

The EULAR points to consider for use of antirheumatic drugs before pregnancy, and during pregnancy and lactation

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Handling editor Tore K Kvien

► Additional material is published online only. To view please visit the journal online (<http://dx.doi.org/10.1136/annrheumdis-2015-208840>).

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Received 30 October 2015

Revised 21 December 2015

Accepted 22 January 2016

ABSTRACT

A European League Against Rheumatism (EULAR) task force was established to define points to consider on use of antirheumatic drugs before pregnancy, and during pregnancy and lactation. Based on a systematic literature review and pregnancy exposure data from several registries, statements on the compatibility of antirheumatic drugs during pregnancy and lactation were developed. The level of agreement among experts in regard to statements and propositions of use in clinical practice was established by Delphi voting. The task force defined 4 overarching principles and 11 points to consider for use of antirheumatic drugs during pregnancy and lactation. Compatibility with pregnancy and lactation was found for antimalarials, sulfasalazine, azathioprine, ciclosporin, tacrolimus, colchicine, intravenous immunoglobulin and glucocorticoids. Methotrexate, mycophenolate mofetil and cyclophosphamide require discontinuation before conception due to proven teratogenicity. Insufficient documentation in regard to fetal safety implies the discontinuation of leflunomide, tofacitinib as well as abatacept, rituximab, belimumab, tocilizumab, ustekinumab and anakinra before a planned pregnancy. Among biologics tumour necrosis factor inhibitors are best studied and appear reasonably safe with first and second trimester use. Restrictions in use apply for the few proven teratogenic drugs and the large proportion of medications for which insufficient safety data for the fetus/child are available. Effective drug treatment of active inflammatory rheumatic disease is possible with reasonable safety for the fetus/child during pregnancy and lactation. The dissemination of the data to health professionals and patients as well as their implementation into clinical practice may help to improve the management of pregnant and lactating patients with rheumatic disease.

INTRODUCTION

With new effective therapies and less long-term disability most women with inflammatory rheumatic diseases (RDs) can contemplate pregnancy though substantial risk for adverse maternal and fetal outcomes remain particularly in RD with organ involvement. Drug treatment during pregnancy may be required in order to control maternal

disease which itself can be a threat for fetal well-being and pregnancy outcome. The risk of leaving active inflammatory RD of the mother untreated for 9 months must be weighed against any potential harm through drug exposure of the fetus.

Adjustment of therapy in a patient planning a pregnancy aims to use medications that support disease control in the mother and are considered safe for the fetus. However, only a limited number of antirheumatic/immunosuppressive drugs fulfil these requirements. With the rapidly increasing number of medications available for the treatment of RD, knowledge on safety in pregnancy lags behind. A consensus paper on use of antirheumatic drugs in pregnancy and lactation was published in 2006¹ with an update on immunosuppressive drugs in 2008.² A European League Against Rheumatism (EULAR) task force regarded it timely to collect new available data from the literature and from several databases, and reach expert consensus on their compatibility during pregnancy and lactation, resulting in EULAR points to consider for use of antirheumatic drugs before pregnancy and during pregnancy and lactation.

PARTICIPANTS AND METHODS

The EULAR task force on antirheumatic drugs during pregnancy and lactation is a multidisciplinary committee consisting of 20 members from 10 European countries and the USA (9 rheumatologists, 3 internists, 1 obstetrician, 2 rheumatologist/epidemiologists, 1 specialist in Obstetric Medicine, 1 geneticist, 2 patients with RD as patients' representatives and 1 research fellow). The objective was to formulate points to consider for the use of antirheumatic drugs during pregnancy and lactation by identifying and critically evaluating recent literature and registry data. The task force followed the procedures outlined in 2004³ and updated in 2014.⁴

Systematic literature review

At the first meeting, the committee decided on the medications to be included in the systematic literature review (SLR): Non-steroidal anti-inflammatory drugs (NSAIDs), glucocorticoids, conventional

To cite: Götestam Skorpen C, Hoeltzenbein M, Tincani A, et al. *Ann Rheum Dis* Published Online First: [please include Day Month Year] doi:10.1136/annrheumdis-2015-208840

