on key questions, guideline content, recommendations and strength of agreement (SOA). Advice contained herein will be linked with relevant sections of Arthritis Research UK patient information leaflets.

Rigour of Development

Scope of the 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 [4]. Studies were

identified by searching Medline and Embase databases using combinations of the key MESH and free terms: pregnancy, lactation, breastfeeding, name of each drug and name of key rheumatic diseases. The full electronic search strategies for Medline and Embase databases are shown in the search strategies appendix. Additional published studies were identified through the Cochrane, LactMed (a National Library of Medicine database on drugs and lactation) and UK Tetralogy Information Service (UKTIS) databases, communication with pharmaceutical companies on the relevant biologics, checking the reference lists and other author publications of articles selected for full-text analysis. At least two independent reviewers screened the title and abstract of retrieved articles to identify studies that met inclusion criteria of randomized and non-randomized controlled trials, cohort studies, case–control studies and case series/reports. Animal studies, abstracts and non-systematic reviews were excluded from the final analysis. Disagreements were resolved by group discussion.

A data extraction sheet was developed and its reliability examined on 10 randomly selected studies. It was then refined accordingly to ensure that relevant data from these studies on pregnancy exposure and related outcomes was captured using the data extraction sheet available in the appendix.

Statement of extent of National Institute for Health and Care Excellence, Royal College of Physicians, Scottish Intercollegiate Guidelines Network guidelines

There are no British Society of Rheumatology (BSR), National Institute for Health and Care Excellence (NICE), Royal College of Physicians (RCP) or Scottish Intercollegiate Guidelines Network (SIGN) guidelines for prescribing in rheumatic disease in pregnancy. EULAR guidelines on prescribing of selected anti-rheumatic drugs in pregnancy are currently in development.

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

This guideline was developed in line with BSR's Guidelines Protocol using RCP, SIGN and Appraisal of Guidelines, for Research, and Evaluation II (AGREE II) methodology to determine the level and strength of evidence. The working group met regularly to formalize the search strategy, review evidence, resolve disagreements and, finally, to determine recommendations. The wording of each suggested recommendation was agreed by all members ($\geqslant$80% was taken as consensus) and subjected to a vote relating to SOA on a scale of 1 (no agreement) to 10 (complete agreement).

The recommendation statements are presented at the end of each drug section, which includes the relevant references selected from our systematic search (see Tables 1–4). For drugs where important papers were published after our final search date and/or information was particularly lacking, additional data derived from these papers and relevant conference abstracts are described in the main text but these data were not included in the final grading of each recommendation, unless there was no other information available. Accompanying each recommendation statement in brackets is the highest level of evidence (LOE) and the grade of recommendation (GOR) based on the body of available evidence, according to SIGN [5], followed by a percentage showing the SOA from voting of all 19 group members. The level of evidence for recommendations from the previous consensus review [2] are shown as a Roman numeral, derived from Miyakis *et al.* [6], which was taken into account in the final GOR and shown only where additional data were lacking. Where no evidence was found and no expert opinion was formed, recommendations were left ungraded.

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

The search was conducted in June 2012 and updated in December 2013. Inclusion criteria were English language and date of publication to avoid overlap with drugs previously reviewed by Ostensen *et al.* [2, 3]. Searches relating to the use of drugs in pregnancy and breastfeeding in the absence of rheumatic disease excluded publications with fewer than five patients. The guideline will be updated in 3 years.

The guideline

Eligibility criteria

This guideline is intended for use by healthcare professionals who are currently (or considering) treating women who are planning pregnancy, currently pregnant or breastfeeding with any of the drugs listed in this document. Recommendations for men trying to conceive on these drugs are also given where sufficient evidence is available.

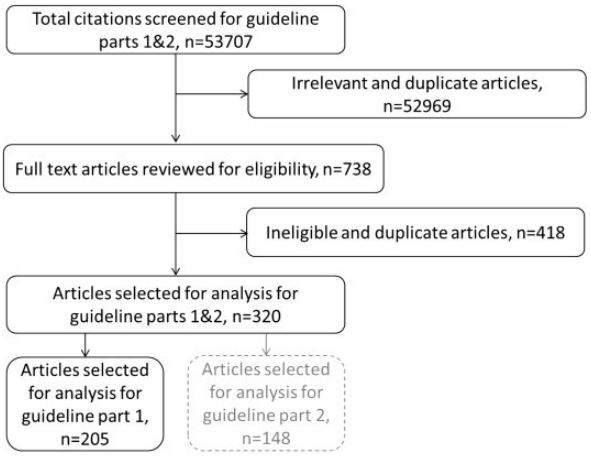
Exclusion criteria

Infertility and animal studies were excluded from the analysis. Gold and penicillamine were excluded because they are not commonly used and there has been no new information on their use in pregnancy and breastfeeding since the last consensus review [2]. A flow diagram of study selection is shown in Fig. 1, displaying the initial number of articles screened, the number of articles selected for full-length review and the number included in the final analysis.

Treatment

Drugs are considered by categories. This part of the guideline, part 1, considers antimalarials, corticosteroids, DMARDs and immunosuppressive therapies and biologics. Part 2 of this guideline considers pain management, NSAIDs and low-dose aspirin, anticoagulants in the management of multisystem rheumatic disease, bisphosphonates, anti-hypertensive medication in the management of multisystem rheumatic disease and pulmonary vasodilators [7]. The findings for each drug are presented as follows: type of study selected, number of

Fig. 1 Flow diagram of studies selected for final analysis



pregnancy exposures, pregnancy duration, birthweight, maternal complications, miscarriages, number and types of congenital anomalies, breastfeeding, long-term follow-up, paternal exposure and recommendations. Where possible, congenital anomalies described in original publications were classified as major or minor according to European Surveillance of Congenital Anomalies (EUROCAT) definitions [8]. An overall summary of compatibility of each drug pre-conception, during pregnancy, during breastfeeding and paternal exposure is shown in Table 1. Evidence summarizing the total number of pregnancies following maternal exposure to each drug is shown in Tables 2 and 3 and, where reported, outcomes of miscarriage, live births and major anomalies are summarized. Outcomes following paternal exposure are shown in Table 4. To reduce the impact of publication and selection bias, only papers with at least five patients are included in Tables 2–4. Other papers included in our search that do not meet these criteria are discussed in the main text.

Corticosteroids

Corticosteroids used to treat rheumatic disease (prednisolone, prednisone and methylprednisolone) are metabolized in the placenta, so $\leqslant$10% of the active drug reaches the foetus, and they are considered to be compatible with pregnancy and breastfeeding [2]. We identified a number of additional studies from 2005 onwards: 47 on prednisolone (n = 1503 pregnancies) comprising 1 Cochrane review [9], 1 systematic review [10], 3 randomized controlled trials (RCTs) [11–13], 3 case–control studies [14–16], 12 cohort studies [17–28], 11 case series [29–39] and 16 case reports [40–55]; 31 on dexamethasone (n = 11 214 pregnancies) comprising 5 systematic reviews [56–60], 1 RCT [61], 11 cohort studies [26, 62–71], 8 case–control studies [16, 72–78], 3 case series [30, 79, 80] and 3 case reports [81–83]; 27 on betamethasone (n = 27 746 pregnancies) comprising 7 systematic reviews [56–58, 84–87], 4 RCTs [88–91], 2 case–control studies [78, 92], 14 cohort studies [63, 64, 66, 68, 69, 93–101] and 1 case report [82]; and 10 on general corticosteroids (n = 785 pregnancies) comprising 1 RCT [102], 4 cohort studies [103–106], 2 case series [80, 107] and 3 case reports [108–110]. The studies 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.

Studies on the use of methylprednisolone in pregnancy were not specifically sought 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 equivalent glucocorticoid (anti-inflammatory) effects at 80% of the prednisolone dose with similar rates of placental transfer to prednisolone [111].

Following prednisolone (or unspecified corticosteroid) exposure, the average pregnancy duration in the majority of RCTs, case–control, cohort and case series studies (where reported) was usually term, at >37 weeks [11, 12, 14, 16, 20, 24, 27, 29, 35, 36, 38, 39]. The exceptions were studies of prednisolone use in patients with haemolysis, elevated liver enzymes and low platelets, where gestation averaged 28–29 weeks [13, 15]; a study of corticosteroid use in the management of pre-eclampsia [102]; one case series of renal transplant patients on MMF averaging 34 weeks [33]; one case series (n = 8) of ulcerative colitis patients being treated for a flare with corticosteroids as well as CSA [and AZA/infliximab (IFX) in some cases], where the average duration was 36 weeks [107]; and one cohort study reporting on 152 RA patients, of whom 56 were taking prednisolone during pregnancy, where a subanalysis demonstrated an association between prednisolone usage and reduced gestational age at delivery [23]. In contrast, in case reports describing preterm deliveries at <34 weeks, the reduction in gestational age was confounded by active disease, mainly SLE [44, 46, 55] and one case of active SS with acute mesangial proliferative glomerulonephritis and vasculitis [40], or concomitant drugs such as MMF [43, 44, 46, 50].

Studies of dexamethasone were particularly confounded by its use in haemolysis, elevated liver enzymes and low platelet count syndrome and/or pre-eclampsia, with preterm deliveries almost universally reported (attributable to the pregnancy complication rather than the steroid administration). In contrast, a systematic review of labour induction in 33 post-term mothers with pregnancies exposed to dexamethasone averaged 41 weeks [60]. Similarly, studies of betamethasone were confounded by its use in preterm birth to reduce respiratory distress-related morbidity, and the average pregnancy duration from all studies ranged from 32 to 37 weeks. Therefore, it is impossible to draw conclusions from these studies as to an effect of either dexamethasone or betamethasone on pregnancy duration.

Birthweights followed a similar pattern and were affected by preterm deliveries and the confounding factors

Table 1 Summary of drug compatibility in pregnancy and breastfeeding

	Compatible peri-conception	Compatible with first trimester	Compatible with second/ third trimester	Compatible with breastfeeding	Compatible with paternal exposure
Corticosteroids					
Prednisolone	Yes	Yes	Yes	Yes	Yes
Methylprednisolone	Yes	Yes	Yes	Yes	Yes
Antimalarials					
HCQ	Yes	Yes	Yes	Yes	Yes[a]
DMARDs					
MTX <20 mg/week	Stop 3 months in advance	No	No	No	Yes[a]
SSZ (with 5 mg folic acid)	Yes	Yes	Yes	Yes[b]	Yes[c]
LEF	Cholestyramine washout—No	No	No	No data	Yes[a]
AZA <2 mg/kg/day	Yes	Yes	Yes	Yes	Yes
CSA	Yes	Yes[d]	Yes[d]	Yes[a]	Yes[a]
Tacrolimus	Yes	Yes[d]	Yes[d]	Yes[a]	Yes[a]
CYC	No	No[e]	No[e]	No	No
MMF	Stop 6 weeks in advance	No	No	No	Yes[a]
IVIG	Yes	Yes	Yes	Yes	Yes[a]
Anti-TNF					
Infliximab	Yes	Yes	Stop at 16 weeks	Yes[a]	Yes[a]
Etanercept	Yes	Yes	Second but not third	Yes[a]	Yes[a]
Adalimumab	Yes	Yes	Second but not third	Yes[a]	Yes[a]
Certolizumab	Yes	Yes	Yes[a]	Yes[a]	No data
Golimumab	No data	No data	No data	No data	No data
Other biologics					
Rituximab	Stop 6 months in advance	No[f]	No	No data	Yes[a]
Tocilizumab	Stop 3 months in advance	No[f]	No	No data	No data[g]
Anakinra	No	No[f]	No	No data	No data[g]
Abatacept	No	No[f]	No	No data	No data[g]
Belimumab	No	No[f]	No	No data	No data[g]

For further information and caveats see relevant recommendations and main text in the executive summary and full guideline. [a]Data are limited. [b]In healthy full-term infants only. [c]Conception may be enhanced by stopping SSZ for 3 months prior to conception. [d]Suggested monitoring of maternal blood pressure, renal function, blood glucose and drug levels. [e]Only consider in severe, life-threatening or organ-threatening maternal disease. [f]Unintentional first-trimester exposure is unlikely to be harmful. [g]Unlikely to be harmful.

described above. For instance, in those RCTs, cohorts, case–control studies and case series with prednisolone exposure that reported average gestations of >37 weeks, average birthweights ranged from 2.6 to 3.4 kg [12, 14, 16, 20, 23, 24, 27, 29, 35, 38, 39]. Overall, prednisolone itself was not felt to have contributed to low birthweight (LBW) in any study. The studies of dexamethasone and betamethasone revealed LBW in preterm deliveries with confounding comorbidity. Only one study [69] attributed LBW to fluorinated steroids, with significantly higher rates of intra-uterine growth restriction and premature rupture of membranes in the exposed group, with the risks of treatment after 34 weeks outweighing the benefits. Reduced birthweight, particularly with betamethasone, was noted in an RCT examining neonatal respiratory distress syndrome after repeat exposure to fluorinated steroids [88]. However, further evaluation of this cohort showed accelerated post-natal growth at 3–5 weeks [101].

