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BSR and BHPR guideline on prescribing drugs in pregnancy and breastfeeding—Part II: analgesics and other drugs used in rheumatology practice

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Key words: rheumatic disease, pregnancy, breastfeeding, prescribing, analgesics, NSAIDs, anticoagulants, antihypertensive drugs.

GUIDELINES

Full guideline

Scope and Purpose

Background

Prescribing of medications in women with rheumatic disease is often required to ensure adequate control of maternal disease activity, satisfactory pregnancy outcome and control of maternal symptoms. These drugs may also be required to control disease activity or symptoms in men with rheumatic disease wishing to father a child. Prescription of many drugs commonly used by rheumatologists 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 registries. This ad hoc system of reporting has identified obvious risks with some drugs and led to uncertainty and theoretical concerns for others. Consequently, withdrawal or denial

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of disease-ameliorating therapies often occurs because of a perceived rather than a proven risk of their lack of safety in pregnancy. It is important to avoid this situation, as 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 effects of anti-inflammatory, immunosuppressive and biologic drugs and other drugs commonly prescribed by rheumatologists 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. Therefore, guidelines are urgently required for medical professionals across the country to have a consistent approach to prescribing 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 or 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.

Areas the guideline does not cover

This guideline does not cover the management of infertility; acute pain relief during labour, hence morphine was excluded; or the indications for these drugs in specific rheumatic diseases in pregnancy.

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 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, UCLH, London.

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Dr Mohamed Nisar, consultant rheumatologist and Dr Subha Arthanari, associate specialist in rheumatology, Burton Hospitals NHS Trust.

Allied health care professional, general practice and patient representatives

Louise Moore, clinical nurse specialist in rheumatology, Rheumatic and Musculoskeletal Disease Unit, Our Lady's Hospice and Care Services, Dublin, Ireland.

Amy Crossley, patient representative, London.

Dr Neetha Purushotham, general practice and clinical teaching fellow, University College London, London.

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 medical subject heading (MeSH) and free terms: pregnancy, lactation, breastfeeding, name of each drug and name of key rheumatic diseases. The full electronic search strategies for the Medline and Embase databases are available in the appendix of part I of the guideline [5]. 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, 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 form available in the appendix of part I of the guideline [5].

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 1–6). 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 [6], followed by a percentage showing the SOA from voting of all 19 group members. The LOE for recommendations from the previous consensus review [2] are shown as a Roman numeral, derived from Miyakis *et al.* [7], which was taken into account in the final GOR and shown only where additional data were lacking.

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 pain drugs [paracetamol, codeine, tramadol, amitriptyline, gabapentin, serotonin and norepinephrine reuptake inhibitors (SNRIs) and selective serotonin reuptake inhibitors (SSRIs)] excluded papers with $<$10 patients. Searches relating to the use of all 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 acute pain relief during labour, i.e. morphine, were excluded from analysis. Other bone protection agents such as denosumab, teriparatide and strontium were not included in the systematic search because their use in the UK is restricted by NICE to postmenopausal women. 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 in the following categories: pain management, NSAIDs and low-dose aspirin (LDA) in the management of multisystem rheumatic disease, anticoagulants, bisphosphonates, anti-hypertensive medication in the management of multisystem rheumatic disease and pulmonary vasodilators. Other drug categories, including antimalarials, corticosteroids, disease-modifying anti-rheumatic and immunosuppressive therapies and biologics are considered in part 1 of this guideline [5]. The findings for each drug are presented as follows: type of studies selected, number of pregnancy exposures, pregnancy duration, birthweight, maternal complications, miscarriages, number and type of congenital anomalies, breastfeeding, long-term follow-up, paternal exposure and recommendation. Where possible, congenital anomalies described in the original publications were classified as major or minor according to European Surveillance of

Table 1 Summary of drug compatibility in pregnancy and breastfeeding

Drug	Compatible peri-conception	Compatible with first trimester	Compatible with second/third trimester	Compatible with breastfeeding	Compatible with paternal exposure
Conventional painkillers					
Paracetamol	Yes	Yes[a]	Yes[a]	Yes	Yes[b]
Codeine	Yes	Yes	Yes	Caution	Yes[b]
Tramadol	Yes	Yes	Yes	Yes[c]	Yes[b]
Other chronic pain treatments					
Amitriptyline	Yes	Yes	Yes	Yes	Yes[b]
Gabapentin	No	Insufficient data[d]	Insufficient data[d]	Insufficient data	No data
Pregabalin	No data	No data	No data	No data	No data
Venlafaxine	Yes	Yes	Yes	Insufficient data[e]	Yes[b]
Fluoxetine	Yes	Yes	Yes	Caution[e]	Yes[b]
Paroxetine	Yes	Yes	Yes	Caution[e]	Yes[b]
Sertraline	Yes	Yes	Yes	Caution[e]	Yes[b]
NSAIDs					
NSAIDs	Yes	Caution[f]	Stop by week 32	Yes	Yes
COX-2 inhibitors	No	No	No	No	No data
Low-dose aspirin	Yes	Yes	Yes	Yes[g]	Yes[b]
Anticoagulants					
Warfarin	No	No	No	Yes	No data
LMWH	Yes	Yes	Yes	Yes[g]	Yes[b]
Rivaroxaban	No data	No data	No data	No data	No data
Dabigatran	No data	No data	No data	No data	No data
Bisphosphonates					
Bisphosphonates	Stop 6 months in advance	No	No	No data	No data
Antihypertensives					
ACEI	Stop when pregnancy confirmed		No	Yes[c]	No data
Nifedipine	Yes	Yes <60 mg/day	Yes <60 mg/day	Yes	Yes[b]
Amlodipine	No data	No data	No data	No data	Yes[g]
Pulmonary vasodilators					
Sildenafil		MDT assessment		No data	No data
Bosentan		MDT assessment		No data	No data
Prostacyclines		MDT assessment		No data	No data

For further information and caveats, see relevant recommendations and main text in executive summary and full guideline. [a]Intermittent use advised—see main text for details. [b]No studies identified, but unlikely to be harmful due to maternal compatibility. [c]Limited evidence, but unlikely to be harmful. [d]Insufficient evidence regarding the use of gabapentin for treatment of chronic pain in pregnancy. [e]Insufficient evidence regarding the use of gabapentin for treatment of chronic pain in pregnancy. [f]Possible association with miscarriage and malformation. [g]No studies identified, but unlikely to be harmful. ACEI: angiotensin-converting enzyme inhibitor; LMWH: low molecular weight heparin; MDT: multidisciplinary team.

Table 2 Summary of maternal exposure to pain drugs including NSAIDs

Drug	Studies included (type and number)	Pregnancy exposures, exposures per trimester[a]	Live births reported	Spontaneous miscarriages/ total pregnancies	Pregnancy duration, birthweight	Major malformations/total births	Recommendation	Level of evidence/ grade of recommendation
Paracetamol[a]	8 ct [9–16], 3 cc [18–20]	59 940, first trimester ⩾34 639, second/ third trimester ⩾31 764)	5131	18/302	No significant adverse effect noted	11/230 (4.78%)Overall no increase in the rate of major malformations attributable to drug, but an association with cryptorchidism noted with exposure during weeks 8–14 [12, 17]	Paracetamol is compatible peri-conception and throughout pregnancyIf possible, intermittent use in pregnancy is advised because of a small increased risk in some studies of wheeze and childhood asthma reported with prolonged paracetamol use in pregnancyAvoid regular use during weeks 8–14 of pregnancy as a small risk of cryptorchidism has been reported	LOE 1−/GOR B, SOA 100%LOE 1−/GOR B, SOA 99.5%LOE 2−/ GOR C, SOA 99.5%
Codeine[a]	2 ct [21, 22], 2 cc [23, 24]	10 752, first trimester ⩾1693, second/ third trimester ⩾1955	2649	NR	No significant adverse effect noted[b]	77/2649 (2.91%)Overall no increase in the rate of major malformations attributable to drug	Codeine is compatible peri-conception and throughout pregnancy	LOE 2++/GOR C, SOA 100%
Tramadol[a]	1 cc [25] with significant confounding (other opiate use)	75, NR	NR	NR	NR	NR	Tramadol is compatible with pregnancy, although there have been no high-quality studies published that investigate the safety of tramadol in pregnancy	LOE 2−/GOR D, SOA 98.4%
Amitriptyline[a]	1 cc [26], 4 ct [13, 27–29]	673, first trimester ⩾273, second/third trimester ⩾216	503	32/212	No significant adverse effect attributable to drug	24/327 (7.33%)No increase in the rate of major malformations attributable to drug.Possible increased risk of perinatal events after third-trimester exposure [27]	Amitriptyline is compatible with pregnancy. There is no evidence of adverse effect on IQ or developmental outcomes	LOE 2+/GOR C, SOA 99.5%
Gabapentin[a]	1 ct [30], 2 cc [31, 32]	142, first trimester ⩾94, second/third trimester NR	44	6/51	Insufficient data to establish any effect	4/135 (2.96%) [30]Overall no increase in the rate of major malformations attributable to drug	There is insufficient evidence to recommend gabapentin for treatment of chronic pain in pregnancy; larger studies with single-drug exposure are required	LOE 2−/GOR D, SOA 99.5%
SNRIs—venlafaxine[a]	1 ct [33], 5 cc [34–38]	4830, first trimester ⩾256, second/third trimester ⩾103	448	18/150	No significant adverse effect noted	21/916 (2.29%)No increase in rate of major malformations attributable to drug	Venlafaxine is compatible at conception and throughout pregnancy. There may be an increased risk of neonatal abstinence syndrome/short-term behavioural effects, but larger studies are needed to evaluate this finding. There is no evidence of a detrimental effect on IQ	LOE 2+/GOR C, SOA 98.9%

(continued)