synthetic DMARDs: methotrexate (MTX), cyclophosphamide, sulfasalazine, leflunomide, antimalarials, azathioprine, colchicine, ciclosporin, tacrolimus, mycophenolate mofetil (MMF), intravenous immunoglobulin (IVIg) and targeted synthetic DMARDs: tofacitinib. Biologic DMARDs included were tumour necrosis factor inhibitors (TNFi) (adalimumab, certolizumab pegol, etanercept, golimumab and infliximab), the T cell costimulation inhibitor abatacept, the anti-B cell agents rituximab and belimumab, the interleukin (IL)-6 receptor-blocking monoclonal antibody tocilizumab, and the IL-1 receptor antagonist anakinra. Biosimilars were not included due to lack of data. Two electronic searches, one for biologic drugs and a separate search for non-biologic drugs were performed in Embase, Medline, PubMed and Cochrane Library from 1 January 2008 to 1 April 2015 by a research librarian at the Norwegian University of Science and Technology University library; Medicine and Health Library, drawing on the Cochrane Musculoskeletal group's strategy for searching for all RDs and adjusting the strategy to make use of the various database search facilities.⁵ The searches were restricted to effects in pregnancy and/or perinatal effects, and excluded reviews (for details see online supplementary figure S1). References of articles found were screened for additional evidence. The search period of 2008–2015 was chosen because inclusion of publications in the consensus paper of 2006 ended early in 2006, and the update of 2008 ended in 2007. As the update publication² did not include all non-biologic drugs, an additional search for the period 2006–2008 was performed for 10 drugs; NSAIDs, glucocorticoids, MTX, cyclophosphamide, sulfasalazine, antimalarials, azathioprine, colchicine, ciclosporin and IVIGs. Because of paucity of lactation data, all reports on lactation exposures to antirheumatic drugs published 1970–2015 derived from LactMed, a database in the Toxicology Data Network, were included.

Publications were restricted to the English language and included prospective and retrospective studies, cohort studies, case-control studies, and case reports. In addition abstracts from major international congresses were included. The search was not limited to RD, but all indications for a given drug were included (see online supplementary figure S1). Results of the different databases were combined and duplicates were excluded; issues regarding inclusion or exclusion of articles were resolved by discussion and consensus between the fellow (CGS) and convenor (MØ).

Registries

The task force obtained access to pregnancy reports from two pharmacovigilance centres and four safety databases from pharmaceutical industries (see online supplementary table S1), and extracted data for all pregnancies with known outcomes.

Data collection sheet

A data collection sheet was constructed to extract relevant data on exposure during pregnancy and lactation. Included were patient characteristics, drug dosing, and exposure time before and during pregnancy/lactation, concomitant medication, and occurrence of pregnancy complications (miscarriages and elective terminations, stillbirth, and preterm delivery) or adverse child outcomes. Congenital malformations, birth weight, neonatal health, infections during the 1st year of life, vaccination responses, and follow-up of children's physical and neurocognitive development were also recorded. Reports that did not disclose the outcome of pregnancy or those for which the temporal association between drug exposure and onset of pregnancy could not be determined were excluded from analysis.

Likewise, incomplete reports on breastfeeding exposures were excluded.

Predefined outcomes

We defined as the primary outcome major congenital malformations in live-born children or aborted fetuses. The only secondary outcome included was miscarriages up to 20 weeks gestation. Other outcomes like termination of pregnancy, pre-eclampsia, prematurity, low birth weight, perinatal and postnatal problems were either incompletely documented or imprecise because of confounding factors. For lactation exposure the primary child outcome was defined as any adverse effect (clinical or laboratory).

Experts' consensus and Delphi rounds

The results of the SLR were presented to the task force members to initiate group discussions and to arrive at statements for the use of antirheumatic drugs in pregnancy and lactation. Statements were based on the consensus papers of 2006/2008^{1, 2} with added evidence from the new SLR as well as unpublished registry data. In the formulation of statements, emphasis was put on congenital malformations since this was the primary outcome that was consistently reported in all publications included. Given the paucity of high quality data and subjective nature of many decisions, the task force agreed that the practicing clinician would be better served by having each expert stating (dis)agreement with the proposed statement and expressing their practice regarding the use of each medication in daily practice (see online supplementary table S2). The Delphi technique⁶ was used to reach consensus on the statements and rate of agreement for the propositions for clinical use.

Strength of evidence

The classical ranking of evidence scores defines systematic reviews of randomised controlled trials (RCTs) as providing the highest level of evidence, followed by individual RCT.⁷ Classical scores of evidence focus on efficacy of an intervention or of drugs, but not on safety. By contrast, evaluation of drugs in pregnancy and lactation has its focus on safety for the embryo/fetus or child, not on efficacy. No adequate ranking system for evaluating strength of evidence (SOE) in regard to safety of drugs in pregnancy and lactation has been developed. After several rounds of discussion, the group decided to use two classical ranking systems in spite of their shortcomings in regard to reproduction issues.

The quality of evidence based on study design was rated according to the Grading of Recommendations Assessment, Development and Evaluation (GRADE) system and Oxford Centre of Evidence Rating.^{8, 9} Data from SLR and data added from registries were subjected to group discussion to establish SOE regarding the statements. For each statement, SOE was graded using a 1–4 ordinal scale for GRADE (see online supplementary table S3) and a 1–5 ordinal scale for Oxford (see online supplementary table S4). The members were then asked to select the proposition that best described their personal current use of each drug during pregnancy and lactation, as described above (see online supplementary table S2). The percentage of consensus for the statements, and agreement for clinical use in pregnancy and lactation were calculated.