High rates of maternal complications compatible with underlying disease were reported for prednisolone and dexamethasone, but none were specifically attributed to these medications. In contrast, an increased incidence of chorioamnionitis was reported with betamethasone exposure compared with drug-free controls in a study of tocolysis [57].

The major congenital malformations observed with prednisolone were frequently confounded by concomitant teratogenic drug exposure, for example, MMF [54], and the overall incidence was not significantly higher than in drug-free controls. Several studies reported major malformations with fluorinated steroid exposure, for example, patent ductus arteriosus, blindness and deafness [64, 84], although none of them were deemed attributable to steroid therapy by the authors. Furthermore, in the majority of cases the steroids were used for the treatment of underlying conditions such as preterm delivery [64], where steroids were found to be beneficial in improving

Table 2 Summary of maternal exposure to DMARDs including antimalarials and steroids

Drug	Studies (type and number)	Pregnancy exposures, per trimester	Live births[a]	Spontaneous miscarriages/ total pregnancy outcomes[a]	Pregnancy duration/ birthweight[a]	Major malformations/total births[a]	Recommendation	Level of evidence/ grade of recommendation
HCQ	2 sr [119, 120] 2 cc [13, 103] 10 ct [16, 19, 20, 22, 25, 102, 104, 121–123] 3 cs [30, 79, 124] 6 cr [42, 43, 45, 51, 125, 126]	810 (first ⩾180, second/ third ⩾171	216	14/192	No significant adverse effect noted	22/370 (5.95%)[b] Overall no increase in rate of major malformations attributable to drug	HCQ remains the antimalarial of choice in women planning a pregnancy with rheumatic disease in need of treatment, and should be continued during pregnancy	LOE 1 ++/GOR A, SOA 100%
Pred	1 Cochr [8]	1503 (first ⩾293, second/ third ⩾383	420	53/395	No significant adverse effect attributable to drug	12/260 (4.62%)	Prednisolone is compatible with each trimester of pregnancy and is the preferred corticosteroid in the treatment of maternal rheumatologic disease in pregnancy	LOE 1 ++/GOR A, SOA 100%
	1 sr [9] 3 rct [10–12] 3 cc [13–15] 12 ct [16–27] 11 cs [28–38] 16 cr [28–54]					No increase in rate of major malformations attributable to drug	Methylprednisolone has similar rates of placental transfer to prednisolone with equivalent anti-inflammatory effects at 80% of prednisolone dose and would therefore be expected to be compatible with pregnancy, breastfeeding and paternal exposure	LOE 4/GOR D, SOA 93.7%
SSZ	3 ct [20, 22, 102] 1 cs [30] 2 cr [126, 142]	178, NR	3	NS	No significant adverse effect noted	Rate not specifically quantified in majority of papers Overall no increase in rate of major malformations attributable to drug	SSZ with folate supplementation (5 mg/day) is compatible throughout pregnancy, and folic acid should be prescribed to women taking SSZ who are trying to conceive	LOE 2+/GOR C, SOA 100%
LEF	3 ct [21, 102, 147]	111, first ⩾58,	105	8/108	No significant adverse effect noted	5/101 (4.95%)	Based on limited evidence, LEF may not be a human teratogen, but there remains insufficient evidence to change previous recommendations and LEF is not the DMARD of choice in women planning pregnancy	LOE 2+/GOR C, SOA 100%

(continued)

Table 2 Continued

Drug	Studies (type and number)	Pregnancy exposures, per trimester	Live births[a]	Spontaneous miscarriages/ total pregnancy outcomes[a]	Pregnancy duration/ birthweight[a]	Major malformations/total births[a]	Recommendation	Level of evidence/ grade of recommendation
	4 case reports [148–150] and [151] (2 cases)	second/third ⩾3				Overall no increase in rate of major malformations attributable to drug, but most cases stopped in first trimester and received cholestyramine washout	Women on LEF considering pregnancy should stop and undergo cholestyramine washout before switching to alternative medication compatible with pregnancy	LOE 2+/GOR C, SOA 100%
							There is no human evidence of increased congenital abnormalities on LEF if washout is given. Therefore, if accidental conception occurs on LEF, the drug should be stopped immediately and cholestyramine washout given until plasma levels are undetectable	LOE 2+/GOR C, SOA 98.9%
AZA	1 sr [9] 5 cc [15, 72, 129, 155, 156] 10 ct [18–20, 23, 24, 27, 102, 122, 157, 158] 6 cs [30, 32, 35, 130, 159, 160] 2 cr [40, 51]	738, first ⩾304, second/ third ⩾250	252	12/84	No significant adverse effect noted	13/238 (5.46%) Overall no increase in rate of major malformations attributable to drug	AZA is compatible throughout pregnancy at a daily dose not exceeding 2 mg/kg/day	LOE 2 ++/GOR B, SOA 100%
MTX	1 cc [129]	27, first trimester ⩾16, second/ third trimester ⩾5	10	NS	Insufficient data; five cases only: three term [130, 131, 135] and two premature [133, 134] with corresponding LBW in patients with SLE	0/8	MTX at any dose should be avoided in pregnancy and stopped 3 months in advance of conception. Recent studies support a shorter drug-free interval of low-dose (⩽20 mg/week) MTX, but further evidence is required to alter previous recommendations	LOE 2−/GOR D, SOA 100%
	32 ct [20, 21, 102]					Remainder is case report data	In women treated with low-dose MTX within 3 months prior to conception, folate supplementation (5 mg/day) should be continued prior to and throughout pregnancy	LOE 1/GOR B, SOA 98.4%
	1 cs [130] 5 cr [131–135]					Case reports of infants exposed during first trimester born without congenital anomalies, but also MTX embryopathy reported in both newborn infants and spontaneously aborted foetuses	In the case of accidental pregnancy on low-dose MTX, the drug should be stopped immediately, folate supplementation (5 mg/day) continued and a careful evaluation of foetal risk carried out by local experts	LOE 4/GOR D, SOA 100%

(continued)

Table 2 Continued

Drug	Studies (type and number)	Pregnancy exposures, per trimester	Live births[a]	Spontaneous miscarriages/ total pregnancy outcomes[a]	Pregnancy duration/ birthweight[a]	Major malformations/total births[a]	Recommendation	Level of evidence/ grade of recommendation
CSA	4 cc [13, 15, 72, 73] 5 ct [19, 23, 24, 27, 102] 3 cs [34, 79, 106]	98, first ⩾68, second/ third ⩾73	85	1/69	Possible trend towards shorter pregnancy duration [23, 34, 73, 106] and LBW [15, 23, 106]	2/26 (7.69%) Data confounded by concomitant AZA/MMF exposure	CSA is compatible throughout pregnancy at the lowest effective dose with suggested monitoring of maternal blood pressure, renal function, blood glucose and drug levels	LOE 1/GOR B, SOA 100%
Tac	3 ct [23, 24, 168] 1 cs [32] 2 cr [40, 53]	26, NR	16	NS	Insufficient data to confirm lack of a significant adverse effect[c] [23]	No data from case series (n > 5) to add to previous consensus	Tacrolimus is compatible throughout pregnancy at the lowest effective dose with suggested monitoring of maternal blood pressure, renal function, blood glucose and drug levels	LOE 2−/GOR D, SOA 99.5%
CYC	1 cs [35] 4 cr [39, 47, 108, 109]	9, first ⩾6, second/ third ⩾2	6	2/5	No effect on pregnancy duration in small case series (n = 5) [35], otherwise only case report data available	0/3 Remainder are case report data insufficient to identify an effect on malformation rate	CYC is a known teratogen and gonadotoxic, 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	LOE 2/GOR C, SOA 100%
MMF	2 ct [23, 27]	90, first ⩾82, second/ third ⩾61	34	15/39	Evidence of reduced pregnancy duration and birthweight	9/23 (39.1%) in case series	MMF remains contraindicated during pregnancy and should not be given to women who are planning pregnancy	LOE 2−/GOR D, SOA 100%
	3 cs [32, 160, 176] 12 cr [42, 45, 49, 50, 53, 177–182]					18/34 live births in all papers including case reports	In view of enterohepatic recirculation and prolonged half-life, treatment with MMF should be stopped at least 6 weeks before a planned pregnancy	LOE 3/GOR D, SOA 100%
IVIG	1 Cochr [8] 1 cc [184] 10 ct [25, 64, 65, 70, 104, 185–189] 1 cs [29] 3 cr [46, 125, 190]	336, first ⩾13, second/ third ⩾77	191	10/158[d]	No significant adverse effect noted	22/101 (22.8%)[d]	IVIG is compatible with pregnancy	LOE 1++/GOR A, SOA 100%

All studies were included that provided some qualitative or quantitative information on the safety of the relevant drug in pregnancy. Numerical outcome data could only be collated from papers where the relevant outcome was clearly quantified. Details of how numerical data shown in this table were derived are available in the appendix on the derivation of summary data. [a]Columns only include data from papers with n > 5, but note selection bias and publication bias cannot be excluded entirely. [b]Many studies confounded by concomitant immunosuppressive use, particularly MMF. [c]Average pregnancy duration 37 weeks in largest cohort (n = 9) but included three premature deliveries, one intrauterine growth restriction and one small for gestational age. [d]Confounded by high-risk pregnancies treated with IVIG. cc: case–control; Cochr: Cochrane review; cs: case series; CS: corticosteroids; cr: case report; ct: cohort; GOR: grade of recommendation; rct: randomized controlled trial; LOE: level of evidence; NR: not reported; NS: not stated; Pred: prednisolone; sr: systematic review; SOA; strength of agreement; tac: tacrolimus.

Table 3 Summary of maternal exposure to biologics

Drug	Studies included (type and number)	Pregnancy exposures, per trimester[a]	Live births reported[a]	Spontaneous miscarriages/ total pregnancies[a]	Pregnancy duration/ birthweight[a]	Major malformations/ total births[a]	Recommendation	Level of evidence/grade of recommendation
Anti-TNF (combined data for all licenced drugs)	See individual drugs below, plus 2 ct [210, 211]	706, first ⩾349,	534	64/474	No significant adverse effect noted	56/428 (13.08%)	See individual drugs below	LOE 2−/GOR D, SOA 97.9%
	1 cs [212]	second/third ⩾252				Overall no increase in rate of major malformations attributable to drug	Limited evidence shows that CZP is compatible with all three trimesters of pregnancy and has reduced placental transfer compared with other TNFis	LOE 4/GOR D, SOA 97.9%
	1cc [129]						There is no evidence upon which to recommend GOL, but it is unlikely to be harmful in the first trimester	
Infliximab	5 ct [102, 193–196] 8 cs [130, 197–203]	265, first ⩾91, second/third ⩾92	223	8/104	No significant adverse effect noted	0/76 in two cohort studies and four case series [194, 195, 197, 199, 201, 203]	IFX may be continued until 16 weeks	LOE 2−/GOR D, SOA 98.9%
	1 cr [204]					Overall, no increase in rate of major malformations attributable to drug	To ensure low/no levels of drug in cord blood at delivery, IFX should be stopped at 16 weeks because of a theoretical increased infection risk in newborns. If these drugs are continued later in pregnancy to treat active disease then live vaccines should be avoided in the infant until 7 months of age	LOE 3/GOR D, SOA 98.4%

(continued)