Table 2 Continued

Drug	Studies included (type and number)	Pregnancy exposures, exposures per trimester[a]	Live births reported	Spontaneous miscarriages/ total pregnancies	Pregnancy duration, birthweight	Major malformations/total births	Recommendation	Level of evidence/ grade of recommendation
Grouped SSRIs[a] (from papers where data not presented by drug class, not separated out into individual drugs)	3 cc [43, 60], plus see individual drugs below	901, first trimester ⩾150, second/ third trimester NS	317	16/150	Possible increased risk of preterm birth and birthweight <2.5 kg [39] when SSRIs grouped for analysis	13/317 (4.10%)	See individual drugs below.Cessation of anti-depressant therapy in the postnatal period is not recommended, due to the risk of relapsing depression	LOE 4/GOR D, SOA 99.5%
Fluoxetine[a]	10 ct [13, 28, 40, 49, 51–54, 57, 68], 17 cc [26, 37–39, 41–48, 50, 55, 56, 58, 59]	23 389, first trimester ⩾7748, second/ third trimester ⩾4869	16 166	157/6977	No significant adverse effect noted	194/4649 (4.17%)Most studies report no evidence of an increased rate of major malformations attributable to drug, but an excess (particularly cardiac malformations) was reported in one study [50].Risk of persistent pulmonary hypertension identified [41]	Fluoxetine, paroxetine and sertraline are compatible with pregnancy	LOE 2++/GOR C, SOA 97.9%
Paroxetine[a]	7 ct [27, 40, 53, 54, 61, 65, 68], 16 cc [58–60, 62–64] [37–39, 41–45, 50, 67]	21 394, first trimester ⩾6464, second/ third trimester ⩾3119	8495	67/4295	No significant adverse effect noted	295/8766 (3.37%) Most studies report no significant increased rate of malformations, but some trends towards malformations (particularly cardiac) noted. Four studies reported a significantly increased risk [40, 54, 61, 62]. Possible risk of persistent pulmonary hypertension in one study [41]. Risk of neonatal adaptation/abstinence syndrome after third trimester exposure in 3 small studies [45, 63, 65]	Fluoxetine, paroxetine and sertraline are compatible with pregnancy	LOE 2++/GOR C, SOA 97.9%
Sertraline[a]	2 ct [53] [40], 9 cc [37–39, 41–44, 58, 59]	20 822, first trimester ⩾8163, second/ third trimester ⩾4680	9143	NR	No significant adverse effect noted	125/3156 (3.96%)Overall, no increase in rate of major malformations attributable to drug, but risks of cardiac malformations [42, 43] and persistent pulmonary hypertension [41] identified	Fluoxetine, paroxetine and sertraline are compatible with pregnancy	LOE 2++/GOR C, SOA 97.9%

(continued)

Table 2 Continued

Drug	Studies included (type and number)	Pregnancy exposures, exposures per trimester[a]	Live births reported	Spontaneous miscarriages/ total pregnancies	Pregnancy duration, birthweight	Major malformations/total births	Recommendation	Level of evidence/ grade of recommendation
NSAIDs	1 sr [69], 5 ct [17, 70–73], 2 cc [74, 75], 1 cr [76]	15 606, first trimester ⩾26, second/ third trimester ⩾12[c]	7986	Risk of spontaneous abortion identified[d]	NR	Rate not specifically quantified in the majority of papers, but risk of cardiac, orofacial and musculoskeletal malformations identified [69, 73]	Discordant findings from retrospective, large studies with population controls on the use of non-selective NSAIDs in the first trimester of pregnancy raise the possibility of a low risk of miscarriage and malformation. Therefore, these drugs should be used with caution in the first trimester of pregnancy.All non-selective NSAIDs except LDA should be withdrawn at gestational week 32 to avoid premature closure of the ductus arteriosus.At present there are limited data on selective COX-2 inhibitors; they should therefore be avoided during pregnancy	LOE 1−/GOR B, SOA 99.5%LOE 4/GOR D, SOA 100%LOE 2+/ GOR D, SOA 98.9%

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 derivation of summary data appendix of part I of the guideline [5]. [a]The search only included papers with >10 patients, but note selection bias and publication bias cannot be excluded entirely. [b]Small increase in preterm delivery (and hence low birthweight) likely due to confounding factors (disease) [23]. [c]Exact numbers not given in the majority of papers, but exposures throughout the first/ second/third trimester included in two large studies (n = 377 and n = 6511). [d]Large registry study [odds ratio 2.43 (95% CI 2.12, 2.79)] [75]. cc: case–control; Cochr: Cochrane review; cr: case report; cs: case series; ct: cohort; GOR: grade of recommendation; IQ: intelligence quotient; LDA: low-dose aspirin; LOE: level of evidence; NR: not reported; ns: not stated; RCT: randomized controlled trial; SNRIs: serotonin-norepinephrine reuptake inhibitors; SOA: strength of agreement; sr: systematic review; SSRIs: selective serotonin reuptake inhibitors.

Table 3 Summary of maternal exposure to anticoagulants including low-dose aspirin

Drug	Studies included (type and number)	Pregnancy exposures, 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
Warfarin	2 ct [111, 124], 1 cs [125], 1 sr [79], 1 cr [121]	47, exposure throughout pregnancy in most cases	48[b]	NRConcern regarding early miscarriage [111]	Insufficient data.No increase in intrauterine growth restriction in one paper [111]	NR9.7% rate of major malformations in one cohort [111]	The use of warfarin in pregnancy is associated with increased foetal risk throughout pregnancy and has limited indications, therefore should only be considered in exceptional circumstances	LOE 1−/GOR B, SOA 100%
Heparin	2 sr [79, 110], 6 RCT [80–83, 108, 109], 2 cc [100, 114], 16 ct [84, 86, 87, 90–99, 111–113], 2 cs [102, 115], 8 cr [116–123]	1285, exposure throughout pregnancy in majority of papers	1014	119/700[c]	No significant adverse effect noted	13/856 (1.52%)Overall no increase in the rate of major malformations attributable to drug (most data confounded by disease (indication for heparin) and other drug use)	LMWH is compatible throughout pregnancy	LOE 1 ++/GOR A, SOA 100%
Low-dose aspirin	2 cs [101, 102], 17 ct [17, 84–99], 1 cc [100], 2 sr [69, 79], 4 RCT [80–83]	4254, exposure throughout pregnancy in majority of papers	4057	69/689Overall no evidence of adverse effect[d]	No significant adverse effect on pregnancy duration noted[e]	11/739 (1.5%)Overall no increase in rate of major malformations attributable to drug	LDA may be continued throughout pregnancy. NICE guidelines (August 2010) for hypertension in pregnancy advises treatment with LDA (for pre-eclampsia) until delivery	LOE 1+/GOR B, 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 derivation of summary data appendix of part I of the guideline [5]. [a]Columns only include data from papers with five patients, but note that selection bias and publication bias cannot be excluded entirely. [b]Including a twin pregnancy. [c]Confounded by frequent use in treatment of recurrent miscarriage and severe maternal disease. [d]Confounded by underlying disease (indication for aspirin). [e]Confounded by underlying disease (indication for aspirin). cc: case–control; cr: case report; cs: case series; ct: cohort; GOR: grade of recommendation; LDA: low-dose aspirin; LMWH: low molecular weight heparin; LOE: level of evidence; NR: not reported; RCT: randomized controlled trial; SOA: strength of agreement; sr: systematic review.

TABLE 4 Summary of maternal exposure to bisphosphonates

Drug	Studies included (type and number)	Pregnancy exposures, 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
Bisphosphonates	2 ct [128] [129], 1 cs [130]	55, first trimester ⩾30, second/third trimester ⩾1	46	8/55[b]	No significant adverse effect noted	3/46 (6.52%)Insufficient data to establish any risk	There is no evidence of harm but insufficient data upon which to recommend bisphosphonates, so they should be stopped 6 months in advance of pregnancy	LOE 4/GOR D, SOA 98.4%

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 derivation of summary data appendix of part I of the guideline [5]. [a]Columns only include data from papers with more than five patients, but note that selection bias and publication bias cannot be excluded entirely. [b]One elective termination. ct: cohort; cs: case series; GOR: grade of recommendation; LOE: level of evidence; SOA: strength of agreement.

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 total number of pregnancies following maternal exposure to each drug is shown in Tables 2–6, and where reported, outcomes of miscarriage, live births and major anomalies are summarized. To reduce the impact of publication and selection bias, only papers with at least 5 patients are included in Tables 3–6 and 10 patients in Table 2. Other papers included in our search that do not meet these criteria are discussed in the main text.

Pain management

Only NSAIDs and analgesics were considered in the 2006 consensus. Therefore, we considered drugs commonly prescribed for pain management in patients with rheumatic disease, including those commonly used to treat chronic widespread pain. In particular, we considered amitriptyline, SNRIs and SSRIs, to cover their use for chronic pain in the rheumatology setting, although they are more commonly prescribed as antidepressants. There were no studies identified examining pregnancy outcomes after paternal exposure to any of these medications.

Conventional Analgesics

Paracetamol

There was one meta-analysis [9], nine cohort [10–18] and three case–control [19–21] studies that examined paracetamol exposure in pregnancy, in which at least 59 940 exposed pregnancies were compared with 238 199 healthy non-exposed controls. There was increased use of other drugs (such as antibiotics and NSAIDs) in the paracetamol group, but no exposure to known teratogens. There was no increased risk of premature delivery or low birthweight (LBW). One study of 172 women using paracetamol during pregnancy showed no association with miscarriage, regardless of the timing or duration of use [16].

The relationship between short-term paracetamol therapy and mean gestational age and birthweight was studied in 38 151 newborn infants from a large Hungarian population–based dataset. Of these, 173 of their mothers had paracetamol treatment during pregnancy. In the exposed infants compared with the unexposed, a 0.4 week increase in mean gestational age was observed. The proportion of preterm births was also reduced in those exposed to paracetamol (3.5 *vs* 9.2%). The authors speculate that these differences may be due to the reduction in prostacyclin production induced by paracetamol in the pregnant women [10].