RESULTS

In the first meeting the task force defined four overarching principles. In the following two meetings and seven online Delphi

rounds (four concerning medication in pregnancy and three concerning medication during lactation) 11 points to consider were developed (table 1).

Result of SLR

The electronic searches identified a total of 5960 references on antirheumatic drugs during pregnancy and lactation. Additional references were added from hand searches. Nine hundred and forty-four duplicates were excluded (see online supplementary figure S1). A total of 319 publications were eligible for analysis: 45 cohort studies (including 7 abstracts), 24 case-control studies (including 1 abstract) and 250 case series/case reports (including 21 abstracts). Unpublished data from six registries were also included (see online supplementary table S1).

Type of studies recorded, references on cohorts and case controls, number of pregnancies included, pregnancy outcomes, and SOE for each drug or group of drugs are presented in table 2. References on case reports and case series are available in online supplementary table S5.

General aspects of SLR

Adverse pregnancy outcomes

Adverse outcomes other than congenital malformations were not consistently reported; this also applies to miscarriages. Rates of miscarriages may be imprecise since they depend on the time point at which a pregnant patient is included in a study. Only MTX and MMF have been consistently shown to increase the rate of miscarriages. Combination therapies with MTX have sometimes also increased the rate of miscarriages (example table 2, abatacept). The observed correlation between NSAIDs and miscarriage in some studies is controversial because of several confounding factors, including confounding by indication, that often have not been addressed in the studies. The majority of data relate to first trimester exposure. Exposures in the second and third trimesters have been reported for medications either regarded as compatible with pregnancy (examples glucocorticoids, azathioprine, antimalarials) or when serious maternal disease requires therapy in pregnancy (example cyclophosphamide). Drug exposures before conception were included for

Table 1 The EULAR points to consider for use of antirheumatic drugs before pregnancy and during pregnancy and lactation

| <i>Overarching principles</i> | | |
|--|--|--------------------------|
| A | Family planning should be addressed in each patient of reproductive age and adjustment of therapy considered before a planned pregnancy. | |
| B | Treatment of patients with rheumatic disease before/during pregnancy and lactation should aim to prevent or suppress disease activity in the mother and expose the fetus/child to no harm. | |
| C | The risk of drug therapy for the child should be weighed against the risk that untreated maternal disease represents for the patient and the fetus or child. | |
| D | The decision on drug therapy during pregnancy and lactation should be based on agreement between the internist/rheumatologist, gynaecologist/obstetrician and the patient, and including other healthcare providers when appropriate. | |
| <i>Points to consider for use of antirheumatic drugs in pregnancy*</i> | | Grade of recommendation† |
| 1 | csDMARDs‡ proven compatible with pregnancy are hydroxychloroquine, chloroquine, sulfasalazine, azathioprine, ciclosporin, tacrolimus and colchicine. They should be continued in pregnancy for maintenance of remission or treatment of a disease flare. | B |
| 2 | csDMARDs‡ methotrexate, mycophenolate mofetil and cyclophosphamide are teratogenic and should be withdrawn before pregnancy. | B |
| 3 | Non-selective COX inhibitors (non-steroidal anti-inflammatory drugs, NSAIDs) and prednisone should be considered for use in pregnancy if needed to control active disease symptoms. NSAIDs should be restricted to the first and second trimesters. | B |
| 4 | In severe, refractory maternal disease during pregnancy methylprednisolone pulses, intravenous immunoglobulin or even second or third trimester use of cyclophosphamide should be considered. | D |
| 5 | csDMARDs‡, tsDMARDs§ and anti-inflammatory drugs with insufficient documentation concerning use in pregnancy should be avoided until further evidence is available. This applies to leflunomide, mepacrine, tofacitinib and selective COX II inhibitors. | B–D |
| 6 | Among bDMARDs¶ continuation of tumour necrosis factor (TNF) inhibitors during the first part of pregnancy should be considered. Etanercept and certolizumab may be considered for use throughout pregnancy due to low rate of transplacental passage. | B |
| 7 | bDMARDs¶ rituximab, anakinra, tocilizumab, abatacept, belimumab and ustekinumab have limited documentation on safe use in pregnancy and should be replaced before conception by other medication. They should be used during pregnancy only when no other pregnancy-compatible drug can effectively control maternal disease. | D |
| <i>Points to consider for use of antirheumatic drugs during lactation*</i> | | Grade of recommendation† |
| 1 | csDMARDs‡ and anti-inflammatory drugs compatible with breast feeding should be considered for continuation during lactation provided the child does not have conditions that contraindicate it. This applies to hydroxychloroquine, chloroquine, sulfasalazine, azathioprine, ciclosporin, tacrolimus, colchicine, prednisone, immunoglobulin, non-selective COX inhibitors and celecoxib. | D |
| 2 | csDMARDs‡, tsDMARDs§ and anti-inflammatory drugs with no or limited data on breast feeding should be avoided in lactating women. This applies to methotrexate, mycophenolate mofetil, cyclophosphamide, leflunomide, tofacitinib and cyclooxygenase II inhibitors other than celecoxib. | D |
| 3 | Low transfer to breast milk has been shown for infliximab, adalimumab, etanercept and certolizumab. Continuation of TNF inhibitors should be considered compatible with breast feeding. | D |
| 4 | bDMARDs¶ with no data on breast feeding such as rituximab, anakinra, belimumab, ustekinumab, tocilizumab and abatacept should be avoided during lactation if other therapy is available to control the disease. Based on pharmacological properties of bDMARDs¶, lactation should not be discouraged when using these agents, if no other options are available. | D |