Table 3 Continued

Drug	Studies included (type and number)	Pregnancy exposures, per trimester[a]	Live births reported[a]	Spontaneous miscarriages/ total pregnancies[a]	Pregnancy duration/ birthweight[a]	Major malformations/ total births[a]	Recommendation	Level of evidence/grade of recommendation
Etanercept	3 ct [20, 102, 193], 3 cs [33, 199, 205] 4 cr [41, 44, 206, 207]	100, first ⩾36, second/third ⩾18	31	5/32	No significant adverse effect noted overall	0/44 in one cohort study and one case series [20, 199] Overall, no increase in rate of major malformations attributable to drug	ETA and ADA may be continued until the end of the second trimester To ensure low/no levels of drug in cord blood at delivery ETA should be avoided in the third trimester because of a theoretical increased infection risk in newborns. If these drugs are continued later in pregnancy to treat active disease then live vaccines should be avoided in the infant until 7 months of age	LOE 2−/GOR D, SOA 98.9% LOE 3/GOR D, SOA 98.4%
Adalimumab	4 ct [20, 102, 188, 194], 5 cs [32, 199, 201–203] 3 cr [204, 208, 209]	89, first ⩾41, second/third ⩾39	74	2/71	No significant adverse effect noted overall	2/66 (3.03%) in two cohort studies and two case series [188, 194, 201, 203] Overall no increase in the rate of major malformations attributable to drug	ADA may be continued until the end of the second trimester To ensure low/no levels of drug in cord blood at delivery ADA should be avoided in the third trimester because of a theoretical increased infection risk in newborns. If these drugs are continued later in pregnancy to treat active disease then live vaccines should be avoided in the infant until 7 months of age	LOE 2−/GOR D, SOA 98.9% LOE 3/GOR D, SOA 98.4%
Rituximab	3 ct [102, 218, 219] 1 cs [220] 4 cr [221–224]	173, first trimester ⩾ 4, second/third trimester ⩾1	109	35/166	No significant adverse effect noted	5/88 (5.68%) Overall, no increase in rate of major malformations attributable to drug	There remains insufficient evidence to be confident that RTX is compatible with pregnancy and it should be stopped 6 months before conception. Limited evidence has not shown RTX to be teratogenic and only second-/third-trimester exposure is associated with neonatal B cell depletion. Therefore, unintentional RTX exposure early in the first trimester is unlikely to be harmful	LOE 2−/GOR D, SOA 97.9%

(continued)

Table 3 Continued

Drug	Studies included (type and number)	Pregnancy exposures, per trimester[a]	Live births reported[a]	Spontaneous miscarriages/ total pregnancies[a]	Pregnancy duration/ birthweight[a]	Major malformations/ total births[a]	Recommendation	Level of evidence/grade of recommendation
Tocilizumab	No full papers (one relevant abstract [226] excluded from systematic search)	33, abstract data only	Of 31 known outcomes, 11 live births	Of 31 known outcomes, 13 elective terminations, 7 spontaneous abortions	NR	0/11 live births in this small abstract series	There are insufficient data and TCZ should be stopped at least 3 months pre-conception, but unintentional exposure early in the first trimester is unlikely to be harmful	LOE 3/GOR D, SOA 96.8%
Anakinra	1 ct [102] 1 cs [228] 1 cr [229]	5, first $\geqslant$3, second/third $\geqslant$4	3	NR	No adverse effect in case series and case report (n = 3)	NR	There is limited evidence on which to base a recommendation for anakinra in pregnancy, but unintentional exposure in the first trimester is unlikely to be harmful	LOE 2−/GOR D, SOA 96.8%
Abatacept	1 cs [132] 1 cr [224]	3	1	1/3 and 1 elective termination	Limited data, case report of one full-term delivery[224]	Limited data, case report of a live birth had no malformations	There are insufficient data to recommend ABA in pregnancy, but unintentional exposure early in the first trimester is unlikely to be harmful	LOE 3/GOR D, SOA 98.9%
Belimumab	No papers included in the search, data described in review and abstracts						There are insufficient data to recommend BEL in pregnancy, but unintentional exposure early in the first trimester is unlikely to be harmful	LOE 3/GOR D, SOA 100%

All studies were included that provided some qualitative or quantitative information on the safety of the relevant drug in pregnancy. Numerical outcome data could only be collated from papers where the relevant outcome was clearly quantified. Details of how numerical data shown in this table were derived are available in the appendix on the derivation of summary data. [a]Columns only include data from papers with n > 5, but note selection bias and publication bias cannot be excluded entirely. ADA: adalimumab; cc: case–control; Cochr: Cochrane review; cr: case report; cs: case series; ct: cohort; ETA: etanercept; GOR: grade of recommendation; IFX: infliximab; LOE: level of evidence; NR: not reported; ns: not stated; rct: randomized controlled trial; RTX: rituximab; SOA: strength of agreement sr: systematic review; TNF: tumour necrosis factor.

Table 4 Pregnancy outcomes after paternal exposure

Drug	Studies included (type and number)	Pregnancy Exposures	Live births reported	Spontaneous miscarriages	Major malformations	Recommendation	Level of evidence/ grade of recommendation
HCQ	1 ct, [20], 1 cs [116]	13	NS	No increase	No increase	Based on maternal compatibility and limited paternal data, men should not be discouraged from taking HCQ while trying to conceive	LOE 2−/GOR D, SOA 98.9%
CS	4 ct, [20, 112–114], 2cs [115, 116]	2127[a]	NS	No increase	No increase	Prednisolone is compatible with paternal exposure	LOE 2+/GOR D, SOA 98.9%
SSZ	3 ct [20, 114, [146], 1 cc [117]	237	NS	No increase	No increase	Men who take SSZ may have reduced fertility. Conception may be enhanced by stopping SSZ for 3 months prior to conception but there is little evidence to suggest that this action is necessary unless conception is delayed >12 months when other causes of infertility should be considered as well	LOE 3/GOR D, SOA 97.4%
LEF	1 ct [20], 1 cr [152]	2	NS	No increase	No increase	Based on very limited evidence LEF may be compatible with paternal exposure but further studies to confirm this compatibility are warranted	LOE 4/GOR D, SOA 98.9%
AZA	6 ct, [20, 112–114, 164, 165], 1cc [117], 2cs [115, 116]	602[b]	NS	No increase	No increase	AZA is compatible with paternal exposure	LOE 2+/GOR D, SOA 100%
MTX	4 ct, [20, 112, 114, 138]3 cs [116, 118] [116], 1cr [139]	263	NS	No increase	No increase	Based on limited evidence, low-dose MTX may be compatible with paternal exposure	LOE 2+/GOR D, SOA 95.8%
CSA	2 ct [113] [167], 2 cs [115, 118]	254[b]	NS	No increase	No increase	Based on limited evidence CSA is compatible with paternal exposure	LOE 2−/GOR D, SOA 98.9%
Tacrolimus	3 ct [113, 167, 171]	41[b]	NS	No increase	No increase	Based on limited evidence tacrolimus is compatible with paternal exposure	LOE 2−/GOR D, SOA 98.4%
MMF	3 cs [113, 167, 183]	72	NS	No increase	No increase	Based on very limited evidence MMF is compatible with paternal exposure but further studies to confirm this compatibility are warranted.	LOE 2−/GOR D, SOA 98.9%
IFX, ETA, ADA	5 ct [112, 20, 196, 146, 215], 2 cs [116, 118], 2 cr [139, 216], 1 cc [117]	131	NS	No increase	No increase	Based on limited evidence IFX, ETA and ADA are compatible with paternal exposure	LOE 2−/GOR D, SOA 98.9%
RTX	1 ct [218]	11	8[b]	2	0	Based on limited evidence RTX is compatible with paternal exposure	LOE 2−/GOR D, SOA 98.4%

Where possible, the number of births and pregnancy outcomes related to individual drug exposures is reported. Most reports are from cohort studies examining multiple drug exposure outcomes, from which the number of specific outcomes could not be extracted, but in which no overall increase in adverse outcomes compared with the general population was reported. Details of how numerical data shown in this table were derived are available in the appendix on the derivation of summary data. [a]Majority prednisolone exposures. [b]Minimum number of pregnancy exposures to drug; additional exposures described but could not be separated from grouped study data. [c]One twin pregnancy, two pregnancies ongoing at time of reporting. ADA: adalimumab; cc: case–control; cr: case report; cs: case series; CS: corticosteroids; ct: cohort; ETA: etanercept; GOR: grade of recommendation; IFX: infliximab; LOE: level of evidence; ns: not stated; RTX: rituximab; SOA: strength of agreement.

outcomes, or treatment of maternal autoantibody-mediated cardiomyopathy [71]. The evidence is also reassuring with regards to cleft palate: two instances of cleft palate were reported from 82 pregnancies, but in neither case was the anomaly attributed to steroid exposure [12, 24]. Furthermore, 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 [106]. Foetal loss in studies of prednisolone and fluorinated steroids was attributed to underlying disease rather than steroid therapy, such as in APS [38] and complete atrioventricular (AV) block [112].

There were few breastfeeding studies on which to base conclusions. An analysis of 320 milk samples from 46 mothers identified a significant delay in the onset of breastfeeding, which may have been compounded by betamethasone exposure in extremely preterm babies [95]. The nursing infant receives only 10 μg/kg even at a maternal prednisolone dose of 80 mg/day [2], ensuring low prednisolone exposure to breastfed infants, although it would seem prudent to restrict the maternal dosage to the minimum possible.

In long-term follow-up studies, no adverse events were reported after prednisolone exposure in pregnancy. In particular, no evidence of immune dysfunction was found 12 months post-partum [14]. Two systematic reviews evaluating the effects of prenatal exposure to fluorinated steroids in mothers at risk of preterm delivery from 20 different studies reported neurosensory disability in 139 of 6811 (2%) preterm deliveries ranging from 24 to 35 weeks duration [56, 84]. Although there were no control data for comparison in these studies, early childhood follow-up from four studies showed no substantive differences in children exposed to repeat prenatal corticosteroids compared with unexposed children for survival or neurosensory disability at 18 months–2 years corrected age [56, 64, 84, 100]. A recent cohort study [100] showed no adverse effect on psychological health in the long-term, but a possible impact on aspects of executive functioning.

Paternal exposure

Four cohort studies [21, 113–115] and two case series [116, 117] reported on outcomes from pregnancies (at least n = 2127) after paternal exposure to prednisolone and a case–control study [118] and a case series [119] reported on outcomes from pregnancies (n = 4) 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.

Recommendations for corticosteroids in pregnancy and breastfeeding

(i) Prednisolone is compatible with each trimester of pregnancy and is the preferred corticosteroid in the treatment of maternal rheumatologic disease in pregnancy (LOE 1++, GOR A, SOA 100%).
(ii) Prednisolone is compatible with breastfeeding (LOE 2−, GOR D, SOA 98.9%).
(iii) Prednisolone is compatible with paternal exposure (LOE 2+, GOR D, SOA 98.9%).
(iv) Methylprednisolone has similar rates of placental transfer to prednisolone with equivalent anti-inflammatory effects at 80% of the prednisolone dose and would therefore be expected to be compatible with pregnancy, breastfeeding and paternal exposure (LOE 4, GOR D, SOA 93.7%).

Antimalarials

The previous review of several hundred pregnancies exposed to HCQ did not find any adverse pregnancy outcomes and recommended HCQ as the antimalarial of choice in women planning pregnancy and to be compatible with pregnancy and breastfeeding [2]. We identified an additional 23 studies—2 systematic reviews [120, 121], 2 case–controls [14, 104], 10 cohort [17, 20, 21, 23, 26, 103, 105, 122–124], 3 case series [31, 80, 125] and 6 case reports [43, 44, 46, 52, 126, 127]—providing further information on 810 pregnancy exposures to HCQ. No new information was found relating to chloroquine. Many of these studies were confounded by primarily reporting pregnancy outcomes in patients with SLE treated with other immunosuppressive agents, particularly MMF, and their utility in anti-Ro/La-positive patients to prevent recurrence of congenital heart block (CHB). Despite these limitations, there were no appreciable effects of HCQ on pregnancy duration or birthweight in the largest studies. Adverse effects on gestation were considered to be related to underlying disease {average gestation 32–33 weeks in one cohort study (n = 40) [105]}. In three other large cohort studies the average gestation was >37 weeks in 156 pregnancies with corresponding average birthweights >2.5 kg [20, 23, 124]. No specific pattern of congenital malformations was observed in association with HCQ exposure. A total of 14 of 192 (7.3%) first trimester miscarriages were reported.

One study followed 15 children for up to 12 months post-partum and found no differences in immune function in terms of absolute lymphocyte count, percentage of B and T lymphocytes and immunoglobulin production compared with women with rheumatic diseases not exposed to drugs in pregnancy [14]. Overall, these studies included relatively large numbers of patients, with generally good outcomes except in case reports. There were no new studies published in the time period of our search on outcomes of infants exposed to HCQ in breastfeeding. Given that the half-life of HCQ is >40 days [128], all infants exposed to HCQ throughout pregnancy will also have been exposed during breastfeeding, and there is no evidence that this exposure is harmful. Case reports identified in the previous consensus found that when breastfeeding is continued, <1% of the maternal dose of HCQ was found in breast milk [2].

A study published after our final search, of 194 first-trimester exposures to HCQ did not identify a significant increase in the risk of congenital malformations, foetal death or neonatal complications in pregnancies of women with chronic autoimmune disease compared

with those who received HCQ before but not during pregnancy [128].