Most studies did not identify an increased risk of malformations. However, a large study reporting data from 22 449 live-born singleton sons of mothers enrolled in the Danish National Birth Cohort (1996–2002) found exposure to paracetamol during the first and second trimesters was associated with increased occurrence of cryptorchidism at an estimated hazard ratio (HR) of 1.33

Table 5 Summary of maternal exposure to angiotensin-converting enzyme inhibitors and other antihypertensives

Drug	Studies included (type and number)	Pregnancy exposures, 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
ACEI grouped	1 sr [132], 1 cc [133], 2 ct [134, 135]	969, first trimester ⩾863, second/ third trimester ⩾179	901	11/158	Preterm deliveries and corresponding low birthweight, confounded by maternal disease activity, concomitant medication and hypertension per se	100/199Foetal renin angiotensin system blockade syndrome described. Suggestion that risk may be reduced following only first trimester exposure, or use of captopril (shorter half-life) [132]	ACEI should be stopped as soon as possible when pregnancy is confirmed in the first trimester and if necessary an alternative antihypertensive compatible with pregnancy givenACEI should be avoided in the second and third trimester	LOE 2 ++/GOR B, SOA 100%LOE 2 ++/GOR B, SOA 100%
Nifedipine	1 RCT [142], 6 sr [143–148], 2 cs [149, 150], 5 cr [120, 137, 151–153]	5613, first trimester ⩾4, second/third trimester ⩾5555	4223	0/11	No significant adverse effect attributable to nifedipine noted[b]	Insufficient data to establish any risk	Nifedipine is compatible with pregnancy with no direct evidence of harm at doses up to 60 mg/ day	LOE 1+/GOR B, SOA 99.5%

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 derivation of summary data appendix of part I of the guideline [5]. [a]Columns only include data from papers with more than five patients, but note that selection bias and publication bias cannot be excluded entirely. [b]Confounded by the main clinical indication to treat maternal complications, such as preterm labour and eclampsia. ACEI: angiotensin-converting enzyme inhibitor; cc: case–control; cr: case report; cs: case series; ct: cohort; GOR: grade of recommendation; LOE: level of agreement; RCT: randomized controlled trial; SOA: strength of agreement; sr: systematic review.

Table 6 Summary of maternal exposure to pulmonary vasodilators

Drug	Studies included (type and number)	Pregnancy exposures, 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
Prostacyclines	4 cr [121, 167, 171, 172], 5 cs [115, 149, 165, 166, 173]	23, first trimester ⩾5, second/third trimester ⩾17	16	0/6	Reduced average pregnancy duration but confounded by maternal pulmonary hypertension	0/5Insufficient data to establish any risk	PHT remains a contraindication to pregnancy. If pregnancy occurs, the use of these pulmonary vasodilator drugs in pregnancy should be considered only as part of a multidisciplinary team assessment.Limited evidence supports the use of prostacyclines to treat PHT during pregnancy	LOE 4/GOR D, SOA 100%LOE 3/GOR D, SOA 99.5%
Sildenafil	1 RCT [162], 2 sr [163, 164], 2 cs [165, 166], 2 cr [121, 167]	36, first trimester ⩾8, second/third trimester ⩾34	32	0/28	Reduced average pregnancy durations and birthweights generally attributed to underlying pathology, not sildenafil	0/4Insufficient data to establish any risk	PHT remains a contraindication to pregnancy. If pregnancy occurs, the use of these pulmonary vasodilator drugs in pregnancy should be considered only as part of a multidisciplinary team assessment.Limited evidence supports the use of sildenafil to treat PHT during pregnancy	LOE 4/GOR D, SOA 100%LOE 3/GOR D, SOA 99.5%
Bosentan	2 sr [163, 164], 1 cs [165], 1 cr [121]	12, first trimester⩾10, second/third trimester⩾6	7	0/8	Insufficient data to confirm lack of a significant adverse effect	0/3Insufficient data to establish any risk	PHT remains a contraindication to pregnancy. If pregnancy occurs, the use of these pulmonary vasodilator drugs in pregnancy should be considered only as part of a multidisciplinary team assessment.Bosentan is teratogenic in animals, and although there is no evidence of harm from human pregnancy, the evidence is insufficient to recommend in pregnancy	LOE 4/GOR D, SOA 98.9%LOE 3/GOR D, SOA 100%

All studies were included that provided some qualitative or quantitative information on the safety of the relevant drug during pregnancy. Numerical 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 derivation of summary data appendix of part I of the guideline [5]. [a]Columns only include data from papers with more than five patients, but note that selection bias and publication bias cannot be excluded entirely. cs: case series; cr: case report; GOR: grade of recommendation; LOE: level of evidence; PHT: pulmonary hypertension; RCT: randomized controlled trial; SOA: strength of agreement; sr: systematic review.

Fig. 1 Flow diagram of studies selected for final analysis

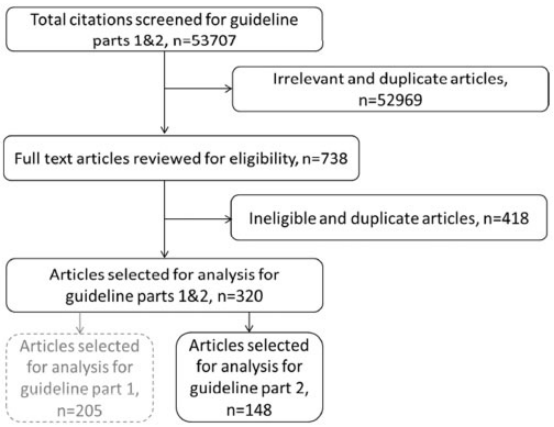

Figure reproduced from part I of the guideline [5]. Reproduced with permission from the British Society for Rheumatology.

(95% CI 1.0, 1.8). Exposure for >4 weeks within the postulated time window of programming testicular descent (gestational weeks 8–14) was associated with a HR of 1.38 (95% CI 1.1, 1.8) for cryptorchidism [18]. Similarly, an increased risk of cryptorchidism was observed in one study (n = 233) designed specifically to examine this issue. The incidence of cryptorchidism was 9.9% following use of paracetamol for >2 weeks compared with 7.0% in controls [odds ratio (OR) 2.8 (95% CI 1.1, 6.8)] [13].

One cohort study considered paracetamol overdose in pregnancy [14]. The overdoses, which occurred in all three trimesters, resulted in no maternal deaths and no increase in foetal malformations. Of those live-born infants with malformations, none had been exposed to paracetamol in the first trimester. The authors emphasize the importance of treating mothers if there is evidence of paracetamol toxicity to prevent foetal toxicity. They conclude, however, that there is no evidence that paracetamol overdose is an indication for termination of pregnancy [14].

Long-term follow-up was completed in eight studies (ranging from 42 to 144 months) and no increased risk of cancer, immunosuppression or developmental delay was reported [11–13, 15, 17, 19–21]. There were, however, conflicting results on the risk of developing wheeze in infants exposed to paracetamol during pregnancy. One large study (n = 49 029) showed a small but significant increased risk of asthma at 7 years old [relative risk (RR) 1.15 (95% CI 1.02, 1.29)] [21]. A large prospective longitudinal study examining 14 541 pregnancies found that paracetamol exposure at 20–32 weeks was associated with an increased risk of wheezing at 30–42 months compared with no exposure [OR 2.10 (95% CI 1.30, 3.41)]. This increased risk was not seen with exposure in early pregnancy (<18–20 weeks). The authors found no relationship between paracetamol use and eczema [17]. Similarly, a smaller study (n = 334) found a significantly increased OR of 1.6 (95% CI 1.01, 2.6) for the development of wheeze [11]. By contrast, one study of 976 children exposed to paracetamol found that the increased risk of wheeze became non-significant after adjusting for maternal BMI [19]. Another study found no increased risk of wheeze in 1505 paracetamol-exposed children [20]. A recent meta-analysis including six studies showed a significant OR of 1.2 (95% CI 1.02, 1.44) [9].

There were no studies identified that specifically examined neonatal outcomes after drug exposure in breast milk. The LactMed database summarizes information from studies reporting low amounts of this drug in breast milk at levels much less than doses usually given to infants, with few reports of adverse events. We identified no studies of paternal exposure to paracetamol.

Recommendations for paracetamol in pregnancy and breastfeeding

(i) Paracetamol is compatible peri-conception and throughout pregnancy (LOE 2+, GOR C, SOA 100%).

(ii) If possible, intermittent use in pregnancy is advised because of a small increased risk of wheeze and childhood asthma reported with prolonged paracetamol use in pregnancy with some studies (LOE 2+, GOR C, SOA 99.5%).

(iii) Avoid regular use during weeks 8–14 of pregnancy, as a small risk of cryptorchidism has been reported (LOE 2+, GOR C, SOA 99.5%).

(iv) LactMed describes paracetamol as a good choice for analgesia and fever reduction in breastfeeding mothers (LOE 4, GOR D, SOA 100%).

(v) There are no data relating to paternal exposure to paracetamol, but due to maternal compatibility, it is unlikely to be harmful (LOE 4, GOR D, SOA 99.5%)

Codeine

There were two cohort [22, 23] and two case–control [24, 25] studies of 10 752 pregnancies in patients with rheumatic and other diseases exposed to codeine, compared with 6037 disease and 59 987 non-exposed healthy control pregnancies. The codeine-exposed group had a significantly higher incidence of rheumatic disease, depression, asthma, cardiac disease, thyroid disease, high BMI and smoking compared with controls. In one study, the majority of patients (98.3%) took codeine in combination with paracetamol [24]. This study of 2666 pregnancies found an increased rate of premature delivery in women exposed to codeine compared with the control group (7.8 *vs* 6.0%) [24]. The increased rate of premature delivery was considered to be secondary to confounding factors and this study did not conclude that there was a causal association between codeine and preterm delivery. The same study also found a greater incidence of reduced birthweight in babies born to codeine-treated mothers compared with the control group (4.7% <2500 g compared with 3.9% <2500 g). There was no adjustment, however, for gestational age, and this finding is likely to be related to the increased rate of preterm delivery.