*Level of evidence is given for each drug separately in table 2.

†A Category I evidence from meta-analysis of randomised controlled trials (1A) or from at least one randomised controlled trial (1B)

B Category II evidence from at least one controlled study without randomisation (2A) or from at least one type of quasi-experimental study (2B), or extrapolated recommendations from category I evidence.

C Category III evidence from descriptive studies, such as comparative studies, correlation studies or case-control studies (3), or extrapolated recommendation from category I or II evidence.

D Category IV evidence from expert committee reports or opinions and/or clinical experience of respected authorities (4), or extrapolated recommendation from category II or III evidence.¹⁰

‡Conventional synthetic DMARDs.

§Targeted synthetic DMARDs.

¶Biologic DMARDs.

Recommendation

Table 2 Characteristics of studies and outcome of pregnancy exposure related to medications used to treat rheumatic diseases, SLR-period 2008–2015*

| Drug | Type of publication in numbers | References on cohorts and case controls | Total pregnancies† (prospective/retrospective) | Number of miscarriages of eligible pregnancies‡ (%) | Number of congenital malformations of live births§ (%) | Comments on miscarriages (MC) and/or congenital malformations (CM) compared with control groups and/or background data¶ | Strength of evidence according to GRADE Oxford | |
|---|--|---|--|---|--|---|--|----|
| Non-selective COX inhibitors (classical NSAIDs) | 3 cohorts 3 case controls | 11–16 | 17 992 (7684/10 308) | 530/5609 (9.4) | 457/ 12 354 (3.7) | No difference MC or CM | ++++ | 2a |
| Selective COX II inhibitors (rofecoxib, celecoxib, etoricoxib) | 3 case controls | 14 15 17 | 215 (0/215) | 11/71 (15.5) | 9/114 (7.9) | Significance for slightly increased rate MC and CM questionable due to confounders | ++ | 3b |
| Glucocorticoids (any route/formulation) | 2 cohorts 5 case controls 17 case reports/series (1 abstract) | 16 18–23 | 3500¶ (94/3406) | 70/331 (21.1) | 34/3180 (1.1) | MC slightly increased confounded by disease indication, no difference CM compared with control groups | +++ | 2b |
| Antimalarials | 2 cohorts 4 case controls | 16 24–28 | 492 (170/322) | 20/170 (11.8) | 23/492 (4.7) | No difference MC or CM | ++++ | 2a |
| Sulfasalazine | 2 cohorts 2 case controls | 16 29–31 | 525 (227/298) | 12/186 (6.5) | 16/339 (4.7) | No difference MC or CM | +++ | 2a |
| Leflunomide | 2 cohorts (1 abstract) 1 case control 4 case reports/series | 16 32 33 | 129 (80/49) | 12/122 (9.8) | 5/129 (3.9) | No difference MC or CM | +++ | 2b |
| Azathioprine | 4 cohorts (1 abstract) 7 case controls 7 case reports/series (1 abstract) | 16 31 34–42 | 1327 (434/893) | 40/559 (7.2) | 65/1327 (4.9) | No significant difference MC or CM compared with disease-matched controls | ++++ | 2a |
| Methotrexate | 2 cohorts 2 case controls 8 case reports/series | 16 27 43 44 | 372 (332/40) | 140/329 (42.6) | 15/143 (10.5) | Increased rate MC Increased rate CM with specific pattern | ++++ | 2b |
| Cyclophosphamide | 2 cohorts 28 case reports/series (2 abstracts) | 45 46 | 276 (160/116) | No separate studies on MC published | 23/86 (26.7) | High rate CM No studies with control group available | +++ | 2b |
| Ciclosporin | 2 cohorts 1 case control 11 case reports/series (1 abstract) | 47–49 | 1126 (1010/116) | 137/953 (14.4) | 9/261 (3.4) | No difference MC or CM | ++++ | 2a |
| Tacrolimus | 1 cohort 1 case control 10 case reports/series | 47 49 | 505 (482/23) | 91/344 (26.5) | 3/107 (2.8) | MC increase confounded by disease indication No difference CM | +++ | 2b |
| Mycophenolate mofetil | 2 cohorts 1 register data 20 case reports/series (2 abstracts) | 47 50 | 333 (199/134) | 119/318 (37.4) | 48/174** (27.6) | In studies without control group high rate MC and CM with specific pattern | +++ | 2b |
| Colchicine | 1 cohort 1 case control 1 case series | 51 52 | 460 (238/222) | 30/417 (7.2) | 11/460 (2.4) | No difference MC or CM | +++ | 2b |
| IVIG | 3 cohorts 3 case reports/series | 53–55 | 96 (93/3) | 24/93 (25.8) | 0/96 | No increase of MC or CM compared with disease-matched controls | ++ | 3b |
| Tofacitinib | 1 case series (abstract) | – | 27 (27/0) | 7/27 (25.9) | 1/15 | In case series and with concomitant MTX exposure high rate MC, no indication of an increased rate CM | + | 4 |
| Infliximab | 9 cohorts (1 abstract) 4 case controls (1 abstract) 2 register data (1 abstract) 16 case reports/series (3 abstracts) | 27 36 56–66 | 1161 (968/ 193) | 64/676 (9.5) | 20/756†† (2.6) | No difference MC or CM | ++++ | 2b |