Paternal exposure

A cohort study [20] and a case series [117] reported on outcomes from 13 pregnancies after paternal exposure to HCQ. In this small number of exposures, no increased risk of adverse foetal outcomes was observed.

Recommendations for HCQ in pregnancy and breastfeeding

(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 (LOE 1++, GOR A, SOA 100%).
(ii) HCQ is compatible with breastfeeding (LOE 4, GOR D, SOA 98.9%).
(iii) Based on maternal compatibility and limited paternal data, men should not be discouraged from taking HCQ while trying to conceive (LOE 2−, GOR D, SOA 98.9%).

DMARDs and immunosuppressive therapies

MTX

MTX is contraindicated in pregnancy and recommended to be stopped 3 months in advance of conception [2]. The UKTIS considers MTX risk in pregnancy to be dependent on its use at high (>20 mg/week) or low (⩽20 mg/week) dosage. In general, the use 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, for example, >500 mg/m^2, or as an abortifacient at 50 mg/m^2. The UKTIS reports that teratogenic insult caused by MTX has not been observed at doses of < 10 mg/week in pregnancy, although the number of case reports from which these data were taken remains too small to identify a safe weekly dose of MTX. Based on current information, the UKTIS found it difficult to draw conclusions about the exact risks high-dose MTX administration poses to a developing foetus. In a significant proportion of the reports, even though high doses were administered in the first trimester, infants were born without evidence of congenital malformations. However, reports exist that suggest an association with first-trimester MTX exposure and a consistent pattern of malformation (MTX embryopathy) in both newborn infants and spontaneously aborted foetuses.

Since the previous consensus, we identified MTX exposure predominantly during the first trimester of pregnancy in 27 pregnancies from three cohort studies [21, 22, 103], one case–control study [130], one case series [131] and five case reports [132–136]. Confounding factors included concomitant treatment with other DMARDs (such as LEF and MMF), steroids and anti-TNF therapies. Pregnancy duration was reported in five patients with SLE, of whom three [131, 132, 136] were term (>39 weeks) while two were premature at 31 and 34 weeks with corresponding LBWs of 1.7 and 2.2 kg [134, 135].

No maternal complications were reported. A total of 10 live births were reported for MTX (dose not stated) used in the first trimester of pregnancy [22, 131, 132, 134–136]. There were four cases with major anomalies, including ventricular septal defect and hydronephrosis [132, 135] and two other cases of major malformations described in patients with SLE taking concomitant MMF [134, 135]. Five minor malformations were described, but no significant patterns emerged. Two first-trimester spontaneous pregnancy losses occurred in patients with RA on concomitant therapy with IFX and abatacept (ABA). There were no studies of breastfeeding. Two cases reported long-term follow-up of 2.8 and 14 months, respectively, in which both had long-term complications of semilobar holoprosencephaly, tracheostomy and requirement for antiepileptic therapy [134, 135]. There were no studies included in our search examining the safety of breastfeeding on MTX.

Three studies published after our final search date provide further information on 367 pregnancies exposed to MTX. Analysis of 23 first-trimester exposures to low-dose MTX identified from three US 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 [129]. Examination of data from the National Birth Defects Prevention Study, a US case–control study of major birth defects, identified 4 of 10 113 (0.04%) mothers of foetuses or infants without major birth defects had been exposed to MTX compared with 16 of 27 623 (0.06%) mothers of live-born infants with a major birth defect who had been exposed to MTX [137]. The dose of MTX was not reported, but indications included a neoplasm of endocrine glands, so it was presumably of high dose in at least one case. Of the 16 cases with major birth defects, 15 were exposed from 3 months pre-conception to the end of the first trimester. A large prospective observational multicentre cohort study of 324 pregnancies exposed to MTX found an increase in cumulative incidence of spontaneous abortion (42.5%) and major congenital anomalies (6.6%) among 188 pregnancies exposed to a median dose of 10 mg/week MTX a median of 4.3 weeks after conception [138]. This difference reached statistical significance when compared with a cohort of women without autoimmune diseases, but not when compared with a disease-matched cohort. In contrast, an increased risk of miscarriage or major congenital anomaly was not found in 136 pregnancies exposed to a median dose of 15 mg/week of MTX that was stopped 3 months pre-conception. Therefore, the conclusion of this study was that a 3-month MTX-free interval prior to conception might not be required.

Paternal exposure

MTX does not impair male fertility [2]. Four cohort [21, 113, 115, 139], three case series [117, 119] and a case report [140] described outcomes from 263 pregnancies after paternal exposure to predominantly low-dose MTX. Overall, the quality of these studies was low, with information

lacking from several studies primarily looking at the safety of other medications. However, a large study published after our final search date of 113 pregnancies after paternal exposure to low-dose MTX did not identify an increased risk of adverse foetal outcomes compared with 412 non-exposed pregnancies [139].

Recommendations for MTX in pregnancy and breastfeeding

(i) MTX at any dose should be avoided in pregnancy and stopped 3 months in advance of conception. Recent studies support a shorter drug-free interval of low-dose (⩽20 mg/week) MTX, but further evidence is required to alter previous recommendations. (LOE 2−, GOR D, SOA 100%).
(ii) In women treated with low-dose MTX within 3 months prior to conception, folate supplementation (5 mg/day) should be continued prior to and throughout pregnancy (LOE 1, GOR B, SOA 98.4%).
(iii) In the case of accidental pregnancy on low-dose MTX, the drug should be stopped immediately, folate supplementation (5 mg/day) continued and a careful evaluation of foetal risk carried out by local experts (LOE 4, GOR D, SOA 100%).
(iv) It is not known whether once-weekly administration of MTX has any significance for the nursing child, given the minute amounts excreted into breast milk. MTX cannot be recommended in breastfeeding because of theoretical risks and insufficient data on outcomes (LOE 4, GOR D, SOA 100%).
(v) Based on limited evidence, low-dose MTX may be compatible with paternal exposure (LOE 2+, GOR D, SOA 95.8%).

SSZ

The previous consensus determined that SSZ is compatible with pregnancy and breastfeeding and can be continued with adequate folate supplementation (5 mg/day). [2] This recommendation was based on six case–control/population studies, which did not find any adverse effects of SSZ on 675 pregnancy outcomes in patients with IBD, where it is used at a maintenance dose of 2–3 g/day and 4–8 g/day during disease flares. In addition, it was recommended that maternal doses of SSZ should not exceed 2 g/day based on a case report of neutropenia in a newborn infant [141]. The use of SSZ in the management of IBD in pregnancy is well established and was recently reviewed by Vermeire *et al.* [142].

We identified three additional cohort studies [21, 23, 103], a case series [31] and two case reports [127, 143] on SSZ exposure in 178 pregnancies in patients with RA, osteoporosis and AS. These studies contained limited information relating to miscarriage rates, pregnancy duration, birthweight or malformation rates, but overall 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 breastfeeding. Minimal amounts of SSZ are expressed in breast milk 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 [2].

Paternal exposure

Male fertility may be affected by SSZ. Oligospermia, reduced motility as well as an increased proportion of abnormal sperm forms have been noted in rats and men taking SSZ and is related to the sulphapyridine moiety of the drug [144]. In addition, a study of the effects of SSZ on 194 paternal exposures after diagnosis of IBD found that of 42 men who experienced a delay of >12 months in achieving conception, more than half (n = 22) reported taking SSZ [145]. This risk was potentially linked to the antagonistic effects of SSZ on folic acid metabolism and relative folic acid deficiency, which is reduced by concomitant folic acid supplementation [146]. Therefore the 2006 consensus recommended that patients wishing to father a child should be counselled to discontinue or not commence this drug for a minimum period of 3 months prior to trying for a baby, as the maturation of sperm takes 3 months [2].

We identified three cohort [21, 115, 147] and one case–control study [118] reporting on outcomes from 237 pregnancies after paternal exposure to SSZ. Overall, no increased risk of adverse foetal outcomes was observed. However, the quality of evidence from these studies was low, with a lack of information on the medical history of fathers, concomitant therapy, compliance with prescribed medication, early first-trimester miscarriages and fertility.

Recommendations for SSZ in pregnancy and breastfeeding

(i) SSZ with folate supplementation (5 mg/day) is compatible throughout pregnancy, and folic acid should be prescribed to women taking SSZ who are trying to conceive (LOE 2+, GOR C, SOA 100%).
(ii) SSZ is compatible with breastfeeding in healthy, full-term infants (LOE 4, GOR D, SOA 100%).
(iii) Men who take SSZ may have reduced fertility. Conception may be enhanced by stopping SSZ for 3 months prior to conception, but there is little evidence to suggest that this action is necessary unless conception is delayed >12 months when other causes of infertility should be considered as well (LOE 3, GOR D, SOA 97.4%).

LEF

Initial recommendations [2, 3] were that LEF is contraindicated during pregnancy and breastfeeding and should be stopped in women planning pregnancy and a cholestyramine washout given to enhance elimination until plasma levels of LEF are undetectable (evidence level IV). An additional three cohort studies [22, 103, 148] and four case reports [149–152] (two cases) were identified with 111 pregnancies exposed to LEF. At least one case

report was confounded by concomitant MTX exposure [151] and cholestyramine washout was given in two cohort studies [22, 148]. Two cohort studies reported an average pregnancy duration of ~37 weeks and an average birthweight >3.1 kg [22, 148]. In the control groups, the reported average pregnancy duration was 38 weeks and the average birthweight was > 3.4 kg. Three case reports reported preterm births in one twin at 29 weeks and two singleton pregnancies [149–151]. Two cases reported normal birthweights [151, 152] and there was one case of low (2.5 kg) birthweight [152].

One prospective controlled study [148] did not show a significant increase in adverse pregnancy outcomes in 64 women on LEF, the majority of whom stopped the drug in the first trimester and were treated with cholestyramine, compared with control pregnancies (n = 108 pregnant women with RA not on LEF and n = 78 healthy controls). In particular, the number of major congenital anomalies (the definition of which fulfilled that for EUROCAT major anomalies) was not increased in the LEF-exposed group. Minor anomalies were defined as structural defects of no cosmetic or functional importance, occurring in <4% of the general population. Examples of these frequently subtle minor structural defects include a missing crease on one or more of the digits, a broad nasal bridge, protruding earlobes or a relatively indistinct philtrum of the upper lip, thus they do not all meet EUROCAT definitions of minor anomalies. Reassuringly, despite the finding of a higher proportion of children in the LEF-exposed group with minor anomalies (n = 51 in total) than in the two control groups, this difference did not reach statistical significance (P = 0.1) and no specific pattern of three or more anomalies was found in LEF-exposed children.

A later smaller cohort study comparing 16 women exposed to LEF during pregnancy with 29 women exposed to LEF <2 years prior to pregnancy [22] found major congenital anomalies in two infants born to LEF-exposed pregnancies and none in those exposed prior to pregnancy. None of these specific defects were reported in the previous cohort study [148]. In addition, there was a potential known alternative aetiology (including spontaneous death of a twin and maternal disease) unrelated to LEF exposure in each case. Minor anomalies were recorded in the same way as the previous cohort study and 35 infants were examined. The frequency of infants with at least three minor anomalies was similar in the two groups, involving seven (50%) infants examined in the during-pregnancy exposure group and nine (42.9%) infants examined in the pre-conception exposure group. No specific pattern of abnormalities was observed and the spontaneous abortion rate was within the normal range seen in the general population [22]. There were no data on breastfeeding.

Paternal exposure

A cohort [21] and case report [153] described outcomes from two pregnancies after paternal exposure to LEF within 3 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.

Recommendations for LEF in pregnancy and breastfeeding

(i) Based on limited evidence, LEF may not be a human teratogen, but there remains insufficient evidence to change previous recommendations and LEF is not the DMARD of choice in women planning pregnancy (LOE 2+, GOR C, SOA 100%).
(ii) Women on LEF considering pregnancy should stop the drug and undergo cholestyramine washout before switching to an alternative medication compatible with pregnancy (LOE 2+, GOR C, SOA 100%).
(iii) There is no human evidence of increased congenital abnormalities on LEF if washout is given. Therefore, if accidental conception occurs on LEF, the drug should be stopped immediately and cholestyramine washout given until plasma levels are undetectable (LOE 2+, GOR C, SOA 98.9%).
(iv) No data exist on excretion into breast milk. Therefore, breastfeeding is not recommended (LOE 4, GOR D, SOA 100%).
(v) Based on very limited evidence, LEF may be compatible with paternal exposure, but further studies to confirm this compatibility are warranted (LOE 4, GOR D, SOA 98.9%).