The same large study looked at antenatal exposure to codeine in 2666 women [24] and found no significant difference in major malformations (2.9% in both the exposed and control groups) or overall malformations (4.9% in the exposed group *vs* 5.0% in the control group). A significant increase in pre-eclampsia (5.9 *vs* 4%) and post-partum haemorrhage [18.3 *vs* 14.5%; OR 1.3 (95% CI 1.1, 1.5)] was observed in 2666 mothers exposed to codeine [24]. The increased rate of pre-eclampsia could be explained by the significantly increased rate of medical co-morbidities in those women exposed to codeine, including SLE, arthritis (not specified) and cardiac disease (13% in the exposed group *vs* 3% in the control group). It was suggested that the increase in post-partum haemorrhage could be due to an opioid effect weakening myometrial contraction, but the precise mechanism remains to be elucidated.

There has been some controversy and conflicting results regarding whether codeine is safe in breastfeeding. In one study, CNS depression was reported by mothers in 16.7% (35/210) of babies exposed to codeine, compared with 0.5% exposed to paracetamol [22]. In the same study there was one neonatal death, and high morphine levels were found post-mortem. The mother had received high doses of codeine (>2 mg/kg/day) and was subsequently found to be an ultra-rapid CYP2D6 metabolizer. Another study demonstrated dose-dependent CNS depression in 24% (17/72) of infants exposed to codeine through breast milk [23]. More recently, a large study of 7804 infants reported conflicting results—specifically, there was no difference in poor Apgar scores, postnatal complications, admission to special care baby units, readmission to hospital, resuscitation or death in infants exposed and not exposed to codeine [25].

As a result of the neonatal death, the US Food and Drug Administration issued a warning that the 'use of codeine by nursing mothers who are CYP2D6 ultra-rapid metabolizers may increase the risk of serious adverse effects in some breastfed infants' [23]. It is acknowledged that due to its unpredictable metabolism, administration of codeine results in delivery of an unknown quantity of morphine. Therefore, despite its widespread use and probable safety in the majority of cases, we would advise caution with prolonged use of codeine in breastfeeding and appropriate advice to the mother to seek medical attention if she has any concerns regarding lethargy or drowsiness in her child. We identified no studies of paternal exposure to codeine.

Recommendations for codeine in pregnancy and breastfeeding

(i) Codeine is compatible peri-conception and throughout pregnancy. There is no consistent evidence to recommend a dose reduction pre-delivery, but neonatologists should be aware of maternal use (LOE 2++, GOR C, SOA 100%).
(ii) Caution is advised with the use of codeine in breastfeeding due to the risk of CNS depression resulting from unpredictable metabolism of codeine to morphine (LOE 2+, GOR D, SOA 98.9%).
(iii) There are no data relating to paternal exposure to codeine, but due to maternal compatibility, it is unlikely to be harmful (LOE 4, GOR D, SOA 98.9%).

Tramadol

One case–control study was identified comparing 75 tramadol-exposed pregnancies with 75 non-exposed controls [26]. A confounding factor of this study is that 49% of the exposed group took other opiates and the entire control group took other opiates (mainly oxycodone). Pregnancy outcomes were not recorded.

Tramadol was found in breast milk, but there was no significant difference reported in neurologic and adaptive capacity scores between infants of the tramadol and control groups. We identified no studies of paternal exposure to tramadol.

Recommendations for tramadol in pregnancy and breastfeeding

(i) Tramadol is compatible with pregnancy, although there have been no high-quality studies published that have investigated the safety of tramadol in pregnancy (LOE 2−, GOR D, SOA 98.4%).
(ii) Based on limited data, tramadol may be compatible with short-term use in breastfeeding (LOE 2−, GOR D, SOA 97.9%).
(iii) There are no data relating to paternal exposure to tramadol, but due to maternal compatibility, it is unlikely to be harmful (LOE 4, GOR D, SOA 98.9%).

Other treatments for chronic pain

Amitriptyline

Amitriptyline is used to treat chronic widespread pain at doses of <75 mg/day. In contrast, the case–control [27] and four cohort [14, 28–30] studies we identified reported outcomes from 673 pregnancies exposed to an antidepressant dosage (usually 150–300 mg/day) of amitriptyline, compared with 120 controls. Only one study of 118 women reported on concomitant drug use, with two-thirds of patients using other drugs and one-third of patients taking benzodiazepines [14]. There were no studies identified that reported outcomes in infants exposed to nortryptiline during pregnancy or breastfeeding.

Two studies (n = 212) reported pregnancy losses of 14.15% (30/212) in the first trimester, 0.94% (2/212) in the second/third trimester and 9.43% (20/212) for elective termination of pregnancy [14, 27]. Two studies (n = 140) reported average full-term deliveries at 39 and 39.5 weeks [27, 29], while one reported 42 of 381 (11%) babies being born preterm, compared with 6.6% of controls [28], and another study reported 5.9% born preterm [14]. It is unclear, however, whether the increased rate of preterm delivery was directly caused by drug exposure, as depression itself is associated with preterm delivery, so there could be confounding by indication. Therefore, overall there was no appreciable effect on pregnancy duration, nor was there any effect on birthweight. No increased risk of congenital malformations was reported [14, 27, 28].

None of our included studies specifically addressed outcomes for infants exposed to amitriptyline in breast milk. Other studies have reported low levels of this drug in breast milk with no immediate side effects (summarized in LactMed).

Long-term outcomes were reported as follows. One study reported an increased risk of neonatal events in infants exposed *in utero* of 43% compared with 34% in controls [28]. One small study of 46 exposed infants showed no difference in developmental outcomes [29] and one study of 80 infants showed no difference in intelligence quotient (IQ) [27]. We identified no studies of paternal exposure to amitriptyline. All of these studies are of women who have been treated with amitriptyline for depression; when this drug is used to treat chronic pain in a rheumatology setting, significantly lower doses of amitriptyline are usually employed.

Recommendations for amitriptyline in pregnancy and breastfeeding

(i) Amitriptyline is compatible with pregnancy. There is no evidence of adverse effect on IQ or developmental outcomes (LOE 2+, GOR C, SOA 99.5%).
(ii) Since very little amitriptyline is found in breast milk with antidepressant doses and it is used at lower doses for chronic pain, it is unlikely to cause adverse effects in breastfed infants (LOE 4, GOR D, SOA 98.4%).
(iii) There are no data relating to paternal exposure to amitriptyline, but due to maternal compatibility, it is unlikely to be harmful (LOE 4, GOR D, SOA 98.4%).

Gabapentin and pregabalin

Gabapentin is frequently used to treat chronic pain at lower doses than when used as an anti-epileptic treatment and the only evidence for gabapentin use in pregnancy comes from studies of epileptic women. One cohort [31] and two case–control [32, 33] studies examined gabapentin exposure in 142 pregnancies of women with epilepsy compared with 836 263 healthy control pregnancies and 239 pregnancies of patients with untreated epilepsy. There was a high level of polypharmacy, with patients commonly taking other anti-epileptic drugs in addition to gabapentin. Only one study [31] reported on pregnancy duration, and although there were 10 infants (out of 51) born prematurely, this finding may be explained by three sets of twins, one case of eclampsia and one case of preterm pre-labour rupture of membranes. Therefore, it is not possible to conclude from these studies whether gabapentin has any effect on pregnancy duration or birthweight. There were no studies identified that reported outcomes in infants exposed to pregabalin during pregnancy or breastfeeding.

Major malformations occurred in 4 of 135 (3%) live births following gabapentin exposure. However, this finding was confounded by concurrent exposure to other anti-epileptic drugs; one infant with hypospadias was also exposed to sodium valproate and one infant with single kidney agenesis had been exposed to phenobarbitol. In the control group, 19 911 of 836 498 (2.4%) infants were born with a major malformation [32, 33]. It is difficult to determine the true effect of gabapentin due to concurrent exposure to other anti-epileptic drugs, but overall there was no evidence of an increased rate of major malformations attributable to gabapentin exposure. No long-term outcomes were reported.

There were no data suitable for inclusion in this analysis on whether gabapentin is present in breast milk. However, LactMed reports low levels of gabapentin have been found in breast milk with no adverse effects on infants in case reports/series ($n < 10$) and that it is recommended in preference to pregabalin, due to a lack of data for the latter. We identified no studies of paternal exposure to gabapentin or pregabalin.

Recommendations for gabapentin and pregabalin in pregnancy and breastfeeding

(i) There is insufficient evidence to recommend gabapentin for treatment of chronic pain in pregnancy; larger studies with single-drug exposure are required (LOE 2−, GOR D, SOA 99.5%).
(ii) There is insufficient evidence to recommend gabapentin for the treatment of chronic pain in breastfeeding (LOE 4, GOR D, SOA 100%).
(iii) There are no data to recommend pregabalin in pregnancy or breastfeeding (LOE 4, GOR D, SOA 100%).
(iv) There are no data on which to base a recommendation regarding paternal exposure to gabapentin or pregabalin (SOA 100%).

SNRIs

One cohort [34] and five case–control studies [35–39] investigated venlafaxine exposure in 4830 pregnancies compared with population controls. Two of these studies reported no other concomitant drug use and two did not specify other drug use. Of the three studies that reported pregnancy duration, the average gestation was >39 weeks [34, 36, 37]. Two studies reported average birthweights of 3.4 and 3.3 kg [36, 37], while another study found no significant difference in birthweight between exposed and control pregnancies [34]. There were no studies identified that reported outcomes in infants exposed to duloxetine during pregnancy or breastfeeding.