Continued

Table 2 Continued

| Drug | Type of publication in numbers | References on cohorts and case controls | Total pregnancies† (prospective/retrospective) | Number of miscarriages of eligible pregnancies‡ (%) | Number of congenital malformations of live births§ (%) | Comments on miscarriages (MC) and/or congenital malformations (CM) compared with control groups and/or background data§ | Strength of evidence according to GRADE Oxford |
|--|--|---|--|---|--|---|--|
| Adalimumab | 10 cohorts (2 abstracts) 5 case controls (1 abstract) 2 register data (1 abstract) 6 case reports/series (1 abstract) | 16 27 36 56–58 60–68 | 524 (266/258) | 23/191 (12.0) | 24/350†† (6.9) | No significant difference MC Increased rate CM in one study, no increase compared with disease-matched controls | +++ 2b |
| Etanercept | 3 cohorts 3 case controls (1 abstract) 2 register data (1 abstract) 11 case reports/series (3 abstracts) | 16 27 57 58 64 65 | 332 (213/119) | 12/74 (16.2) | 9/251†† (3.6) | No difference MC or CM | +++ 2b |
| Certolizumab | 2 cohorts 1 case control 2 case reports/series | 61 63 65 | 362 (243/119) | 52/339 (15.3) | 12/267†† (4.5) | No increased rate MC or CM No studies with control group available | ++ 3b |
| Golimumab | 1 cohort 1 case series (abstract) | 65 | 50 (38/12) | 13/47 (27.7) | 0/26†† | With concomitant MTX exposure high rate MC, no indication of an increased rate CM No studies with control group available | + 4 |
| All TNF inhibitors, including studies not differentiating between them | 10 cohorts (3 abstracts) 5 case controls (1 abstract) 2 register data (1 abstract) 32 case reports/series (7 abstracts) | 16 27 36 56–68 | 2492 (1734/758) | 265/2258 (11.7) | 75/2110 (3.6) | No difference in MC or CM in pregnancies exposed to TNF inhibitors compared with controls | +++ 2b |
| Rituximab | 1 register data 20 case reports/series | – | 256 (72/184) | 48/210 (22.9) | 6/172 (3.5) | Increased rate MC confounded by disease indication, no increased rate CM No studies with control group available | ++ 4 |
| Anakinra | 1 register data 3 case reports | – | 40 (not reported) | 4/40 (10.0) | 2/34 (5.9) | No increased rate MC or CM No studies with control group available | + 4 |
| Abatacept | 1 case series‡‡ 1 case report | – | 152 (94/58) | 40/151 (26.5) | 7/87 (8.0) | With concomitant MTX exposure high rate MC and CM No studies with control group available | ++ 4 |
| Tocilizumab | 1 register data 2 case series (2 abstracts) | – | 218 (180/38) | 47/218 (21.6) | 5/128 (3.9) | With concomitant MTX exposure high rate MC, no indication of an increased rate CM | ++ 4 |
| Ustekinumab | 1 register data 4 case reports/series (1 abstract) | – | 108 (104/4) | 15/108 (13.9) | 1/58 (1.7) | No increased rate MC or CM No studies with control group available | ++ 4 |
| Belimumab | 1 register data 1 case series (abstract) | – | 153 (152/1) | 41/153 (26.8) | 7/ 71 (9.9) | High rate MC and CM Concomitant medication possible confounder No studies with disease-matched controls available | ++ 4 |

Strength of evidence based on previous consensus papers^{1 2} and new SLR and registry data.