AZA

The previous consensus reported on seven studies with 405 pregnancies with maternal exposure to AZA or its active metabolite 6-mercaptopurine (6-MP) and concluded that AZA is compatible with pregnancy, but there is a lack of consensus on its use in breastfeeding given a theoretical risk of immunosuppression, carcinogenesis and growth restriction in the infant [2]. Two of these seven studies noted a relationship between the dose of AZA and birth abnormalities, as well as depressed haematopoiesis in pregnancies whose mothers were treated with >2 mg/kg AZA daily [154, 155].

An additional 28 studies were identified relating to the use of AZA in pregnancy and breastfeeding. Of these studies, 24 included pregnancy outcome data [10, 16, 19–21, 24, 25, 28, 31, 33, 36, 41, 52, 73, 103, 123, 130, 131, 156–161]. Only four of these papers directly addressed the safety of thiopurines in pregnancy [130, 156, 158, 159]. Four papers specifically analysed the use of AZA in breastfeeding [35, 162–164].

Studies relating to pregnancy included 5 case–control studies [16, 73, 130, 156, 157], 10 cohort studies [19–21, 24, 25, 28, 103, 123, 158, 159], 1 systematic review [10], 6 case series [31, 33, 36, 131, 160, 161] and 2 case reports [41, 52]. Studies examining AZA in breastfeeding included one case series [35] and three cohort studies [162–164]. The studies of 738 AZA-exposed pregnancies included a wide range of diagnoses and concomitant medications, compared with 1121 disease and 667 healthy control

pregnancies. The average pregnancy duration recorded from 283 pregnancies exposed to AZA ranged from 35 to 39 weeks [16, 20, 24, 31, 36, 41, 52, 131, 156, 158, 160, 161], while the average pregnancy duration for 403 control pregnancies ranged from 36 to 39.6 weeks [16, 33, 156, 158, 160]. The average birthweight for 321 AZA-exposed pregnancies ranged from 2.2 [41] to 3.2 kg [157], whereas average weights for 389 control pregnancies ranged from 3 [33] to 3.5 kg [16]. Reporting of maternal complications in these studies was limited and no firm conclusions can be drawn due to the likelihood of confounding of pregnancy outcomes by underlying disease- and pregnancy-related complications.

In 238 AZA-exposed pregnancies [10, 25, 36, 123, 156, 158, 161], 13 major malformations were recorded. Overall, there was no indication of an increased rate or specific phenotype of congenital malformations due to AZA above the background population. In addition, there was no indication of increased first-trimester losses among AZA-exposed pregnancies compared with controls. Two second-/third-trimester losses were reported in 5 AZA- and corticosteroid-exposed pregnancies in a larger cohort study of mothers with pemphigus vulgaris, compared with none in 405 control pregnancies, but these deaths were attributed to foetal pemphigus in one pregnancy and CMV infection in the other [10].

Four studies directly addressed the safety of AZA in pregnancy. One study followed 30 children exposed to thiopurines *in utero* for up to 6 years post-partum and found no effect on long-term development or immune function [159]. Another study of 189 women exposed to AZA in pregnancy compared with 230 drug-free controls concluded that there was no increase in birth defects, but exposure was associated with lower birthweights and prematurity [156]. A study of 19 births exposed to AZA compared with 74 controls did not detect any increase in congenital anomalies and did not find any association with increased risk of preterm birth, LBW at term or adverse neonatal outcomes [158]. A study of 187 IBD pregnancies exposed to thiopurines alone compared with 29 exposed to TNF-α inhibitors (TNFis), 37 exposed to both and 318 unexposed disease controls found that the use of thiopurines was associated with a favourable global pregnancy outcome [130].

A total of 26 infants breastfed by mothers on AZA or its active metabolite 6-MP were identified. One study of eight AZA-exposed mothers found that 6-MP was predominantly excreted into breast milk within 4 h of maternal ingestion, and based on the maximum concentration measured, infant ingestion of 6-MP was $<$0.008 mg/kg/24 h [162]. An analysis of 31 breast milk samples from 10 AZA-exposed mothers revealed detectable concentrations of 6-MP at 3 and 6 h after ingestion in 2 samples from a single infant but was undetectable in the other 29 samples [163]. Furthermore, 6-MP and its metabolites—6-thioguanine nucleotides—were undetectable in neonatal blood and there were no clinical or haematological signs of immunosuppression in the 10 neonates studied [163]. In a study of four women treated with AZA during breastfeeding, 6-MP concentration measured in the milk of two mothers revealed an absolute relative infant dose $<$0.09% of the maternal weight-adjusted dose and no adverse events occurred in any of the four infants [35]. In a case series of four infants exposed to AZA in breast milk, neither 6-MP nor 6-thioguanine nucleotides was detected in any of the infants [164].

Paternal exposure

Six cohort studies [21, 113–115, 165, 166], a case–control study [118] and two case series [116, 117] reported on outcomes from 602 pregnancies after paternal exposure to AZA. Overall, no increased risk of adverse foetal outcomes was observed.

Recommendations for AZA in pregnancy and breastfeeding

(i) AZA is compatible throughout pregnancy at a daily dose not exceeding 2 mg/kg/day (LOE 2++, GOR B, SOA 100%).
(ii) AZA is compatible with breastfeeding. It may pass into breast milk at very low concentrations, but levels of active metabolites are undetectable in infants. Theoretical concerns of adverse effects in infants have not been confirmed in small studies, but long-term follow-up is lacking (LOE 2−, GOR D, SOA 99.5%).
(iii) AZA is compatible with paternal exposure (LOE 2+, GOR D, SOA 100%).

CSA

More than 800 human pregnancies exposed to CSA were reviewed in the previous consensus and it was considered compatible with pregnancy at the lowest effective dose with monitoring of blood pressure and renal function [2]. These recommendations were based on evidence of compatibility mostly from pregnancies in transplant recipients treated with a maintenance dose of 2–6 mg/kg/day and reports of embryotoxicity in animal pregnancies at high dosages of 25–100 mg/kg/day.

A search from 2005 onwards identified an additional four case–control studies [14, 16, 73, 74], five cohort studies [20, 24, 25, 28, 103], three case series [35, 80, 107] and a case report [167] (studying the effect of breastfeeding) of 98 pregnancies in patients with a variety of different diseases [including IBD, solid organ transplantation and autoimmune rheumatic disease (ARD)] and multiple concomitant medications exposed to CSA at 2–6 mg/kg during pregnancy. Pregnancy duration was quantified in four studies (n = 23 pregnancies) and the average ranged from 35.3 to 38 weeks [24, 35, 74, 107]. The average birthweight was reported in exposed pregnancies in three studies as low (n = 1) [16], 2.3 kg (n = 11) [24] and 2.9 kg (n = 8) [107]. In contrast, an average birthweight of 3.5 kg (n = 80) [16] and 3.1 kg (n = 15) [14] was reported in control groups.

Multiple maternal complications and two stillbirths were described in 11 women on CSA after renal transplantation [24]. A second-/third-trimester foetal death occurred in a mother with protein S deficiency in a case series of eight

pregnancies in eight patients with ulcerative colitis [107]. Malformations were quantified in 26 pregnancies in two studies [28, 107] and two major malformations were reported, but these pregnancy outcomes were confounded by concomitant treatment with either AZA or MMF [28].

The previous consensus described findings from several case reports and case series that found small amounts of CSA in breast milk and almost universally undetectable blood levels in infants [2]. We found one further study specifically examining breastfeeding in a renal transplant recipient on 2.1 mg/kg/day CSA (as well as AZA 0.9 mg/kg and prednisolone) in whom subtherapeutic blood levels and lower levels in breast milk were detected at a mean milk to maternal blood concentration of 0.94, with undetectable blood levels in the infant [167]. No adverse effects during breastfeeding were reported in this study. Long-term follow-up of 10 infants exposed to CSA *in utero* revealed no complications at 11–14 months [14, 73, 80].

Paternal exposure

Two cohort studies [114, 168] and two case series [116, 119] reported on outcomes from at least 254 pregnancies after paternal exposure to CSA. Overall, the quality of these studies was low, but they did not identify an increased risk of adverse foetal outcomes.

Recommendations for CSA in pregnancy and breastfeeding

(i) CSA is compatible throughout pregnancy at the lowest effective dose with suggested monitoring of maternal blood pressure, renal function, blood glucose and drug levels. (LOE 1, GOR B, SOA 100%).

(ii) Mothers on CSA should not be discouraged from breastfeeding (LOE 3, GOR D, SOA 100%).

(iii) Based on limited evidence, CSA is compatible with paternal exposure (LOE 2−, GOR D, SOA 98.9%).

Tacrolimus

Tacrolimus was considered compatible with pregnancy and breastfeeding in the previous consensus [2, 3]. An additional seven studies were identified. Six of these studies (three cohort studies [24, 25, 169], one case series [33] and two case reports [41, 54]) included 26 pregnancies exposed to tacrolimus, as well as one pharmacokinetics study of drug levels in the umbilical cord and breast milk [169]. One cohort study addressed tacrolimus in breastfeeding only [170]. The largest study [24] included women after renal transplantation, one reviewed patients treated for autoimmune hepatitis [25], one was a case report of a single patient with LN [41] and two studies addressed the effect of MMF where tacrolimus was used concomitantly in some pregnancies [33, 54]. There were complex confounding issues in all of these studies.

The average pregnancy duration from the largest cohort study (n = 9) was 37 weeks, but included three premature deliveries, one case of intra-uterine growth restriction and one small-for-gestational-age infant [24]. Three other studies of five pregnancies (concomitant MMF in four of the five cases) reported preterm deliveries of 30–35 weeks.

Maternal complications were considered to be related to maternal disease or concomitant medication. Three major congenital malformations were reported in two studies of MMF in pregnancy [33, 54]. In contrast, no major or minor malformations were reported in the remaining pregnancies reported following tacrolimus exposure. No spontaneous miscarriages were reported and one elective termination was carried out, where the pregnancy had concomitant MMF exposure. Overall, no increased risks were observed with exposure at conception or during pregnancy.

One study measured the mean umbilical cord venous plasma and unbound drug concentrations and found that they were approximately one-fifth of the respective maternal concentrations [169]. Infant exposure through breast milk was <0.3% of the mother's weight-adjusted dose in a single case in which tacrolimus pharmacokinetics was studied. A study [170] examining samples from 12 breastfed infants found that following delivery of babies exposed to tacrolimus *in utero*, blood levels of tacrolimus were not increased in breastfed compared with bottle-fed infants, with equal rates of elimination post-partum. The maximum estimated absorption from breast milk was 0.2% of the maternal weight-adjusted dose. Exposure to the drug during breastfeeding is relatively insignificant compared with exposure *in utero*, which has not been shown to be associated with any long-term adverse effects. A recent case series published after our final search reported the successful treatment of nine pregnant patients with LN, with no adverse effects on pregnancy duration or birthweight and no congenital abnormalities [171].

Paternal exposure

Three cohort studies [114, 168, 172] reported on outcomes from >120 pregnancies after paternal exposure to tacrolimus. Overall, the quality of these studies was low, but they did not identify an increased risk of adverse foetal outcomes.

Recommendations for tacrolimus in pregnancy and breastfeeding

(i) Tacrolimus is compatible throughout pregnancy at the lowest effective dose with suggested monitoring of maternal blood pressure, renal function, blood glucose and drug levels (LOE 2−, GOR D, SOA 99.5%).

(ii) Mothers on tacrolimus should not be discouraged from breastfeeding (LOE 3, GOR D, SOA 99.5%).

(iii) Based on limited evidence, tacrolimus is compatible with paternal exposure (LOE 2−, GOR D, SOA 98.4%).

CYC

CYC is a known human teratogen and is gonadotoxic in men and women [2]. In addition to a potential long-term impact on spermatogenesis (and hence fertility) in men

[173], there is evidence of male-mediated teratogencity from animal studies [174], although this has not been proven in humans [175]. An additional case series [36] and four case reports [40, 48, 109, 110] of predominantly first-trimester use of CYC in nine pregnancies of mothers with severe maternal disease (mostly acute renal failure) were identified in patients with SS (n = 3) and SLE (n = 6) on concomitant medication including HCQ, AZA and prednisolone.

In a case series (n = 5), the average pregnancy duration was 38 weeks [36], and in three case reports it was 27, 28 and 40 weeks. One preterm birth occurred at 28 weeks in a patient with a new diagnosis of acute renal failure and SS in the second trimester of pregnancy who was treated with CYC, prednisolone and haemodialysis [40]. Birthweights were recorded in case reports and were appropriate for age in two preterm births (1.1 kg at 27–28 weeks) [40, 110], while a term delivery (40 weeks) was growth restricted at 1.8 kg in an infant with Klippel–Feil syndrome [48].