The incidence of major/minor malformations was not significantly increased in studies investigating this outcome, with overall 2.3% major malformations reported in 916 exposed pregnancies compared with 4.5% of controls [34, 35, 38, 39]. A small study of 11 infants showed an increased risk of neonatal abstinence syndrome and short-term behavioural effects in the first 6 days of life of infants exposed to venlafaxine [34]. One study investigating IQ in 62 6-year-old children found no difference in children exposed to venlafaxine, SSRIs, or untreated maternal depression. Average IQ, however, was significantly lower in all groups when compared with the IQ of infants of non-depressed mothers [36].

The presence of the drug in breast milk was not examined in these studies. There were no papers meeting our inclusion criteria examining whether venlafaxine is present in breast milk. However, LactMed reports that infants receive venlafaxine and its active metabolite in breast milk and the metabolite of the drug can be found in the plasma of most breastfed infants, but no proven drug-related side effects have been reported in small case series. We identified no studies of paternal exposure to SNRIs.

Recommendations for SNRIs in pregnancy and breastfeeding

(i) Venlafaxine is compatible at conception and throughout pregnancy. There may be an increased risk of neonatal abstinence syndrome or short-term behavioural effects, but larger studies are needed to evaluate this finding. There is no evidence of a detrimental effect on IQ (LOE 2+, GOR C, SOA 98.9%).

(ii) There is insufficient evidence to recommend venlafaxine for treatment of chronic pain in breastfeeding women (LOE 4, GOR D, SOA 98.9%).

(iii) There are no data relating to paternal exposure to SNRIs, but due to maternal compatibility, they are unlikely to be harmful (LOE 4, GOR D, SOA 98.9%).

SSRIs

The SSRIs are used to treat chronic pain at similar doses used to treat depression. There were 36 overlapping studies reporting on fluoxetine, sertraline and paroxetine use in pregnancy in large numbers of patients with depression compared with huge population control groups [14, 27–30, 38–68]. In the majority of these studies, patients were on concomitant medication (including other antidepressants, benzodiazepines and antipsychotics) or concurrent drug exposure was not reported. Although the majority of studies showed no significant effect on gestation or birthweight, one large study showed that when SSRI exposures were grouped, there was a significant OR for preterm delivery of 1.4 (95% CI 1.2, 1.7) and a significant OR for birthweight <2.5 kg of 1.4 (95% CI 1.3, 1.6) [40]. Where reported, the rates of pregnancy loss across all trimesters were similar for fluoxetine, paroxetine and sertraline and there was no increased risk compared with controls. There were no studies identified that reported outcomes in infants exposed to duloxetine during pregnancy or breastfeeding.

Fluoxetine

There were 10 cohort [14, 29, 41, 50, 52–55, 58, 69] and 17 case–control studies [27, 38–40, 42–49, 51, 56, 57, 59, 60] investigating fluoxetine exposure in 23 389 pregnancies. There was no appreciable adverse effect on pregnancy duration or birthweight from these studies, reporting an average gestation of 38.2–40 weeks [27, 29, 40, 42, 47, 48, 50, 51, 56–58], with 6.2–8.1% preterm deliveries in four studies [13, 42, 48, 53], and an average birthweight of 3.2–3.6 kg overall [14, 27, 29, 40, 47–51, 56–58].

The incidence of major malformations was not increased in the majority of studies. Overall, there were 194 major malformations in 4649 exposed pregnancies (4.2%) in data from 17 studies [14, 27, 38–40, 43, 44, 47–49, 51–53, 55, 56, 59, 60] compared with 54 962 of 1 669 335 (3.3%) in the control groups in 14 studies [27, 38–40, 43, 44, 47–49, 51, 55, 56, 59, 60]. The vast majority of studies concluded that exposure to fluoxetine during pregnancy did not significantly increase the risk of major congenital malformations. One study of 346 pregnancies showed a 2-fold increased risk of major malformations, with a significant OR of 4.5 for cardiac malformations [51]. One large study grouped major and minor malformations and was therefore excluded from the above calculations [37]. This study found 3.9% of 926 exposed infants had major/minor malformations, compared with 4.7% of 873 876 non-exposed controls. It concluded no significant increased risk for malformations following fluoxetine exposure. An increased risk of persistent pulmonary hypertension (PHT) was observed in a single large high-quality study, with 9 of 7988 exposed infants affected and an OR of 2.0 (95% CI 1.0, 3.8) [41].

Three studies investigated neonatal outcomes after exposure in breast milk [47, 50, 54]. One study showed no difference in neurological development at 1 year [47] and one small study of 26 infants found temporarily reduced growth in exposed infants but no other adverse outcomes [50]. Another study of 29 infants exposed to fluoxetine in breast milk showed no significant difference in weight gain compared with non-exposed infants [54]. We identified no studies of paternal exposure to fluoxetine.

Paroxetine

There were 7 cohort [28, 41, 54, 55, 62, 66, 69] and 16 case–control studies [38–40, 42–46, 51, 59–61, 63–65, 68] investigating paroxetine exposure in a total of 21 394 pregnancies. Overall there was no adverse effect on pregnancy duration or birthweight. Four studies showed no effect on pregnancy duration, with an average gestation of 38.3–39.1 weeks [40, 42, 51, 65] and 6.9–12.0% of exposed infants born prematurely in four studies [40, 43, 54, 61]. One study reported preterm deliveries in 20% (11/55) of pregnancies [64]. In this small study, increased rates of preterm delivery could be attributed to confounders such as maternal depression or smoking. Six studies showed no effect on birthweight [40, 42, 51, 61, 64, 65]; across four studies the average birthweight was 3.1–3.3 kg [40, 51, 64, 65] and two studies found 3.1–5.3% of exposed infants to be small for their gestational age [42, 61].

The majority of studies showed no significant increase in major malformations in paroxetine-exposed infants. Data collated from 13 studies found major malformations in 3.36% (295/8766) of pregnancies [28, 38–40, 43, 44, 51, 55, 59, 60, 62, 63, 68]. Control data from the same 13 studies showed a rate of 3.6% for major malformations in 1 724 959 unexposed infants. Ten studies concluded that there was no significant increased risk of malformations following paroxetine exposure during pregnancy, whereas three studies reported a significantly increased risk (described below) [55, 62, 63]. One large study grouped

major and minor malformations and was therefore excluded from the above calculations. This study found 4.8% of 959 exposed infants had major/minor malformations, compared with 4.7% of 873 876 non-exposed controls. It showed no significant increased risk for all malformations but a significant relative risk of 1.63 (95% CI 1.05, 2.53) for cardiac malformations. Thirteen of the 20 cardiac malformations in this study were septal heart defects [41]. One study of 815 pregnancies showed a significantly increased OR of 1.9 (95% CI 1.2, 3.0) for all malformations [62]. One small study of 92 pregnancies showed a significant relative risk of 2.2 (95% CI 1.1, 4.4) for any cardiac malformation after paroxetine exposure. This risk was based on four cases, three of which were ventricular septal defects [55]. Another study of 542 pregnancies found a possible dose-dependent increased risk in malformations, as there was a 2-fold increase in all malformations and a 3-fold increase in cardiac malformations, but only at doses >25 mg/day—the increased risk became non-significant when grouping all doses of paroxetine exposure [63].

Several studies showed a non-significant trend towards an increased risk of cardiac malformations or major malformations in general. A study of 463 pregnancies showed a non-significant 2-fold increased risk of malformations [51]. A study of 676 exposed pregnancies showed the association between paroxetine and cardiac defects was approaching significance [OR 1.8 (95% CI 0.8, 3.7)] [40]. Finally, one study reported a non-significant trend towards cardiac malformations and a significant OR of 4.7 (95% CI 1.5, 14.7) for right-ventricular outflow tract anomalies, although this finding was only based on three cases [59].

An increased risk of persistent PHT was observed in a single large high-quality study, with 5 of 3798 exposed infants affected and a significant OR of 2.8 (95% CI 1.2, 6.7) [42]. Three small studies found third-trimester paroxetine exposure increased the risk of behavioural signs such as jitteriness, insomnia, restlessness and poor feeding, known as neonatal adaptation/abstinence syndrome: 30% (8/60) of infants showed symptoms with a dose-dependent response [46]; 22% (12/55) exposed infants had neonatal complications [64] such as poor adaptation and mild respiratory distress at birth; the third paper, reporting three cases of transient neonatal symptoms, found no difference in development at 8 months in a total of 17 exposed infants [66]. One of these studies also followed up 36 women who continued taking paroxetine during breastfeeding; 8 of 36 mothers reported neonatal symptoms (including alertness, constipation, sleepiness and irritability), whereas no adverse neonatal effects were reported in the control group [64].

One study of 15 infants exposed to paroxetine in breast milk showed no significant difference in weight gain compared with non-exposed infants [67]. No other studies evaluated outcomes after paroxetine exposure in breast milk or long-term outcomes. We identified no studies of paternal exposure to paroxetine.

Sertraline

Two cohort [40, 53] and nine case–control studies [38–40, 42–45, 59, 60] investigated sertraline exposure in a total of 20 822 pregnancies. There was no adverse effect on pregnancy duration or birthweight. Pregnancy duration was reported in four studies—in two studies the average gestation was 38.2–39 weeks [40, 42] and in three studies the proportion of preterm delivery ranged from 5.6 to 11.9% [40, 43, 54]. One study demonstrated no effect of sertraline exposure on birthweight, with a mean birthweight of 3.3 kg [40].