*As the update publication did not include all non-biologic drugs, an additional search for the period 2006–2008 was performed for 10 drugs; NSAIDs, glucocorticoids, MTX, cyclophosphamide, sulfasalazine, antimalarials, azathioprine, colchicine, ciclosporin and IVIG.

†Total reported pregnancies for a given drug, where CM and/or MC are reported, and where the pregnancies have been exposed in the window of susceptibility for the reported outcome.

‡Nominator represents exposed pregnancies with MC as outcome. Denominator represents the total number of exposed pregnancies where MC is reported.

§Nominator represents exposed pregnancies with CM in live births as outcome; mainly major CM but in some publications major and minor CM are not differentiated. Denominator represents the total number of exposed pregnancies resulting in live births.

¶One cohort of 2295 pregnancies looks only at isolated clefts.

**Nominator includes CM in elective terminations in addition to CM in live births. Denominator includes elective terminations with anomalies in addition to live births.

††Several publications report congenital malformations for women using different TNF inhibitors; nominator/denominator reflects numbers in which each TNF inhibitor is reported separately.

‡‡Publication after 15 April (replacing earlier abstract).

IVIG, intravenous immunoglobulin; MTX, methotrexate; NSAID, non-steroidal anti-inflammatory drug; SLR, systematic literature review; TNF, tumour necrosis factor.

agents with a long half-life, mainly biologics, with a safety margin five times the half-life.

For cyclophosphamide, ciclosporin, tacrolimus, glucocorticoids and IVIG the number of new publications shown in [table 2](#) is lower than the number of citations retrieved in the literature search. The reason is that these drugs were often administered in combination therapies, and pregnancy outcomes in reports were given for a drug combination, not for each drug separately. The rate of miscarriage and congenital malformations can therefore be given only for studies reporting single drug exposure ([table 2](#)).

Several factors limit the completeness and reliability of pregnancy reports from pharmacovigilance centres and from pharmaceutical safety databases: spontaneously reported data often lack preciseness and completeness, and can be biased towards abnormal pregnancy outcomes, particularly in retrospectively collected cases. Information on concomitant medication is frequently absent. A major limitation of global safety databases is the high rate of pregnancies with unknown outcomes and high lost to follow-up rates up to 50%.⁶⁹

Lactation

Studies on excretion of drugs into human breast milk are rare and mostly based on single-dose or short-term treatment, therefore grading of evidence for all drugs in [table 3](#) is 'very low' (+) according to GRADE (see online supplementary table S3) and score 4–5 according to Oxford evidence rating (see online supplementary table S4). Even when transfer of a drug into milk has been investigated, children were often not breast fed, and the effect of the drug on the nursing infant remains unknown. References concerning lactation are available in online supplementary table S6.

Follow-up of children

Pregnancy exposures in any trimester might have the potential to impair organ function, alter the immune response or influence neurocognitive development in children. Studies published between 2006 and 2015 deal mainly with biologics, have a short follow-up time and show large gaps in reported outcomes (see online supplementary table S7). The available data for several biologics and immunosuppressives show no adverse effects on physical or neurocognitive development nor impaired immunocompetence in children during the 1st year of life.

Biologics

Biologics are derivatives of IgG, and differ in structure, half-life and placental passage. The half-life ranges from 9 days to 23 days in complete IgG1 monoclonal antibodies and between 4 days and 13 days in Fc-fusion proteins (etanercept, abatacept).⁷² Active transport of biologics containing the Fc part of IgG1 is mediated by the fetal Fc receptor expressed in the placenta.⁷² Transfer is thought to be very low during organogenesis, but to increase steadily after week 13 throughout pregnancy. Treatment of the mother with IgG antibodies expressing high affinity to the fetal Fc receptor after gestational week 30 can lead to fetal/cord serum levels equal to or higher than maternal levels.⁶¹ IgG has a prolonged half-life, up to 48 days⁷³ in the newborn; they typically disappear from the child's serum within the first 6 months of life.

The biologics with most pregnancy experience are the TNFi which have been in use for 15 years, including for indications outside rheumatology. For biologics approved <5 years ago,

data on pregnancy and lactation are either sparse or completely absent ([tables 2](#) and [3](#)).

Results of Delphi voting

There was 90–100% consensus between experts of the task force on all statements on antirheumatic drugs during pregnancy ([tables 4](#) and [5](#)). Propositions regarding actual use of antirheumatic drugs during pregnancy and lactation in clinical practice received lower levels of agreement ([tables 4](#) and [5](#)). Disagreement between experts on clinical use during lactation was between 10–20% in general, and 25–31% for several biologics without data on transfer into breast milk (abatacept, tocilizumab, belimumab).