No maternal complications of CYC were reported. These nine pregnancies ended in two first-trimester miscarriages, six healthy infants and one major congenital anomaly (Klippel–Feil syndrome). There were no breastfeeding studies. Follow-up to 87–90 months in four live births reported normal development in three children [36] and the single case of Klippel–Feil syndrome [48].

Paternal exposure

No further studies of paternal disease were identified.

Recommendations for CYC in pregnancy and breastfeeding

(i) CYC is a known teratogen and gonadotoxic, therefore it should only be considered in pregnancy in cases of severe life- or organ-threatening maternal disease when there is appreciable risk of maternal and foetal morbidity and mortality without this therapy (LOE 2, GOR C, SOA 100%).
(ii) There is no evidence to recommend the use of CYC in breastfeeding (LOE 4, GOR D, SOA 100%).
(iii) Paternal exposure to CYC is not recommended (LOE 4, GOR D, SOA 98.4%)

MMF

MMF is a known teratogen and is recommended to be stopped at least 6 weeks before a planned pregnancy [2, 3]. It is rapidly absorbed following oral administration and hydrolysed to form the active ingredient mycophenolic acid. 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 i.v. dose [176]. Therefore, MMF is advised to be stopped at least 6 weeks before conception.

An additional 2 cohort studies [24, 28], 3 case series [33, 161, 177] and 11 case reports [43, 46, 50, 51, 54, 178–183] including 90 pregnancies exposed to MMF were identified, mostly from renal transplant patients in whom there was concomitant exposure to prednisolone and tacrolimus. In the majority of cases, pregnancy duration was appreciably shortened to 29–33 weeks in two cases [43, 182] and 34–36 weeks in three cases [51, 54, 181] and one case series [33] and to preterm (<37 weeks) in one case series [177], with only four term (>37 weeks) deliveries [161, 177, 178, 180]. There was a corresponding increased risk of LBW, with two cases <1 kg [43, 50], three cases of 1–2.5 kg [54, 179, 181] and 2.5–3.0 kg in one case and one case series [33, 178].

Reported maternal complications included cases of anaemia, hypertension, pre-eclampsia, urinary tract infection, graft loss due to haemorrhagic shock, sepsis, eclampsia, premature rupture of membranes and preterm labour [28] and two lupus flares [51]. Major congenital malformations were reported in 18 of 34 live births and 2 elective terminations. Where the type of malformation was specified, 14 of 15 cases included malformations typical for the previously described MMF embryopathy (including cleft lip and/or palate, microtia with aural atresia, micrognathia and ocular anomalies).

There were no reported cases of spontaneous miscarriage. There were no breastfeeding data. The only reports of long-term follow-up described one case who was small for age with otherwise normal development [43] and in another study reporting on three of six exposed children where one was normal, one had hearing aids and one had motor and speech delays [33].

Paternal exposure

Three cohort studies [114, 168, 184] reported on outcomes from at least 72 pregnancies after paternal exposure to MMF. Overall, the quality of these studies was low, but they did not identify an increased risk of adverse foetal outcomes.

Recommendations for MMF in pregnancy and breastfeeding

(i) MMF remains contraindicated during pregnancy and should not be given to women who are planning pregnancy (LOE 2−, GOR D, SOA 100%).
(ii) In view of enterohepatic recirculation and prolonged half-life, treatment with MMF should be stopped at least 6 weeks before a planned pregnancy (LOE 3, GOR D, SOR 100%).
(iii) No data exist on excretion into breast milk; breastfeeding is therefore not recommended (LOE 4, GOR D, SOA 99.5%).
(iv) Based on very limited evidence, MMF is compatible with paternal exposure, but further studies to confirm this compatibility are warranted (LOE 2−, GOR D, SOA 98.9%).

IVIG

IVIG is compatible with pregnancy and breastfeeding [2, 3]. An additional 16 studies including 336 pregnancies exposed to IVIG were identified. The studies comprised 1 Cochrane review [9], 1 case–control study [185], 10 cohort studies [26, 65, 66, 71, 105, 186–190], 1 case

series [30] and 3 case reports [47, 126, 191]. These pregnancies were identified from studies of 409 women with ARD, including APS, SLE and SS, as well as 284 patients with other diagnoses (including 128 with asymptomatic anti-Ro/La antibody positivity). All but two studies examined IVIG therapy in APS or prevention of CHB in anti-Ro/La-positive mothers. None of the papers specifically addressed the safety of IVIG; eight studies examined strategies for the prevention of AV block in foetuses at high risk [26, 30, 65, 66, 71, 105, 126, 188] and eight other studies examined strategies for the management of recurrent spontaneous abortion in APS and subfertility/infertility [9, 47, 185–187, 189–191]. Concomitant drug therapy included heparin, dexamethasone or prednisolone in many studies.

A limited number of studies reported pregnancy duration and birthweight. In one study of 18 exposed pregnancies there were 3 preterm deliveries of <37 weeks and 4 of 18 were small for gestational age [26]. In six other studies (n = 58 exposed pregnancies) the average pregnancy duration was >36 weeks [47, 65, 66, 126, 185, 189]. In the remaining study (n = 17 pregnancies), the average gestation was 33–34 weeks [71]. Mean birthweights were recorded in six studies (n = 95) and ranged from 2.65 to 3.27 kg [47, 66, 126, 185, 189, 190]. Pregnancy outcomes for IVIG were confounded by the condition requiring treatment.

Twelve maternal complications were reported, including one case of pre-eclampsia occurring in a study of patients with APS and recurrent miscarriages, 43 of whom received IVIG [187]. A total of 23 major congenital malformations from 102 live births were reported [26, 30, 71, 126, 187, 188], largely in studies in which IVIG was used to treat CHB or foetal cardiomyopathy. In particular, 16 malformations listed under endomyocardial fibroelastosis occurred in a study of the use of IVIG and corticosteroids in the treatment of 20 maternal autoantibody-mediated cases of cardiomyopathy [71]. In addition, a case of DiGeorge syndrome occurred in a study of infertile mothers undergoing treatment with adalimumab, enoxaparin and/or corticosteroids depending on the immune profile, as well as IVIG [189]. Three first-trimester and two second-trimester pregnancy losses were recorded out of 43 IVIG exposures in a study of pregnancy outcome in patients positive for APS [187].

There were no studies of breastfeeding. Three studies described long-term follow-up of 34–42 months [66, 71, 126]. However, details are lacking except from one case of heart block in the Eliasson study, which also included eight neonatal deaths and was looking at the use of IVIG in foetal AV block.

The studies identified were focused on therapeutic efficacy rather than the safety of IVIG, hence all outcomes are confounded by use in patients with high-risk pregnancies. The number and type of maternal and foetal complications observed are compatible with known effects of the underlying maternal disease on pregnancy rather than being specific to IVIG. In particular, one small (n = 9) study found an improved outcome for foetuses treated with IVIG and steroids to treat maternal autoantibody-mediated cardiomyopathy [71]. The studies reviewed did not raise any new concerns to question the accepted safety of IVIG in pregnancy. None of the studies addressed the use of IVIG in breastfeeding or with paternal exposure.

Recommendations for IVIGin pregnancy and breastfeeding

(i) IVIG is compatible with pregnancy (LOE 1++, GOR A, SOA 100%).
(ii) IVIG is compatible with breastfeeding (LOE 4, GOR D, SOA 98.9%).
(iii) There is no evidence related to paternal exposure, but based on maternal compatibility, it is unlikely to be harmful (LOE 4, GOR D, SOA 98.9%).

Biologics

Biologic therapies are commonly used as second-line agents to treat various forms of ARD. 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 the majority of these biologic agents is required for their active placental transfer, which does not take place until the 16th week of pregnancy onwards. Due to the relative lack of evidence pertaining to biologics use for rheumatic disease while breastfeeding, five case series of biologics use for non-rheumatic disease while breastfeeding were also reviewed and included if relevant. Biologic drugs are often given alongside other DMARDs, and decisions regarding continuation of treatment should be made for each drug independently.

Anti-TNF-α drugs

There are five biologic agents that inhibit TNF-α that are currently licenced to treat ARD: etanercept (ETA), IFX, adalimumab (ADA), golimumab (GOL) and certolizumab pegol (CZP). Three of these drugs (IFX, 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 and CZP is an antigen binding fragment (Fab′) of a monoclonal anti-TNF-α antibody that lacks the Fc region of IgG1 and has been conjugated with polyethylene glycol. These drugs have different half-lives, bioavailability and rates of placental transfer that are relevant when considering their potential use in pregnancy.

The previous 2006–8 consensus recommendations advised avoidance of ETA, IFX and ADA in pregnancy and breastfeeding due to a lack of evidence rather than evidence of harm, and the 2010 BSR guidelines [192] (currently under revision) concur, unless the risks of stopping the treatment are perceived to be high. Further evidence has now accumulated predominantly from first-trimester exposure to these drugs, which do not cross the placenta until week 16 of pregnancy onwards. The majority of relevant studies show compatibility with pregnancy and a consensus statement considers anti-TNF-α drugs for treatment of IBD (IFX, ADA and CZP) to be low risk in the first and second trimester of pregnancy [192].

A search for publications from 2008 onwards (since the last consensus) identified 5 cohort studies [103, 194–197], 8 case series [131, 198–204] and 1 case report [205] of 265 IFX-exposed pregnancies; 3 cohort studies [21, 103, 194], 3 case series [34, 200, 206] and 4 case reports [42, 45, 207, 208] of 100 ETA-exposed pregnancies; 4 cohort [21, 103, 189, 195], 5 case series [33, 200, 202–204] and 3 case reports [205, 209, 210] of 89 ADA-exposed pregnancies; and a case series of 10 CZP-exposed pregnancies [204]. In addition, two cohort studies [211, 212], one case series [213] and one case–control study [130] reported combined outcomes from 201 pregnancies exposed to ETA, IFX, ADA and/or CZP. All of these studies examined TNFi use in patients with rheumatic disease or IBD. There remain no published studies of GOL in human pregnancy or breastfeeding.

These studies examined outcomes from 706 TNFi-exposed pregnancies of patients with predominantly IBD but also rheumatic disease and two studies of non-autoimmune-mediated recurrent spontaneous miscarriage [189, 211] compared with 399 disease and 170 healthy control pregnancies. At least 349 exposures occurred in the first trimester and 252 in the second trimester. There were multiple confounders of concomitant therapies (including MTX, LEF and MMF) and active inflammatory disease. Of those studies describing pregnancy duration, birthweight, maternal complications and/or miscarriages, the majority reported term deliveries, mean birthweights >3 kg, few maternal complications (which were mostly disease related) and a total of 56 of 474 first-trimester miscarriages and 8 of 474 second-/third-trimester foetal loss. Therefore, no consistent adverse effects of any TNFi were observed. Similarly, although various major malformations were described, there were no consistent patterns of abnormalities and the incidence was not increased compared with the control groups. Interestingly, in a large case–control study, a lower incidence of preterm delivery (<37 weeks) was observed in 6.1% of 253 TNFi-treated IBD pregnancies compared with 9.1% of 318 non-TNFi- or thiopurine-exposed IBD pregnancies [130].

If TNFi therapy is given in the third trimester, live vaccines should be avoided in the infant, as a case of fatal TB-like disease has been reported after Bacillus Calmette–Guérin in an infant who was not breastfed but was exposed to IFX throughout pregnancy [214]. It is likely that very little drug is absorbed from breast milk.

Of the breastfeeding studies that we identified, ADA was detectible in breast milk (n = 2) but not in infant serum [203], and both ETA (n = 3) as well as IFX (n = 3) were detectable in breast milk at very low levels [42, 201, 207, 208], while IFX (n = 1) was undetectable in another study [199], with no adverse effects detectable in any of these breastfed infants. In contrast, CZP was undetectable in longitudinal breast milk samples (five in the first month) taken from one patient [204]. None of these latter studies examined for the presence of drug in neonatal serum, and given the size of monoclonal antibodies, they are likely to be digested in the infant digestive tract.

There were long-term follow-up data on ETA to 9 months with no problems in 12 healthy children [42, 200, 206–208] and up to 7 months in a case series of 11 children, with reports of hand-foot-mouth disease at 9 months in one infant and upper respiratory tract infections in two others [204], as well as ADA to 14–15 months [203] and CZP to 1 month [204] with no complications reported.

A study published after our final search of 56 first-trimester exposures to TNFi (ETA, IFX and ADA) did not identify a significant increase in the risk of congenital malformations, foetal death or neonatal complications in pregnancies of women with chronic autoimmune disease compared with those who received TNFi before but not during pregnancy [129].

