RHEUMATOLOGY

Rheumatology 2016;55:1698–1702
doi:10.1093/rheumatology/kev405
Advance Access publication 10 January 2016

Guidelines

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

Executive Summary

Scope and purpose of the guideline

Need for guidelines

The prescribing of many drugs in pregnancy is complicated by a lack of knowledge regarding their compatibility, leading to patient misinformation and withdrawal/denial of disease-ameliorating therapies. This situation should be avoided because active rheumatic disease is associated with adverse pregnancy outcomes [1] and there is growing evidence of drug safety in pregnancy.

NICE has accredited the process used by the BSR to produce its guidance on prescribing drugs in pregnancy and breastfeeding. Accreditation is valid for 5 years from 10 June 2013. More information on accreditation can be viewed at www.nice.org.uk/accreditation. For full details on our accreditation visit: www.nice.org.uk/accreditation.

Objectives of the guideline

To provide evidence-based recommendations, which do not imply a legal obligation, for clinicians to follow when prescribing drugs commonly used in the management of multisystem rheumatic conditions before/during pregnancy and breastfeeding, updating previous recommendations [2, 3]. For recommendations on prescribing

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Submitted 17 June 2015; revised version accepted 4 November 2015

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anti-rheumatic drugs in pregnancy and breastfeeding, see the BSR and BHPR guideline part I [4].

Target audience

Health professionals directly involved in managing patients with rheumatic disease in the UK who are or are planning to become pregnant and/or breastfeeding, men planning to conceive and patients who have accidentally conceived while taking these medications.

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.

Key recommendations from the guideline

Specific questions were considered in relation to each drug. 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. These findings are summarized in Table 1. An accompanying description of evidence and full recommendations are given in the full guideline, available as supplementary data at *Rheumatology* Online.

Recommendations for paracetamol in pregnancy and breastfeeding

(i) Paracetamol is compatible peri-conception and throughout pregnancy [level of evidence (LOE) 2+, grade of recommendation (GOR) C, strength of agreement (SOA) 100%].
(ii) Intermittent use is advised because of a small risk of wheeze and childhood asthma with prolonged paracetamol use in pregnancy (LOE 2+, GOR C, SOA 99.5%).
(iii) Avoid regular use during weeks 8–14 of pregnancy due to a small reported risk of cryptorchidism (LOE 2+, GOR C, SOA 99.5%).

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[d]	Yes[b]
Fluoxetine	Yes	Yes	Yes	Caution[d]	Yes[b]
Paroxetine	Yes	Yes	Yes	Caution[d]	Yes[b]
Sertraline	Yes	Yes	Yes	Caution[d]	Yes[b]
NSAIDs					
NSAIDs	Yes	Caution[e]	Stop by week 32	Yes	Yes
COX-2 inhibitors	No	No	No	No	No data
Low-dose aspirin	Yes	Yes	Yes	Yes[f]	Yes[b]
Anticoagulants					
Warfarin	No	No	No	Yes	No data
LMWH	Yes	Yes	Yes	Yes[f]	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 <60mg/day	Yes <60mg/day	Yes	Yes[b]
Amlodipine	No data	No data	No data	No data	Yes[f]
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 the relevant recommendations and main text in the 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 use for treatment of chronic pain in pregnancy. [e]Possible association with miscarriage and malformation. [f]No studies identified, but unlikely to be harmful. ACEI: angiotensin-converting enzyme inhibitor; COX: cyclooxygenase; LMWH: low molecular weight heparin; MDT: multidisciplinary team.

(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 on paternal exposure to paracetamol, but due to maternal compatibility, it is unlikely to be harmful (LOE 4, GOR D, SOA 99.5%).

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 98.4%).
(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%).

Recommendations for tramadol in pregnancy and breastfeeding

(i) Tramadol is compatible with pregnancy, although there have been no high-quality studies published investigating 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%).

Recommendations for amitriptyline in pregnancy and breastfeeding

(i) Amitriptyline is compatible with pregnancy (LOE 2+, GOR C, SOA 99.5%).
(ii) Low-dose amitriptyline for chronic pain 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%).

