Prescribing anti-rheumatic drugs in pregnancy and breastfeeding - the BSR guideline scope

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The guideline will be developed using the methods and processes outlined in Creating Clinical Guidelines: Our Protocol (1). This development process to produce guidance, advice and recommendations for practice has National Institute for Health and Care Excellence (NICE) accreditation.

Why the guideline is needed

The BSR guidelines on prescribing anti-rheumatic drugs in pregnancy and breastfeeding (parts I and II) were published in 2016 (2, 3). The literature search for these guidelines was run in December 2013. Subsequently, there has been an appreciable increase in the number of published pregnancy exposures to biologic disease modifying anti-rheumatic drugs (bDMARDs) and two of these drugs are now licenced for use in pregnancy. In addition, therapeutic advances in management of various inflammatory rheumatic diseases (IRDs) have led to an expansion of bDMARDs and biosimilars with different modes of action as well as a new class of targeted synthetic DMARDs (tsDMARDs).

Additional evidence-based guidelines from the European League Against Rheumatism (EULAR) (4, 5), BSR (6) and the American College of Rheumatology (ACR) (7) have now been published. These guidelines advise on the management of various rheumatic diseases in women of childbearing age and discuss drug usage during pregnancy. In addition, recent EULAR recommendations have been produced following a consensus review detailing a core data set for pregnancy registries in rheumatology (8). This data-set is important because it could allow us, in the future, to gather better quality evidence from registries and has already been shown to be feasible in daily clinical practice (9). Although, these publications have greatly increased awareness amongst healthcare professionals of how to collect data and which anti-rheumatic drugs may be compatible with pregnancy the continuing expansion of existing and novel DMARDs means that uncertainty remains around use of many of these drugs in pregnancy. This uncertainty may still lead to withdrawal of treatment from pregnant women unnecessarily (10). Discontinuation of treatment in preparation for or during early pregnancy can increase the risk of disease activity and flares during pregnancy, and are reported following discontinuation of biologics in patients with inflammatory rheumatic disease (IRD), such as rheumatoid arthritis (RA) and axial spondyloarthritis (AxSpA) (11).

Therefore, an update of the guidelines is now required to address the use of various drugs, particularly bDMARDs and other novel therapies, in patients planning pregnancy, during pregnancy and breastfeeding. This updated information will provide advice for healthcare professionals and patients to ensure more confident prescribing in these scenarios and will highlight any medications that should be stopped and/or avoided in the reproductive age group unless contraception is used.

Key facts and figures

Chronic disease adversely affects pregnancy. Data from Mothers and Babies: Reducing Risk through Audits and Confidential Enquiries across the UK (MBRRACE-UK), reports regularly from a national programme of work conducting surveillance and investigating the causes of maternal deaths, stillbirths and infant deaths. Data from 2015-17, found that 9.2 women per 100,000 died during pregnancy or up to six weeks after childbirth or the end of pregnancy and most women who died had multiple health problems or other vulnerabilities (12). Although the main causes of maternal death related to cardiovascular, thromboembolic and mental health conditions, women with other

long-term health conditions were represented in the data. Precise figures however, on the incidence of pregnancy in patients with IRD are lacking. Based on the UK prevalence of RA and SLE in women of reproductive age there are ~24,000 women in the UK who may plan or become pregnant (13).

Improved treatments for IRDs mean that many women with these conditions are now achieving improved disease control, enhanced quality of life and thus considering pregnancy. Many questions remain however, regarding management of these patients before, during and immediately after their high-risk pregnancies. Questions that are frequently asked by patients are: - how will pregnancy affect my arthritis?; how will arthritis affect my pregnancy?; and what drugs are safe in pregnancy and when breastfeeding? Currently, it is difficult to give precise answers to these questions because data on the effect of pregnancy on rheumatic diseases are conflicting. Historically, pregnancy was considered to have a largely ameliorative effect on RA based on largely retrospective studies lacking objective measures of disease activity. Modern prospective studies however, using validated measures of disease activity reveal less ameliorative effects of pregnancy, such that only 60% of women with active RA improved during pregnancy and nearly 50% had a disease flare within six months postpartum (14). There are conflicting results of the impact of pregnancy on SLE activity and a recent systematic review describes an overall flare rate of around 25 % that were mostly mild, with a severe flare rate of around 5% (15).

Consideration of active rheumatic disease in pregnancy is important because it is associated with a number of adverse pregnancy outcomes (APO). In particular, RA and SLE have an increased burden of APO, including hypertension in pregnancy (13-23%), fetal growth restriction (5%) and preterm delivery (16-18). Novel biomarkers however, to predict APO independently of disease activity in both RA and SLE are lacking. Therefore, DMARDs compatible with pregnancy are required to control disease activity before and during pregnancy to ensure an optimal pregnancy outcome.