Interestingly, data are emerging that TNFis have different rates of placental transfer with CZP (a pegylated Fab′ fragment of an anti-TNF-α antibody) shown to have the lowest rates of placental transfer compared with other TNFis, consistent with its structure, which lacks the Fc component found in other monoclonals, and is compatible with pregnancy. A study of 31 pregnant women with IBD receiving IFX (n = 11), ADA (n = 10) or CZP (n = 10) throughout pregnancy found that concentrations of IFX and ADA, but not CZP, were higher in blood from infants at birth and their cord blood than in their mothers blood. The levels of CZP in infants and cord blood were <2 μg/ml. The median level of IFX in the cord blood was 160% that of the mother, the median level of ADA in the cord blood was 153% that of the mother and the median level of CZP in the cord blood was 3.9% that of the mother. The median time from last dose to delivery was 35 days for IFX, which then took up to 7 months for infant levels to become undetectable; 5.5 weeks for ADA, which took up to 11 weeks to become undetectable in the infant; and 19 days for CZP. No congenital anomalies or serious complications were reported in any of the children. This study provided clear evidence that IFX and ADA are transferred across the placenta and can be detected in infants at birth, and for up to 7 months afterwards in the case of IFX. In contrast, CZP had the lowest levels of placental transfer of the three drugs tested [204]. Two case studies have also shown low rates of placental transfer of ETA administered throughout pregnancy, with cord levels at delivery of 3.6% and 7.4% those of maternal serum in patients [42, 208]. Therefore, discontinuation of ADA, ETA and CZP at the end of the second trimester would ensure negligible or no drug is detectable in cord blood at delivery. For IFX however, its prolonged bioavailability and high rate of placental transfer mean that it may need to be stopped earlier in pregnancy for it to be undetectable in cord blood at delivery.

Recent data published in abstract form after our final search, highlighted by UCB Pharma through open consultation on this guideline, looked at the UCB Pharma global safety database for all cases of pregnancy exposures to CZP. As of September 2014, 625 CZP-exposed pregnancies had been reported; 579 were maternal, mostly first-trimester exposure, and 46 were paternal.

Pregnancy outcomes were available for 339 of these pregnancies: 192 in women with Crohn's disease and 118 in women with rheumatic diseases. For the 118 pregnancies in women with rheumatic diseases, 83 (70%) resulted in a live birth, 17 (14%) in spontaneous miscarriage and 17 (14%) in elective termination. Congenital anomalies were reported in 12 babies among 254 live births following maternal CZP exposure (n = 132): 1 had 22q11.2 deletion syndrome, unilateral right kidney, hypospadias and inguinal hernia; 1 had congenital morbus Hirschsprung disease and club foot; and 10 were born with one of the following: anal fistula, left-sided vesicoureteric reflux, pyloric stenosis, cleft palate, club foot, polydactyly, right aortic arch with aberrant left subclavian artery, renal cyst (no treatment required), posterior ankyloglossia or diaphragmatic hernia. Based on these findings, CZP exposure was not considered to adversely affect pregnancy outcomes [215].

Paternal exposure

Five cohort studies [21, 113, 147, 197, 216], two case series [117, 119], two case reports [140, 217] and a case–control study [118] reported on outcomes from 131 pregnancies after paternal exposure to IFX, ETA and ADA. Overall, the quality of these studies was low, but they did not identify an increased risk of adverse foetal outcomes. Furthermore, improved sperm motility was observed in 15 TNFi-treated patients with AS compared with 11 non-TNFi-treated patients with AS [218].

Recommendations for anti-TNF medications in pregnancy and breastfeeding

(i) IFX may be continued until 16 weeks and etanercept (ETA) and adalimumab (ADA) may be continued until the end of the second trimester (LOE 2−, GOR D, SOA 98.9%).
(ii) To ensure low/no levels of drug in cord blood at delivery, ETA and ADA should be avoided in the third trimester and IFX should be stopped at 16 weeks because of a theoretical increased infection risk in newborns. If these drugs are continued later in pregnancy to treat active disease, then live vaccines should be avoided in the infant until 7 months of age (LOE 3, GOR D, SOA 98.9%).
(iii) Limited evidence shows that CZP is compatible with all three trimesters of pregnancy and has reduced placental transfer compared with other TNFis (LOE 2−, GOR D, SOA 97.9%).
(iv) There is no evidence upon which to recommend GOL, but it is unlikely to be harmful in the first trimester (LOE 4, GOR D, SOA 97.9%).
(v) Based on limited but reassuring data, women should not be discouraged from breastfeeding while on TNFis, but caution is recommended until further information is available (LOE 3, GOR D, SOA 98.4%).
(vi) Based on limited evidence, IFX, ETA and ADA are compatible with paternal exposure (LOE 2−, GOR D, SOA 98.9%).

Rituximab

Due to limited published experience with rituximab (RTX) its use has not previously been recommended in pregnancy. It is a monoclonal IgG1 that targets CD20 to deplete B cells and therefore actively crosses the placenta from 16 weeks of pregnancy onwards. We identified three cohort studies [103, 219, 220], one case series [221] and four case reports [222–225] on 173 RTX-exposed pregnancies that met our inclusion criteria. The majority of these exposures are accounted for in a report on pregnancy outcomes from the RTX global drug safety database in which most patients received the drug for non-rheumatic disease, including serious haematological disease and non-Hodgkin's lymphoma [219]. Where stated, the timing of RTX exposure varied from 6 to 22 months pre-conception in 8 pregnancies, 0–3 months pre-conception in 6 pregnancies and during pregnancy in 72 pregnancies. In the largest cohort study describing the RTX global drug safety database data on 153 patients with known pregnancy outcomes exposed to RTX before or during pregnancy, 90 resulted in live births, 33 in spontaneous miscarriage, 1 in second-/third-trimester foetal loss and 28 in elective termination. Twenty-two infants were born before 37 weeks, but none at <30 weeks, with one neonatal death at 6 weeks. Eleven neonates had haematological abnormalities, including transient neonatal lymphopenia or B cell depletion, and none of these neonates had corresponding infections, while infections were reported in four other neonates. Two congenital malformations were identified: clubfoot in one twin and cardiac malformation in a singleton birth. One maternal death from pre-existing autoimmune thrombocytopenia occurred [219].

Reported outcomes from other studies were pregnancy duration of 14 term deliveries, 2 at 34–37 weeks and 3 at 30–34 weeks; birthweights of 2.35 kg at 36 weeks, 2.42 at 37 weeks, mean 3.25 kg in four SLE pregnancies and 2.9 kg in a term Granulomatosis with Polyangitis pregnancy; maternal complications in four pregnancies related to maternal disease; and two congenital abnormalities, a case of oesophageal atresia (child born to a mother exposed to RTX for 12 months and alendronic acid for 6 months pre-conception) and a case of Turner syndrome diagnosed pre-RTX therapy [220–225]. Long-term follow-up was reported from 11 months to 4.5 years in three children, one of whom had a prolonged QT interval in an anti-Ro-positive mother [224, 225]. Only one of these studies measured the B cell count at birth in twins born to a mother with RA given RTX 6 weeks pre-conception and found it to be normal [222]. Since Ostensen *et al.* [3], case reports of RTX exposure in at least 15 other pregnancies of patients with non-rheumatic disease have been published. These studies reported reassuring pregnancy outcomes but found low B cells at birth in 6 of 11 children tested, 5 of whom were exposed to RTX in the second/third trimester, while 5 of 6 children with pre-conception or first-trimester RTX exposure had normal B cell levels, reviewed in Hyrich and Verstappen [226]. No human breastfeeding data studies were identified.

Given that RTX does not cross the placenta until week 16 of pregnancy, reports of satisfactory pregnancy outcomes are accumulating and its maximum plasma half-life is 35 days, it is reasonable to shorten the interval between stopping the drug and conception to at least 6 months from the manufacturer's recommendation of 12 months.

Paternal exposure

A cohort study [219] reported on outcomes from 11 pregnancies after paternal exposure to RTX. The quality of this study was low, with no information provided about paternal dose of RTX, maternal health or concomitant medications in exposed pregnancies. There were seven live births with no complications, two miscarriages and two ongoing pregnancies.

Recommendations for RTX in pregnancy and breastfeeding

(i) There remains insufficient evidence to be confident that RTX is compatible with pregnancy and it should be stopped 6 months before conception. However, limited evidence has not shown RTX to be teratogenic and only second-/third-trimester exposure is associated with neonatal B cell depletion. Therefore, unintentional RTX exposure early in the first trimester is unlikely to be harmful (LOE 2−, GOR D, SOA 97.9%).
(ii) There are no data upon which to base a recommendation for RTX use in breastfeeding (SOA 100%).
(iii) Based on limited evidence, RTX is compatible with paternal exposure (LOE 2−, GOR D, SOA 98.4%).

Tocilizumab

Tocilizumab (TCZ) is a humanized monoclonal IgG1. There are limited human data and patients have been advised to use effective contraception for 3 months after the last TCZ infusion. No full-length articles were identified. The outcomes of 33 pregnancies in 32 patients have been published in abstract form [227]. Of 32 RA patients, 26 received TCZ/MTX combination therapy and 6 received TCZ monotherapy or a concomitant DMARD other than MTX. Elective termination of pregnancy was performed in 13 cases, 7 aborted spontaneously (5 received concomitant MTX at conception) and 11 patients (2 with TCZ monotherapy and 9 with concomitant MTX) delivered 10 healthy new-borns at term. One infant died of respiratory distress syndrome 3 days after emergency caesarean section for intrapartum foetomaternal haemorrhage due to placenta praevia. The outcome was unknown for two pregnancies.

Recommendations for TCZ in pregnancy and breastfeeding

(i) There are insufficient data and TCZ should be stopped at least 3 months pre-conception, but unintentional exposure early in the first trimester is unlikely to be harmful (LOE 3, GOR D, SOA 96.8%).
(ii) There are no data upon which to base a recommendation for TCZ use in breastfeeding (SOA 99.5%).
(iii) There are no data relating to paternal exposure to TCZ, but it is unlikely to be harmful (LOE 4, GOR D, SOA 97.9%).

Anakinra

Anakinra is a recombinant form of human interleukin-1 receptor antagonist with a high molecular weight that was not found to cross *ex vivo* full-term human placentae [228]. We identified data from five pregnancies in a cohort study [103], case series [229] and case report [230]. In three patients with adult-onset Still's disease there were no appreciable adverse effects on pregnancy [229, 230]. In a cohort study of 393 pregnancies identified from 34 169 women of reproductive age with RA, one patient in the elective abortion group (n = 37) was taking anakinra, which was not statistically significant compared with the successful delivery group (n = 281 pregnancies), in which one patient was also on anakinra [103]. There were no human breastfeeding data, and no studies of paternal exposure were identified.

Recommendations for anakinra in pregnancy and breastfeeding

(i) There is limited evidence on which to base a recommendation for anakinra in pregnancy, but unintentional exposure in the first trimester is unlikely to be harmful (LOE 2−, GOR D, SOA 96.8%).
(ii) There are no data upon which to base a recommendation for anakinra use in breastfeeding (SOA 100%).
(iii) There are no data relating to paternal exposure to anakinra, but it is unlikely to be harmful (LOE 4, GOR D, SOA 98.9%).

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 about week 16 onwards. Animal studies published in abstract form, conducted in the absence of concomitant medications (such as low-dose MTX), have not shown any adverse effects of ABA on fertility or foetal development [231]. There remains very limited published human pregnancy experience with ABA. We identified one case series [133] and one case report [225] reporting on three pregnancies exposed to ABA in the first trimester. These pregnancies were all confounded by concomitant MTX use. There were two (one spontaneous and one elective) first-trimester miscarriages [133] and a full-term delivery of a healthy infant followed to 3.5 years of age with no complications [225].

Although it did not meet our search inclusion criteria, a review article has reported pregnancy outcomes from eight patients in the double-blind and open-label phases of studies of ABA [231]. All of these patients were on concomitant MTX (n = 7) or LEF (n = 1). Spontaneous first-trimester abortion occurred in three patients (two of whom

had a prior history of spontaneous abortion) and elective abortion was performed in two patients. The remaining three patients were still pregnant at the time the study report was written. This review article also described the spouse of a man treated with ABA, who became pregnant and delivered a healthy baby [231].

Recommendations for ABA in pregnancy and breastfeeding

(i) There are insufficient data to recommend ABA in pregnancy, but unintentional exposure early in the first trimester is unlikely to be harmful (LOE 3, GOR D, SOA 98.9%).
(ii) There are no data upon which to base a recommendation for ABA use in breastfeeding (SOA 100%).
(iii) There are no data relating to paternal exposure to ABA, but it is unlikely to be harmful (LOE 4, GOR D, SOA 98.9%).