In data from 7 studies [38–40, 43, 44, 59, 60], the incidence of major malformations was not increased following sertraline exposure, occurring in 4% (125/3156) of the total number of exposed infants compared with 3.4% (53 834/1 599 889) controls. All studies concluded that there was no significantly increased OR for major malformations in general. One study of 352 pregnancies showed an increased OR of 3.0 (95% CI 1.4, 6.4) for cardiac malformations and 3.3 (95% CI 1.5, 7.5) for septal heart defects [43]. Another study of 259 pregnancies reported a significantly increased risk of septal heart defects, with an OR of 3.3 (95% CI 1.2, 8.8) [44]. One large study grouped major and minor malformations and was therefore excluded from the above calculations [37]. This study found 3.5% of 1906 exposed infants had major/minor malformations, compared with 4.7% of 873 876 non-exposed controls.

An increased risk of persistent PHT was observed in a single large high-quality study, with 10 of 6696 exposed infants affected and a significant OR of 2.3 (95% CI 1.3, 4.4) [42]. One study of 25 infants exposed to sertraline in breast milk showed no significant difference in weight gain compared with non-exposed infants [54]. It has been reported that sertraline has one of the lowest rates of transmission to breast milk of any SSRI (LactMed website). We identified no studies of paternal exposure to sertraline.

Summary of key findings of SSRIs

Overall, the majority of studies do not show an increased rate of major malformations following maternal exposure to fluoxetine, paroxetine and sertraline. Despite one large study showing a small but significantly increased risk of persistent PHT with all SSRIs, the actual risk remains extremely small and concern regarding a small increased risk of cardiac malformations in some studies is not universally reported. Since there is no robust evidence of a superior safety profile for any one drug, switching between drugs is not recommended if depression is stable on treatment. There is limited information on the use of these drugs in breastfeeding. One small study showed temporarily reduced growth during exposure to fluoxetine in breast milk. There have been no studies specifically investigating the compatibility of paroxetine and sertraline with breastfeeding, but sertraline is reported as having one of the lowest rates of transmission to breast milk.

Recommendations for SSRI s in pregnancy and breastfeeding

(i) Fluoxetine, paroxetine and sertraline are compatible with pregnancy (LOE 2++, GOR C, SOA 97.9%).
(ii) Cessation of anti-depressant therapy in the postnatal period is not recommended due to the risk

of relapsing depression (LOE 4, GOR D, SOA 99.5%).

(iii) Based on limited but reassuring data, women should not be discouraged from breastfeeding on SSRIs, but caution is recommended until further information is available (LOE 4, GOR D, SOA 98.4%).

(iv) There are no data relating to paternal exposure to SSRIs, but based on maternal compatibility, they are unlikely to be harmful (LOE 4, GOR D, SOA 98.4).

NSAIDs

In the 2006 consensus it was concluded that non-selective cyclooxygenase (COX) inhibitors are not teratogenic and can be continued during the first and second trimester. All NSAIDs except LDA should be withdrawn at gestational week 32 because of the increased risk of early closure of the ductus arteriosus. Agreement was lacking on when to stop LDA before delivery with some experts advising cessation one week before a planned delivery with epidural anaesthesia while others advocated continuation in patients with APS. There was insufficient evidence on selective COX-2 inhibitors so they were not recommended at any stage during pregnancy.

NSAIDs and COX-2 inhibitors

A search for additional relevant studies on naproxen, diclofenac, ibuprofen, indomethacin, etodolac, meloxicam, celecoxib and etoricoxib from 2005 onwards revealed one systematic review [70], five cohort studies [18, 71–74], two case–control studies [75, 76] and one case report [77] on 15 606 patients compared with 250 143 controls throughout pregnancy. These studies gave limited information on concomitant (particularly over the counter) drug use, pregnancy duration, birthweight and maternal complications. Although effects on fertility were excluded from our search, it should be noted that NSAIDs, particularly selective COX-2 inhibitors, have been associated with luteinized unruptured follicle syndrome [78].

Data from the Quebec Pregnancy Registry quantified the association between spontaneous abortion and exposure to non-aspirin NSAIDs in pregnancy. Of 4705 women who had a spontaneous abortion, 352 (7.5%) were exposed and in 47 050 controls there were 1213 (2.6%) exposed. Adjusting for potential confounders (but not over-the-counter medications), the use of any type or dose of non-aspirin NSAID during pregnancy was significantly associated with the risk of spontaneous abortion [OR 2.43 (95% CI 2.12, 2.79)] [76]. Data from 47 400 live-born singleton sons of mothers enrolled in the Danish National Birth Cohort (1996–2002) found that exposure to paracetamol in the first and second trimester, but not ibuprofen, acetylsalicylic acid and aspirin, was associated with cryptorchidism [18]. A systematic review of articles from 1966 to 2008 [including 22 case–control, 7 cohort and 1 randomized controlled trial (RCT)] concluded that exposure to aspirin or NSAIDs during the first trimester of pregnancy was associated with an increased risk of gastroschisis (in six of eight aspirin studies), cardiac malformations (in three of eight NSAIDs studies) and orofacial malformations (in two of two naproxen studies) [70]. The reliability of these conclusions has been questioned, however, given their reliance upon observational studies (the best evidence available) and lack of quality assessment [79]. There were no breastfeeding or post-partum follow-up data.

A recently published case–control study on 377 cases exposed throughout pregnancy did not reveal evidence to support the hypothesis that maternal consumption during pregnancy of NSAIDs overall or ibuprofen in particular is associated with the risk of persistent PHT in children [75]. In addition, a cohort study on 5152 pregnancies exposed to non-selective COX inhibitors and 114 to COX-2 selective inhibitors (celecoxib, etoricoxib, rofecoxib) did not show an association with an increased risk of major malformations in general, although an increased risk for musculoskeletal malformations was found following exposure to COX-2 selective inhibitors [74].

LDA

LDA is used to prevent thrombosis and pre-eclampsia in high-risk groups rather than as an analgesic/anti-inflammatory drug throughout pregnancy in patients with rheumatic diseases. In our search for studies on the use of LDA (60–150 mg/day) in pregnancy and breastfeeding, we identified an additional 2 systematic reviews [70, 80], 4 RCTs [81–84], 17 cohort studies [18, 85–100], 1 case–control study [101] and 2 case series [102, 103] describing 4254 pregnancies exposed to LDA compared with 16 221 healthy controls throughout pregnancy. The studies were confounded by the use of multiple other drugs, most frequently heparin, HCQ, prednisolone, bendroflumethiazide, losartan, MMF, methyldopa and nifedipine. Pregnancy duration was specified in 11 of the 28 papers identified and all papers reported an average gestation of >37 weeks. Birthweight was specified in 13 of 28 papers, but was often confounded by the indication for aspirin. One paper (n = 61) [87] reported an average birthweight of <2500 g, six papers (n = 234) [86, 89, 95, 97, 99, 103] reported an average birthweight between 2500 and 3000 g and five papers (n = 263) [81, 83, 84, 90, 91] reported an average birthweight >3000 g. Maternal complications occurred in 113 patients and were compatible with disease flare. Similarly, congenital malformations and miscarriages were confounded by disease indication, with no evidence of increased risk compared with the background risk for these disease groups. In particular, the use of LDA in the third trimester of pregnancy is not associated with premature closure of the ductus arteriosus, and NICE guidelines (August 2010) for hypertension in pregnancy advise treatment with LDA until delivery [104]. There were no studies of breastfeeding or long-term follow-up.

Paternal exposure

Two cohort studies [105, 106] reported on outcomes from 888 pregnancies after paternal exposure to NSAIDs. The

quality of these studies was low, but they did not identify an increased risk of adverse foetal outcomes.

Recommendations for NSAIDs, COX inhibitors and LDA in pregnancy and breastfeeding

(i) Discordant findings from retrospective, large studies with population controls on the use of non-selective NSAIDs in the first trimester of pregnancy raise the possibility of a low risk of miscarriage and malformation. Therefore, these drugs should be used with caution in the first trimester of pregnancy (LOE 1−, GOR B, SOA 99.5%).

(ii) All non-selective NSAIDs except LDA should be withdrawn at gestational week 32 to avoid premature closure of the ductus arteriosus (LOE 4, GOR D, SOA 100%).

(iii) LDA may be continued throughout pregnancy and NICE guidelines (August 2010) for hypertension in pregnancy advise treatment with LDA (for prophylaxis of pre-eclampsia) until delivery (LOE 1+, GOR B, SOA 100%).

(iv) At present, there are limited data on selective COX-2 inhibitors; they should therefore be avoided during pregnancy (LOE 2+, GOR D, SOA 98.9%).

(v) Non-selective NSAIDs are excreted into breast milk but there is no published evidence of harm (LOE 4, GOR D, SOA 98.9%).

(vi) Non-selective NSAIDs are compatible with paternal exposure (LOE 2−, GOR D, SOA 98.9%).

(vii) There are no data relating to the use of LDA during breastfeeding or paternal exposure to LDA, but there are no theoretical concerns (LOE 4, GOR D, SOA 98.9%).

Anticoagulants in rheumatic disease

Existing guidelines for the use of anticoagulants in APS in pregnancy (the most frequent rheumatic indication) were referenced in the 2006 consensus. The deleterious effects of warfarin and compatibility of heparin in pregnancy are well described and evidence-based guidelines for the management of venous thromboembolism and thrombophilia in pregnancy exist [80]. Furthermore, these and other systematically produced guidelines describe the management of venous thromboembolism and pregnancy morbidity in pregnant patients with APS [107, 108]. Both heparin and warfarin are compatible with breastfeeding.

Heparin

We searched from 2005 onwards for the use of heparin in pregnancy and identified 6 RCTs [81–84, 109, 110], 2 systematic reviews [80, 111], 16 cohort studies [85, 87, 88, 91–100, 112–114], 2 case–control studies [101, 115], 2 case series [103, 116] and 8 case reports [117–124] on 1285 pregnancies. The use of heparin in these studies was frequently confounded by disease activity, concomitant use of other drugs (particularly aspirin), as well as limited reporting on maternal complications and pregnancy outcomes. Overall, there were no consistent adverse effects and heparin was compatible with pregnancy.