Recommendations for gabapentin and pregabalin in pregnancy and breastfeeding

(i) There is insufficient evidence to recommend gabapentin for the treatment of chronic pain in pregnancy (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 when 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%).

Recommendations for serotoninand norepinephrine reuptake inhibitors in pregnancy and breastfeeding

(i) Venlafaxine is compatible at conception and throughout pregnancy. There may be an increased risk of neonatal abstinence syndrome/short-term behavioural effects, but larger studies are needed to evaluate this finding (LOE 2+, GOR C, SOA 98.9%).
(ii) There is insufficient evidence to recommend venlafaxine for the treatment of chronic pain in breastfeeding women (LOE 4, GOR D, SOA 98.9%).
(iii) There are no data relating to paternal exposure to serotonin and norepinephrine reuptake inhibitors, but due to maternal compatibility, they are unlikely to be harmful (LOE 4, GOR D, SOA 98.9%).

Recommendations for selective serotonin reuptake inhibitors 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 data, women should not be discouraged from breastfeeding on selective serotonin reuptake inhibitors (LOE 4, GOR D, SOA 98.4%).
(iv) There are no data relating to paternal exposure to selective serotonin reuptake inhibitors, but based on maternal compatibility, they are unlikely to be harmful (LOE 4, GOR D, SOA 98.4%).

Recommendations for NSAIDs, cyclooxygenase 2 (COX-2) inhibitors and low-dose aspirin (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 National Institute for Health and Care Excellence 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%).

Recommendations for anticoagulants in pregnancy and breastfeeding

(i) Low molecular weight heparin is compatible throughout pregnancy (LOE 1++, GOR A, SOA 100%).
(ii) Although no additional data on heparin use during breastfeeding were found, 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 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 of human data and concerns from animal studies (LOE 4, GOR D, SOA 100%).

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 before 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%).

Recommendations for angiotensin-converting enzyme inhibitors (ACEIs) in pregnancy and breastfeeding

(i) ACEIs 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) ACEIs should be avoided in the second and third trimester (LOE 2++, GOR B, SOA 100%).
(iii) There is limited evidence on the use of ACEIs 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 ACEIs, but there are no theoretical concerns (LOE 4, GOR D, SOA 100%).

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 (LOE4, GOR D, SOA 98.9%).

Recommendations for pulmonary vasodilators in pregnancy and breastfeeding

(i) Pulmonary hypertension (PHT) remains a contraindication for pregnancy. If pregnancy occurs, the use of these pulmonary vasodilator drugs in pregnancy 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 during pregnancy, the evidence is insufficient to recommend its use 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%).

Funding: No specific funding was received from any funding bodies in the public, commercial or not-for-profit sectors to carry out the work described in this article.

Disclosure statement: K.S. has received educational support from Daiichi Sankyo. C.G. has undertaken consultancies and received honoraria from Bristol-Myers Squibb, GlaxoSmithKline, MedImmune, Merck Serono and UCB, has been a member of the speakers' bureau for GlaxoSmithKline, UCB and Lilly and has received research grant support from UCB, but none of these activities have been related to the use of any specific drug in pregnancy. L.M. has received support from AbbVie and Pfizer to attend education meetings and received participation honoraria from MSD. I.G. has received unit support from AbbVie, MSD, Roche, Bristol-Myers Squibb and Sobi and participated on advisory boards for Pfizer and received fees for participation in an educational meeting by UCB. D.W. has received financial support for an independent PhD studentship from GlaxoSmithKline and Alere and acted as a consultant for Roche Diagnostics. M.N. has received unit and individual support to attend meetings from UCB and Jansen UK and participated on an expert panel for UCB. M.K. has received individual support to attend meetings from GlaxoSmithKline, UCB and Astra-Zeneca, chairing fees from Bristol-Myers Squibb and honoraria from GlaxoSmithKline/Human Genome Sciences, MedImmune, INOVA Diagnostics and Merck. M.G. has received individual support to attend a meeting from Roche. All other authors have declared no conflicts of interest.

Supplementary data

The full guideline is available as supplementary data at *Rheumatology* Online.

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