Belimumab

Belimumab (BEL) is a fully humanized monoclonal IgG1 that inhibits B cell activating factor. It is licensed for use in the UK but does not have National Institute for Health and Clinical Excellence approval. We did not identify any publications that met our search criteria on use of this drug in human pregnancy.

A recent review article summarized human pregnancy data from unintended pregnancies that occurred during the manufacturer's placebo-controlled phase 2 and 3 studies of this drug in patients with SLE [232]. In these studies, patients received BEL and concomitant therapy (corticosteroids, immunosuppressives, antimalarials, NSAIDs or a combination thereof); when each pregnancy was discovered, BEL was stopped immediately and the patient removed from the trial. A total of 83 pregnancies had known outcomes: 24% elective terminations, 27.7% spontaneous abortions and 42% live births. Of the three congenital anomalies (rate of 3.6%) that developed in these pregnancies, one was a chromosomal translocation also found in the mother, and thus was unrelated to BEL. The BEL pregnancy registry has been set up to study the health of pregnant women receiving BEL within 4 months prior to and/or during pregnancy (http://clinicaltrials.gov/show/NCT01532310). The first two pregnancy outcomes from the BEL registry have recently been reported in abstract form [233].

Given the paucity of information, further unpublished data from the BEL pregnancy registry was obtained describing known outcomes (as of 8 September 2014) from a total of 118 SLE pregnancies: 28% elective terminations and 28.8% spontaneous abortions, all with no apparent congenital anomaly; 37.3% live healthy births; and 4.2% live births with congenital anomaly, although no specific pattern was observed [234].

Recommendations for BEL in pregnancy and breastfeeding

(i) There are insufficient data to recommend BEL in pregnancy or breastfeeding, but unintentional exposure early in the first trimester is unlikely to be harmful (LOE 3, GOR D, SOA 100%).
(ii) There are no data upon which to base a recommendation for BEL use in breastfeeding (SOA 100%).
(iii) There are no data relating to paternal exposure to BEL, but it is unlikely to be harmful (GOR D, SOA 98.9%).

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 4 month post-partum period by clinical practitioners with expertise in the management of rheumatic disease in pregnancy, in addition to their routine obstetric care. They should have access to written information on relevant medications in pregnancy and breastfeeding that is accurate and allows them to make informed decisions regarding the 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 when to stop MTX pre-conception and the compatibility of TNFi in breastfeeding. Data relating to the impact of paternal exposure to these drugs (both fertility and male-mediated teratogenicity), as well as breastfeeding exposure, are particularly limited, and further research in these areas are urgently required.

Mechanism for audit of the guideline

An audit pro forma to assess compliance with these guidelines is available on the British Society for Rheumatology website.

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Appendices
Search Strategies

PubMed/Embase search strategy: three separate searches set up and then combined (diseases, drugs and pregnancy)

http://www.pubmed.gov: Mesh terms and individual words. http://www.evidence.nhs.uk> journals and databases > advanced > Athens login > Embase: Map to thesaurus and explode to search Embase thesaurus terms.

Disease

''Rheumatoid arthritis'' or RA; ''Inflammatory arthritis''; ''Juvenile idiopathic arthritis'' or JIA; ''Juvenile rheumatoid arthritis''; ''Psoriatic arthritis''. Sjogrens or Sjogren* or Sicca; ''Spondylitis, Ankylosing'' or ''Spondylitis'' or ''Spondylarthritis'' or ''Spondylarthropathies'' or ''Spondylarthropathy'' or ''Spondylosis'' or (''spondylitis'' and ''ankylosing'') or ''ankylosing spondylitis'' or

''spondylitis'' or ''spondylarth*'' or ''spondyloarth*'' or ''spondylosis''. ''lupus'' or ''SLE''. ''antiphospholipid syndrome'' or antiphospholipid or aps or ''Hughes Syndrome''. ''fibromyalgia'' or ''chronic widespread pain''. ''Scleroderma, Systemic'' or ''Scleroderma'' or ''Limited Scleroderma'' or ''Localized Scleroderma'' or ''Diffuse Scleroderma'' or ''Systemic Sclerosis''. ''Raynauds'' or Raynaud* or ''Raynaud's phenomenon''. ''Paternal exposure'' or father* (which includes fatherhood, fathered, expectant father).

Drugs

Individual drug names, not names of groups (e.g. analgesics), dates as listed below. All searched as individual words, as well as PubMed Mesh/Embase thesaurus terms (exploded) where available.

List of drugs to search 2005 onwards: Analgesics: paracetamol; Low dose aspirin; Anticoagulants: heparin, warfarin; Antimalarials: hydroxychloroquine, chloroquine; Anti-rheumatics: sulfasalazine, leflunomide, azathioprine, methotrexate, ciclosporin, cyclophosphamide, tacrolimus, mycophenolate, intravenous immunoglobulin; Bisphosphonates: alendronate, etidronate, risedronate, pamidronate, zoledronate; NSAIDs: naproxen, diclofenac, ibuprofen, indomethacin, etodolac, meloxicam, celecoxib; Steroids: prednisone, prednisolone, dexamethasone.

List of drugs to search 2008 onwards: Anti-rheumatics: leflunomide, tacrolimus, mycophenolate; Biologics: etanercept, infliximab, adalimumab, abatacept, rituximab.

List of drugs to search 1960 onwards: Analgesics: codeine, morphine, tramadol, amitriptyline, nortryptiline, gabapentin, pregabalin, duloxetine, venlafaxine, fluoxetine, sertraline, paroxetine; Anticoagulants: rivaroxaban, dabigatran; ACE inhibitors: captopril, imidapril, enalapril, lisinopril, perindopril, ramipril, trandolapril; Calcium channel blockers: nifedipine cilazapril, moexipril, quinapril, fosinopril; Antimalarials: mepacrine; Biologics: Cimzia (certolizumab), golimumab, tocilizumab; Steroids: betamethasone; Acupuncture and Cognitive behavioural therapy. PubMed Mesh terms: 'acupuncture', 'acupuncture therapy', 'cognitive therapy'. Embase thesaurus terms: 'acupuncture', 'acupuncture analgesia', 'cognitive therapy'. Pulmonary vasodilators: bosentan, epoprostenol, sildenafil.

Pregnancy

''pregnancy'' (all fields) or ''pregnant'' (all fields) or ''pregnan*'' (all fields) or ''lactation'' (all fields) or ''lactat*'' (all fields) or ''breast feeding'' (all fields) or ''breast-feeding'' (all fields) or ''breastfeeding'' (all fields) or 'Breast Feeding' (Embase only—thesaurus term exploded) or 'Pregnancy' (Embase only—thesaurus term exploded) or 'Lactation' (Embase only—thesaurus term exploded)

Cochrane Search Strategy

http://www.thecochranelibrary.com Advanced Search. Tick to search all of the Cochrane library. pregnancy or pregnant or pregnan* or lactation or lactat* or (breast and feeding) or breast-feeding or breastfeeding [search all text] and ((Disease term A) or (Disease term B)...) [search all text] and ((Drug A) or (Drug B)...) [search all text].

LactMed Search Strategy

http://toxnet.nlm.nih.gov Lactmed. Database with respect to breastfeeding only. To use for general drug searches (not disease specific) and review references to identify gaps in literature search from other sources. Search all drugs individually (each has an individual record, with American versions of names, e.g. acetaminophen not paracetamol).

Data extraction sheet

Relevant information from each paper selected for inclusion was entered on this data sheet.

Identification	Drug of interest
	Title of paper
	First author
	Date
	Design
Cases—number of patients (not pregnancies)	Diagnosis—rheumatic diseases
	Rheumatic disease (n)
	Diagnosis—other
	Other diagnosis (n)
	No. exposed to all drugs in study (n)
	No. exposed to drug of interest (n)
Cases—number of pregnancies	No. exposed to all drugs in study
	No. exposed to drug of interest
Controls (number of patients)	Drug-free controls (n)—not exposed to any drug in study
	Drug-free controls (n)—not exposed to drug of interest
	Rheumatic disease in drug-free controls (n)
	Other disease in drug-free controls (n)
	Disease-free and drug-free controls (n)

(continued)

Continued

Controls (number of pregnancies)	Drug-free controls (n)—not exposed to any drug in study
	Drug-free controls (n)—not exposed to drug of interest
	Rheumatic disease in drug-free controls (n)
	Other disease in drug-free controls (n)
	Disease-free and drug-free controls (n)
	Comments
Exposure overall (number of patients)	Duration exposure, pre-partum (weeks)
	First-trimester exposure
	Second-/third-trimester exposure
	Duration exposure, post-partum
Exposure for drug of interest if specified (number of patients)	Duration exposure, pre-partum (weeks)
	First-trimester exposure
	Second-/third-trimester exposure
	Duration exposure, post-partum
	Concomitant drug therapy of patients on drug of interest
	List other drugs
	Comments
Outcomes for drug of interest—particular drug exposed group (if not available, list overall outcomes for all cases and mark in italics)Note these columns all relate to the number of exposed patients in column AM	Number of cases in which fertility was assessed
	Infertility (n)
	Normal fertility (n)
	Number of pregnancy outcomes reported for drug of interest (n)
	If this does not equal the number of drug-exposed cases, column K, please say why
	Average pregnancy duration (weeks)
	C-section (n)
	Vaginal delivery (n)
	Mean birthweight (g)
	Birthweight (S.D.)
	Maternal complications during pregnancy (n)
	Maternal complications during pregnancy (type)
	Live births
	First-trimester foetal loss (n)
	Second-/third-trimester foetal loss (n)
	Elective termination (n)
	Healthy babies
	Major malformations (n)
	Major malformations (type)
	Minor malformations (n)
	Minor malformations (type)
	Presence of drug in breast milk
	Minimum length of follow-up (months)
	Maximum length of follow-up (months)
	Average length of follow-up (months)
	Long-term healthy children (n)
	Long-term complications (n)
	Long-term complications (type)
	Comments
Outcomes (not exposed to drug of interest), drug-free	Number of cases in which fertility was assessed
	Infertility (n)
	Normal fertility (n)
	Number of pregnancy outcomes reported for patients not exposed to drug of interest (n)
	If this does not equal the number of drug-free controls (column N or column 0), please say why
	Average pregnancy duration (weeks)
	C-section (n)
	Vaginal delivery (n)
	Mean birthweight (g)
	Birthweight (S.D.)
	Maternal complications during pregnancy (n)
	Maternal complications during pregnancy (type)
	Live births (n)
	Spontaneous first-trimester foetal loss (n)
	Spontaneous second-/third-trimester foetal loss (n)

(continued)

Continued

	Elective termination (n)
	Healthy babies (n)
	Major malformations (n) affecting major organ or e.g. limb loss
	Major malformations (type)
	Minor malformations (n), e.g. extra toe
	Minor malformations (type)
	Presence of drug in breast milk
	Minimum length of follow-up (months)
	Maximum length of follow-up (months)
	Average length of follow-up (months)
	Long-term healthy children (n)
	Long-term complications (n)
	Long-term complications (type)
	Comments
Conclusion based on data supplied in paper	Grade
	Safe
	Comment/clarify
	Long-term follow-up
	Quality
	Consistency
	Directness
	Comments
	Level of recommendation
	Consensus rating

Derivation of summary data

Numerical data are therefore collated only from papers where the relevant outcome was clearly quantified and each column reports as follows. Studies (type and number): all included studies provide some qualitative or quantitative information on the safety of the relevant drug in pregnancy. Pregnancy exposures (exposures per trimester): total number of pregnancy exposures to the drug of interest, collated from all studies where this information was quantified. Trimester in which drug exposure occurred is not specified in all papers, hence the numbers given here are the minimum exposures in the first and second/third trimesters. Live births: total number of live births from all studies where this information was reported specifically for exposure to the drug of interest (studies where quantitative outcomes particular to the drug of interest cannot be deduced from the manuscript are not included here). Spontaneous miscarriages/total pregnancy outcomes: rate of spontaneous miscarriage collated from studies where both live births and foetal/neonatal deaths (miscarriages, live births, still births and elective terminations) have been quantified (studies reporting on live birth outcomes only are not included here). Pregnancy duration/birthweight: summarized from all papers where quantitative or qualitative information specific to the drug of interest was provided. Major malformations/total births: number of babies with a major malformation, collated from studies where this information was specifically quantified for the drug of interest. However, in a few cases it is not clear whether two or more major malformations occurred in a single baby or across several babies, in which case the total number of malformations is included here (e.g. 3 malformations in a cohort of 100 live births: if it is specified 1 baby with 3 major malformations, and 99 babies without malformations, this is presented as 1/100, whereas if it is not clear whether those 3 malformations were in 3 separate children or all in 1 child, it is presented as 3/100).