Current practice

The concept of treat to target (T2T) with DMARDs and/or immunosuppressive drugs to induce remission or low disease activity is well established in various IRD (19, 20) and has been proposed in pregnancy (13). Maintenance of this strategy however, in pregnancy is often limited by concern of healthcare professionals and/or patients to limit medication exposure for fear of doing harm to the fetus from congenital anomaly. Despite the existence of multiple evidence-based guidelines advising on the management of various IRDs and pregnancy compatible drug-usage in women of reproductive age, prescription of many DMARDs remain complicated by safety concerns and these guidelines are unable to provide secure recommendations for all drugs, particularly new therapies with a limited evidence base relating to use in pregnancy (2, 4, 7). Consequently, many DMARDs are avoided or withdrawn in pregnancy, thus contributing to increased disease activity with associated risk of irreversible joint damage as well as APO during this period (11).

Therefore, continued surveillance of published data is required to update healthcare professionals on cumulative pregnancy exposures and risk to mother/baby with individual drugs. Information on medication safety, however, accumulates slowly from case reports/series, small observational studies and registry studies that frequently lack controls. Data from randomised controlled trials are the exception. Since pregnancy is routinely an exclusion criterion in study of new drugs, any initial approval for clinical use of these drugs in humans generally advises to avoid use in pregnancy. Therefore, it takes many years for an appreciable number (hundreds let alone thousands) of pregnancy exposures to be reported in relation to any new drug for rheumatic diseases.

Clinicians who do not primarily work in obstetric settings may be less familiar with general sources of evidence based information on fetal risk, such as the UK Teratology Information Service (UKTIS) that provides a national service on all aspects of the toxicity of drugs and chemicals in pregnancy (21). Therefore, in the midst of busy clinical practice clinicians will refer to speciality-based documents. For that reason, the BSR guidelines on prescribing anti-rheumatic drugs in pregnancy are one of the most highly cited and downloaded of all BSR guidelines, and are thus likely to have influenced clinical practice. Similarly the EULAR (4) and more recent ACR (7) documents are highly informative on mediation usage in pregnancy.

These documents produced by rheumatologists and other relevant women's health specialists were written with a focus on prescribing and managing medication in pregnancy in patients with rheumatic disease, thus are most relevant to daily rheumatology practice. They have all advanced management of rheumatic disease in pregnancy whilst acknowledging limitations of evidence, particularly on medication usage, and requirement for further research in this field. Inevitably however, all are limited by search and publication date (May 2017 for most recent ACR guidelines (7)) as to current information on new bDMARDs and tsDMARDs.

Given that medication usage during pregnancy is common, around 9 in 10 women taking at least one medicine during pregnancy, and 7 in 10 taking at least one prescription medicine (22) an update on prescribing anti-rheumatic drugs in pregnancy is required on a regular basis.

2 Who the guideline is for

The primary audience consists of health professionals in the UK directly involved in managing patients with rheumatic disease who are (or are planning to become) pregnant and/or breastfeeding, men planning to conceive, and patients who have accidentally conceived whilst 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 dermatologists and general practitioners who may prescribe these medications to patients in pregnancy.

3 What the guideline will cover

3.1 Who is the focus?

Groups that will be covered

- Women of reproductive age who are considering pregnancy; pregnant; or breastfeeding.
- Women of reproductive age who are not considering pregnancy and are taking drugs that are not compatible with pregnancy to help them understand the need for appropriate contraception and risks of unplanned pregnancy.
- Men of reproductive age who are planning to conceive.

3.2 Settings

Settings that will be covered

- Primary care settings
- Secondary/tertiary care rheumatology and obstetric settings

3.3 Activities, services or aspects of care

Key areas that will be covered

To expand and update the previous BSR guidelines on prescribing anti-rheumatic drugs in pregnancy by systematically reviewing all current evidence on pregnancy outcomes in relation to medication exposure in pregnancy. Where possible recommendations will be made regarding compatibility with paternal exposure.

Areas that will not be covered

- Management of infertility
- Indications for these drugs in specific rheumatic diseases in pregnancy.
- Contraceptive measures that should be used in patients on drugs that are not compatible with conception and pregnancy

Related guidance

- Gotestam Skorpen C, Hoeltzenbein M, Tincani A, Fischer-Betz R, Elefant E, Chambers C, et al. The EULAR points to consider for use of antirheumatic drugs before pregnancy, and during pregnancy and lactation. Ann Rheum Dis. 2016;75(5):795-810.

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3.4 Key issues and draft questions

To expand and update the previous BSR guidelines 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 will be made regarding compatibility with paternal exposure.

A systematic literature review will be performed, based on population, intervention, comparator and outcome (PICO) questions, to identify studies using combinations of the key MESH and free terms relating to: pregnancy; lactation; breast feeding; and name of each drug, shown in appendix A.

The guideline is expected to be published in 2022.

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