DISCUSSION

Available data from the literature and from registries show that a large proportion of medications can be taken by pregnant and lactating women with RD without causing measurable harm to the children. The SLR of the last decade strengthens the evidence for glucocorticoids, sulfasalazine, antimalarials, azathioprine, colchicine, ciclosporin, tacrolimus and IVIGs as being compatible with pregnancy and lactation ([table 1](#)). Major changes in regard to the 2006/2008 consensus paper are the following: The SLR and registry data support the use of TNFi in the first half of pregnancy. A study published after the completed Delphi voting showed a slight increase of birth defects at first trimester exposure to TNFi without any pattern of malformations. Given the absence of disease-matched controls the clinical significance of this finding is not yet clear.⁶⁵

The difference in placental transfer related to molecule structure and half-life needs to be taken into account when selecting a TNFi for women of fertile age ([table 5](#)). As a consequence, infliximab and adalimumab may preferentially be stopped at 20 weeks, and etanercept at week 30–32 of pregnancy. The safety of certolizumab in using it throughout pregnancy needs confirmation by extended published reports. Sound evidence for fetal/child safety is still lacking for certolizumab, golimumab, abatacept, tocilizumab, rituximab, belimumab and anakinra, but SLR and registry data do not suggest any evidence of harm from these agents when used before conception or in the first trimester ([table 5](#)).

The SLR and registry data showed only cyclophosphamide, MTX and MMF to be teratogenic necessitating their withdrawal before a planned pregnancy. For all other drugs labelled with a statement to discontinue them before or early in pregnancy, the reason is insufficient evidence that they are safe for the fetus, rather than evidence of harm.

Since 30–50% of pregnancies are unplanned, a major question is how to manage pregnancies that occur in women receiving therapy with teratogenic drugs. Some patients opt for immediate termination whereas others contemplate continuation of the pregnancy. Confirmation of pregnancy by a gynaecologist and determination of exact exposure dates for individual risk assessment and counselling are mandatory. A detailed ultrasound examination of the fetus should be offered to all patients who have an unintended pregnancy while taking a teratogenic drug. Macroscopic anomalies can be assessed by experienced fetal medicine specialists at the end of the first trimester and scans should be repeated at later stages of the second trimester. Other prenatal tests like amniocentesis or chorionic villous biopsy are usually not indicated after maternal drug exposure, but might be considered in patients with high risk of chromosomal problems or anomalies at ultrasound examination.

Table 3 Lactation data on non-steroidal anti-inflammatory drugs (NSAIDs), non-biologic and biologic drugs used to treat rheumatic diseases (publications 1970–2015)

| Drug | Number of cases* | Drug detected in breast milk† | Weight-adjusted dose‡, therapeutic infant dose or milk:plasma ratio | Infant serum level | Reported side effects in breastfed children | Comments |
|---|------------------|--|---|---|---|--|
| Non-selective COX inhibitors (classical NSAIDs) | 28 | Not detected (n=20) Detected (n=14) | Weight-adjusted dose <0.1% (minimal). Dose <0.1–5% of therapeutic infant dose | No data | No adverse events (n=25) | Weak acids, with poor excretion in breast milk, but short half-life agents preferred in neonatal period |
| Selective COX II inhibitors | 25 | Not detected (n=9) Detected (n=16) | Weight-adjusted dose 0.1–1.2% (minimal) | Not detected (n=2) | No adverse events (n=2) | Data only for celecoxib |
| Prednisone | 24 | Detected (n=16) | Weight-adjusted dose < 1.5% (minimal) if maternal dose ≤ 50 mg | No data | No adverse events (n=7) | Consider a 4 h delay before breast feeding after prednisone dose >50 mg |
| Hydroxychloroquine | 18 | Detected (n=10) | Weight-adjusted dose < 2% (minimal) | No data | No adverse events (n=9) | Long half-life |
| Chloroquine | 61 | Detected (n= 61) | Weight-adjusted dose 0.6–14% (minimal–moderate) | No data | No data | Long half-life |
| Mepacrine (quinacrine) | 0 | No data | No data | No data | No data | |
| Sulfasalazine (SSZ) | 29 | Mesalamine not detected (n=1) Mesalamine detected low level (n=3) Sulfapyridine detected (n=7) | No data | SSZ not detected (n=5) SSZ detected (n=2) Sulfapyridine ≤ 10% of maternal serum level (n=6) | No adverse events (n=6) Bloody diarrhoea (n=1) | SSZ consists of sulfapyridine and mesalamine (5-aminosalicylic acid) which is considered to be the active component Caution in premature children, G6PD deficit and hyperbilirubinaemia |
| Leflunomide | 0 | No data | No data | No data | No data | Long half-life |
| Azathioprine§ | 72 | Not detected (n=14) Detected (n=11) | Weight-adjusted dose < 1% (minimal). Dose < 0.1% of paediatric transplant dose | Not detected (n=16) Detected low level (n=1) | No adverse events (n=56) Neutropenia (n=1) | Caution in thiopurine methyltransferase-deficient individuals |
| Methotrexate | 3 | Not detected (n=1) Detected low level (n=2) | No data | No data | No adverse events (n=1) | Limited excretion in breast milk due to mainly lipid insoluble form at physiological pH |
| Cyclophosphamide | 3 | Detected (n=1) | No data | No data | Neutropenia and bone marrow suppression (n=2) | Alkylating agent; risk for side effects in breastfed child |
| Ciclosporin | 76 | Detected; variable titres (n=19) | Weight-adjusted dose <2% (minimal). Dose <2% of paediatric transplant dose | Not detected (n=12) Detected (n=2) | No adverse events (n=68) | Lipophilic Titres in milk dependent on fat content in sampled milk |
| Tacrolimus | 154 | Detected; variable titres (n=20) | Weight-adjusted dose <0,5% (minimal). Dose <0.5% of paediatric transplant dose | Not detected (n=15) Detected, level declining with time (n=4) | No adverse events (n=136) | Lipophilic Titres in milk dependent on fat content in sampled milk |
| Mycophenolate mofetil | 7 | No data | No data | No data | No adverse events (n=7) | Blocks purine synthesis and inhibits lymphocyte proliferation |