There were no additional studies of heparin in breastfeeding, but LactMed states that no particular caution is required since the molecular weight of heparin is such that it is unlikely to be appreciably excreted into breast milk. No studies were identified examining pregnancy outcomes after paternal exposure to heparin.

Warfarin

We identified one systematic review [80], two cohort studies [112, 125], one case series [126] and one case report [122] on the use of warfarin in pregnancy. In most studies, patients were on additional drugs, such as aspirin. A cohort study summarized 30 years of data on 155 live births in women with prosthetic heart valves, in whom 25 women continued warfarin throughout pregnancy and 23 women stopped warfarin at week 6 [112]. They found an association of warfarin with early miscarriage and a 9.7% rate of major malformations. Frequency of intrauterine growth restriction or small for gestational age, defined as a birthweight <2 S.D. of normal for gestation, was not different from healthy controls [112]. In contrast, no maternal or foetal complications were observed in a small cohort study [125] of 16 pregnancies exposed to low-dose anticoagulation therapy in women with mechanical aortic valve replacement. However, until these findings are confirmed in larger studies, heparin remains the anticoagulant of choice in pregnancy for the majority of patients considered to be at increased thrombotic risk.

We identified no studies of warfarin use during breastfeeding, but evidence cited by LactMed is reassuring, both with regards to low drug levels in breast milk and infant serum and no reported adverse effects. We identified no studies of paternal exposure to warfarin.

New Anticoagulants

There is limited information on the use of new antiplatelet and anticoagulant drugs in human pregnancies or breastfeeding. In patients with APS, new oral anticoagulants such as the direct factor Xa inhibitor (rivaroxaban) and thrombin inhibitor (dabigatran) have theoretical advantages over warfarin and may enter routine clinical use for this disease, hence questions over their prescribing in pregnancy will undoubtedly arise. Currently, however, no published human data exist for either of these drugs in pregnancy and they have both been shown to cause adverse obstetric outcomes in animal studies, described in the summary of product characteristics [127, 128].

Rivaroxaban crosses the placenta in animals and causes marked maternal haemorrhagic complications in rats and an increased incidence of post-implantation pregnancy loss in rabbits. In addition, increased foetal toxicity (of increased resorptions, decreased number of live foetuses and decreased foetal body weight) in rabbits occurred at doses $\sim$4 times the human exposure of unbound drug and decreased foetal body weights occurred in rats at doses $\sim$14 times the human exposure. Furthermore, maternal bleeding and maternal and foetal death (at doses about six times the human exposure) have

been reported. No increased risk of structural malformation or impairment of fertility was observed. Rivaroxaban and/or its metabolites were excreted into the milk of rats. It is not known if rivaroxaban is excreted in human milk and the effects in nursing infants are unknown.

Dabigatran has been shown to reduce the number of implantations when male and female rats were treated pre-conception and up to day 6 post implantation at doses ~2.5–3.0 times the human exposure. In addition, rats treated after implantation experienced an increase in the death of offspring and vaginal/uterine bleeding resulting in maternal death. Although dabigatran caused an increased incidence of delayed or irregular ossification of foetal skull bones and vertebrae in rats, it did not cause major malformations in rats and rabbits. There are no data on the excretion of dabigatran into human breast milk.

Recommendations for anticoagulants in pregnancy and breastfeeding

(i) Low molecular weight heparin is compatible throughout pregnancy (LOE 1++, GOR A, SOA 100%).
(ii) Although there are no data on heparin use during breastfeeding, there are no theoretical concerns (LOE 4, GOR D, SOA 98.9%).
(iii) The use of warfarin in pregnancy is associated with increased foetal risk throughout pregnancy and has limited indications and therefore should only be considered in exceptional circumstances (LOE 1–, GOR B, SOA 100%).
(iv) Warfarin is compatible with breastfeeding (LOE 1–, GOR B, SOA 100%).
(v) There are no data regarding paternal exposure to warfarin or heparin, but there are no theoretical concerns (LOE 4, GOR D, SOA 100%).
(vi) Rivaroxaban and dabigatran cannot be recommended in pregnancy or breastfeeding due to a lack to human data and concerns from animal studies. Further research is required to evaluate whether these drugs are compatible in these situations (LOE 4, GOR D, SOA 100%).

Bisphosphonates

Bisphosphonates are not ideal in women planning pregnancy since the absolute risk of fracture is small in this age group and the skeletal half-life of these drugs is very long. In the 2006 consensus, pregnancy was not recommended until 6 months after cessation of bisphosphonates, and breastfeeding could not be safely advised, due to insufficient data [2]. We identified two cohort studies [129, 130] and one case series [131] that met our inclusion criteria on 55 pregnancies in patients with rheumatic disease, predominantly exposed during the first trimester, and no studies of paternal exposure.

The studies were confounded by concomitant medication. Pregnancies were term (38–39 weeks), with mean birthweights of 2.89–3.1 kg. No maternal complications were described. Three major congenital malformations were described out of 46 live births: one ventricular septal defect (exposed to clodronic acid), one kidney and cardiac malformation (exposed to alendronate) in a case series (n = 10) [131] and a case of Aperts syndrome (an autosomal dominant acrocephalosyndactyly) linked to a maternal genetic mutation in a cohort study (n = 21) [130]. A total of 8 first-trimester miscarriages, 1 elective termination of pregnancy and 46 live births were described. There were no studies of breastfeeding or long-term follow-up data.

A number of other case reports that did not meet our inclusion criteria have been published on a total of 78 bisphosphonate-exposed pregnancies with 69 live births and no serious adverse events specifically related to bisphosphonates [132]. Overall, the number of human pregnancy exposures remains limited and bisphosphonates are not drugs of choice in women planning pregnancy. We identified no studies of bisphosphonate use during breastfeeding or of paternal exposure to bisphosphonates.

Recommendations for bisphosphonates in pregnancy and breastfeeding

(i) There are insufficient data upon which to recommend bisphosphonates in pregnancy or to advise a specific time for them to be stopped pre-conception. Given their biological half-life in bone of up to 10 years and no evidence of harm from limited reports of their use in pregnancy, a pragmatic recommendation is that they should be stopped 3 months in advance of pregnancy (LOE 4, GOR D, SOA 98.4%).
(ii) There are no data on which to base a recommendation for the use of bisphosphonates during breastfeeding (SOA 99.5%).
(iii) There are no data on which to base a recommendation for paternal exposure to bisphosphonates (SOA 100%).

Antihypertensive medication in rheumatic disease

Patients with autoimmune rheumatic disease (ARD), particularly renal SLE and SSc, frequently require antihypertensive treatment, therefore we considered commonly prescribed drugs used to manage this condition rather than management of pre-eclampsia *per se*, which is covered in more detail in the NICE guidelines for the management of hypertension in pregnancy [104].

Angiotensin blockade

A comprehensive systematic review of studies of pregnancy outcomes following exposure to angiotensin-converting enzyme inhibitors (ACEIs) was published in 2012 [133], therefore we searched for additional studies relating to pregnancy outcomes from 2011 onwards and from 1960 onwards for studies relating to breastfeeding and paternal exposure. In addition to the systematic review, a further case–control [134] and two cohort [135, 136] studies were identified on a total of 969 pregnancy exposures, mostly first trimester, to captopril (n = 59), enalapril (n = 57), lisinopril (n = 36), monopril (n = 8), quinapril

(n = 6), ramipril (n = 3), cilazapril (n = 3), benzapril (n = 2) and grouped as opposed to individual ACEI outcomes (n = 795). The main indication for these drugs was maternal hypertension that required treatment during pregnancy.

Maternal and foetal outcomes in these studies were confounded by maternal disease activity, concomitant medication and hypertension *per se*, which may be responsible for congenital anomalies and/or LBW. The majority of ACEI-exposed pregnancies reported preterm deliveries and corresponding LBW. In particular, a mean gestational age of 34.7 weeks and mean birthweight of 2.1 kg from 118 ACEI-exposed pregnancies were described by Bullo *et al.* [133]. Maternal complications mostly related to hypertension, such as renal crisis or pre-eclampsia. Disruption of the renin-angiotensin system (RAS) in pregnancy leads to abnormal renal development and is known as foetal RAS blockade syndrome. This condition has been shown to occur after maternal treatment with ACEI. Of 118 exposures reported in the systematic review, 61 newborns did not have foetal RAS blockade syndrome and significantly more newborns without foetal RAS blockade syndrome were exposed at the beginning of the pregnancy only [133]. Interestingly, this same review noted that 24 of 25 newborns who experienced no complications and were exposed at the end of the pregnancy or during the entire pregnancy had been exposed to captopril, which has a short elimination half-life. Two large studies describing (n = 795) pregnancy outcomes following first-trimester exposure to ACEIs as a whole did not find a statistically significant increase in congenital anomalies after first-trimester exposure in comparison with unexposed [135], hypertensive [136] pregnancies. An increased incidence of miscarriage was noted in one study [134].

A previous systematic review has shown that low to negligible amounts of enalapril and captopril are transferred into breast milk, with no adverse effects reported on the breastfed infants of mothers treated with short-acting ACEIs [137]. Previous reports of long-term follow-up of infants exposed to ACEIs include 6 months following captopril exposure [138–140] and 43 months following lisinopril exposure in a child who was small for age but in mainstream schooling with age appropriate psychomotor development [141].

No studies of paternal ACEI exposure were identified for inclusion in our analysis. Interestingly, low-dose lisinopril (2.5 mg/day) has been shown to increase total sperm count and motility in a randomized controlled crossover pilot study of normotensive men with idiopathic oligospermia leading to an unassisted pregnancy rate of 48.5% [142].

Recommendations for ACEI in pregnancy and breastfeeding

(i) ACEI should be stopped as soon as possible when pregnancy is confirmed in the first trimester and if necessary an alternative antihypertensive compatible with pregnancy should be given (LOE 2++, GOR B, SOA 100%).

(ii) ACEI should be avoided in the second and third trimester (LOE 2++, GOR B, SOA 100%).

(iii) There is limited evidence on use of ACEI in breastfeeding. The human breast may selectively restrict the passage of captopril and/or enalapril from blood into breast milk, so it is unlikely to cause adverse effects in breastfed infants (LOE 3, GOR D, SOA 98.9%).

(iv) There are insufficient data on which to base a recommendation regarding paternal exposure to ACEI, but there are no theoretical concerns (LOE 4, GOR D, SOA 100%).

Calcium channel antagonists

Calcium channel antagonists were not covered by the previous consensus, therefore we searched from 1960 onwards. Fourteen studies, including one RCT [143], six systematic reviews [144–149], two case series [150, 151] and five case reports [121, 138, 152–154] were identified, covering 5613 pregnancy exposures to nifedipine in patients with rheumatic disease (SLE and SSc). A further six papers comprising three case series [155–157] and three case reports [158–160] referred solely to exposure during breastfeeding, using nifedipine as a treatment for RP of the nipple.

The selected studies were confounded by their main clinical indication to treat maternal complications, such as preterm labour and eclampsia, and concomitant drug therapy, including other antihypertensives, corticosteroids and anticoagulants. Therefore, although most large studies did not report pregnancy duration, in 8 of the 14 studies that did, they reported preterm deliveries of 34–37 weeks in 5 studies [121, 138, 143, 150, 151] and 26–33 weeks in 3 studies [152–154]. Preterm birthweights of 1.7 kg [138], 2.4 kg [146] and an average 3.1 kg [150] at 34–37 weeks, 1.9 kg at 33 weeks [152] and 0.6 kg at 26 weeks [154] were recorded.

Maternal complications of pre-eclampsia, eclampsia and premature labour were indications for treatment with nifedipine. A large systematic review [144] noted a significant increase in maternal complications, especially in tachycardia and hypotension if the dose of nifedipine exceeded 60 mg. Other maternal adverse events reported to be associated with high-dose nifedipine included myocardial infarction, palpitations, pulmonary oedema, cyanosis, hypoxia, loss of deep tendon reflexes, colonic pseudo-obstruction and ileus. The only reported malformation was an asymptomatic non-communicating duplication of the oesophagus [121], where the foetus was also exposed to MMF. Only one foetal loss was described in the third trimester of a mother with advanced PHT who subsequently died [150].

Low doses of nifedipine were present in breast milk in one case series 3 days post-dose, with favourable outcomes in all cases (n = 11), with the authors concluding that exposure to nifedipine through breast milk is not significant. Other case reports agree that nifedipine is compatible in breastfeeding up to 20 mg/day [148]. There was only one study with long-term follow-up (up to 27 months), in which subgroup analysis suggested no significant effect

of *in utero* nifedipine exposure on neurodevelopmental status at 2 years of age or psychosocial and motor functioning [147].

Amlodipine data were scarce, with one case report where it was concomitantly used with MMF in a mother with LN [161]. The baby was delivered at 35 weeks with a birthweight of 2.2 kg and had multiple congenital malformations attributed to MMF. We identified no studies of paternal exposure to calcium channel blockers.

Recommendations for calcium channel blockers in pregnancy and breastfeeding

(i) Nifedipine is compatible with pregnancy, with no direct evidence of harm at doses up to 60 mg/day (LOE 1+, GOR B, SOA 99.5%).
(ii) Nifedipine is compatible with breastfeeding (LOE 3, GOR D, SOA 100%).
(iii) There are insufficient data to recommend amlodipine in pregnancy, but there is no evidence of harm during pregnancy and an absence of evidence during breastfeeding (LOE 3, GOR D, SOA 99.5%).
(iv) There are no data relating to paternal exposure to calcium channel blockers, but they are unlikely to cause harm (LOE 4, GOR D, SOA 98.9%).

Pulmonary vasodilators

PHT is a rare complication of certain ARDs and remains a contraindication to planned pregnancy, with high mortality rates. Accidental pregnancy and/or patient choice, however, means that treatment of this condition with specific pulmonary vasodilators may be required in pregnancy. These drugs were not considered in the previous consensus, therefore we searched for relevant information on sildenafil, tadalafil, bosentan, iloprost and epoprostenol from 1960 onwards. No studies were identified examining pregnancy outcomes after paternal exposure to these pulmonary vasodilators.

Sildenafil

There is very limited information on sildenafil in human pregnancy. Animal data have not shown evidence of teratogenicity or fetotoxicity at doses up to 40 times the maximum recommended human dose [162]. We identified seven studies—one RCT [163], two systematic reviews [164, 165], two case series [166, 167] and two case reports [122, 168]—with all but one lacking control data. These studies described 36 pregnancies complicated by PHT (n = 19) and pre-eclampsia (n = 17) that were treated with sildenafil (8 throughout pregnancy and 34 in the second/third trimester) as well as multiple other medications, including bosentan (in 16 pregnancies). One study reported 17 pregnancies with a mean gestational age at 31 weeks and a mean birthweight of 1.4 kg, but adverse outcomes were attributed to background disease and not to sildenafil [163]. One case series [166] reported four successful pregnancy outcomes, with babies delivered by caesarean section and a mean gestational age of 34 weeks. Pregnancy duration of 37 weeks was reported in one case report with a birthweight of 2.8 kg [122] and an average birthweight of 1.8 kg in two pregnancies [164]. Maternal complications included right heart failure [167], pulmonary thromboembolism [165] and hypotension with concomitant epoprostenol therapy [166], none of which were attributed to sildenafil. No malformations or miscarriages were reported. There are no breastfeeding data, and at 3 months follow-up post-partum, no adverse events were reported in one child [122].

Bosentan

Similarly, there is limited information on bosentan in human pregnancy. Animal data have revealed teratogenicity, including malformations of the head, mouth, face and large blood vessels in addition to an increased number of stillbirths and increased mortality [169]. We identified two systematic reviews [164, 165], one case series [166] and a case report [122], describing its use in 12 pregnancies of women with PHT treated with bosentan in pregnancy as well as multiple other medications, including sildenafil (n = 12) and iloprost (n = 11). Pregnancy duration of 37 weeks was reported in one case report with a birthweight of 2.8 kg [122] and birthweight alone of 1.4 kg described in another case report [164]. Mothers had PHT, but no other maternal complications or foetal loss were described. There are no breastfeeding data, and at 3 months follow-up post-partum, no adverse events were reported in one infant [122].

Prostacyclines

Rodent studies of iloprost have revealed evidence of fetotoxicity, although these effects were not found in primate studies even at considerably higher doses than those used in humans [170]. In contrast, animal studies of epoprostenol have failed to reveal evidence of fetotoxicity or impaired fertility at doses 2.5–4.8 times the recommended human dose [171]. There are no controlled data on either drug in human pregnancy.

Our search identified four case reports [122, 168, 172, 173] and five case series [116, 150, 166, 167, 174] on 23 pregnancies of patients with PHT (3 with SLE) treated with iloprost (n = 5 pregnancies) or epoprostenol (n = 15 pregnancies) and 3 other prostacyclines (unspecified type). These patients were taking multiple other medications including immunosuppressants, sildenafil and bosentan (n = 12).

The case series' reported average pregnancy durations of 32 weeks (n = 3) [174], 34 weeks (n = 11) [116, 150, 166] and 36–37 weeks (n = 2) [167]. Corresponding birthweights were 1.9 kg (n = 3) [174] at 32 weeks, 1 kg (n = 3) [116] and 3.1 kg (n = 2) [150] at 34 weeks and 2.4 kg (n = 2) [167] at 36–37 weeks.

In three case reports, pregnancy durations and corresponding birthweights were 35 weeks and 2.2 kg [173], 36 weeks and 3.1 kg [172] and 37 weeks and 2.8 kg [122]. There were no control data to enable the effects of maternal PHT or concomitant drug therapy to be differentiated from those of prostacycline treatment.

Maternal complications were attributable to PHT. One foetal loss occurred in the third trimester [150]. Long-term follow-up to 24 months of a child and mother who

continued on epoprostenol reported no complications [172]. There are no breastfeeding data on either drug.

Recommendations for pulmonary vasodilators in pregnancy and breastfeeding

(i) PHT remains a contraindication to pregnancy. If pregnancy occurs, the use of these pulmonary vasodilator drugs should be considered only as part of a multidisciplinary team assessment (LOE 4, GOR D, SOA 100%).
(ii) Limited evidence supports the use of prostacyclines to treat PHT during pregnancy (LOE 3, GOR D, SOA 99.5%).
(iii) Limited evidence supports the use of sildenafil to treat PHT during pregnancy (LOE 3, GOR D, SOA 99.5%).
(iv) Bosentan is teratogenic in animals and although there is no evidence of harm from human pregnancy, the evidence is insufficient to recommend in pregnancy (LOE 3, GOR D, SOA 100%).
(v) There are no data relating to breastfeeding or paternal exposure to pulmonary vasodilators on which to base a recommendation (SOA 100%).

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 and other drug therapy. These data would also be used to answer specific questions where data are currently lacking. Data relating to the impact of paternal exposure to these drugs (both fertility and male mediated teratogenicity) as well as breastfeeding exposure is particularly limited, and further research in these areas is urgently needed.

Mechanism for audit of the guideline

An audit pro forma to assess compliance with these guidelines is available on the BSR 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)
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)

(continued)

Continued	
	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)
	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).