Continued

Table 3 Continued

| Drug | Number of cases* | Drug detected in breast milk† | Weight-adjusted dose‡, therapeutic infant dose or milk:plasma ratio | Infant serum level | Reported side effects in breastfed children | Comments |
|---------------|------------------|---|---|--|---|--|
| Colchicine | 154 | Detected (n=6) | Weight-adjusted dose < 10% (moderate) | Not detected (n=1) | No adverse events (n=149) | Reconsider breast feeding if infant has diarrhoea. Due to drug interaction, be aware of macrolide prescription in breastfed infants. |
| IVIg | 149 | IgG normal (n=1) IgG high (n=1) | No data | No data | No adverse events (n=146) Transient rash (n=1) | Normal component of breast milk |
| Tofacitinib | 0 | No data | No data | No data | No data | Low molecular weight might facilitate its passage into milk |
| Infliximab§ | 25 | Not detected (n=5) Detected low level (n=17) | Milk:plasma ratio 1:200 (minimal) | Detected low level (n=1) Not detected (n=2) | No adverse events (n=18) | Large protein molecule, absorption unlikely due to low bioavailability |
| Adalimumab§ | 10 | Not detected (n=6) Detected low level (n=3) | Milk:plasma ratio 1:100–1:1000 (minimal) | Not detected (n=2) | No adverse events (n=7) | Large protein molecule, absorption unlikely due to low bioavailability |
| Golimumab§ | 0 | No data | No data | No data | No data | Large protein molecule, absorption unlikely due to low bioavailability |
| Etanercept§ | 4 | Detected low level (n=4) | Milk:plasma ratio 1:1000–1:2000 (minimal) | Detected at birth, but not during breastfeeding period (n=2) | No adverse events (n=1) | Large protein molecule, absorption unlikely due to low bioavailability |
| Certolizumab§ | 8 | Not detected (n=1) | No data | Not detected (n=1) | No adverse events (n=8) | Large protein molecule, absorption unlikely due to low bioavailability |
| Rituximab | 0 | No data | No data | No data | No data | Large protein molecule, absorption unlikely due to low bioavailability |
| Anakinra | 1 | No data | No data | No data | No adverse events (n=1) | IL-1Ra is a normal component of human milk |
| Ustekinumab | 0 | No data | No data | No data | No data | Large protein molecule, absorption unlikely due to low bioavailability |
| Tocilizumab | 0 | No data | No data | No data | No data | Large protein molecule, absorption unlikely due to low bioavailability |
| Abatacept | 0 | No data | No data | No data | No data | Large protein molecule, absorption unlikely due to low bioavailability |
| Belimumab | 0 | No data | No data | No data | No data | Large protein molecule, absorption unlikely due to low bioavailability |

*Publications on breast feeding including maternal drug levels, infant drug levels or reports on side effects in breastfed children. Publications may include one, two or all three parameters.

†The definition of detected or not detected agent in breast milk varies by method and chosen cut-off value.

‡Weight-adjusted dose is child dose (mg/kg in child) relative to mother dose (mg/kg in mother): <2%=minimal, 2–5%=low, 5–10%=moderate, 10–50%=high.⁷⁰

§Caution with the use of TNF inhibitors + thiopurines. These combinations might increase the risk of infant infections.⁷¹

IVIg, intravenous immunoglobulin; TNF, tumour necrosis factor.

Table 4 Consensus on statements and expert opinion on use of non-steroidal anti-inflammatory drugs (NSAIDs) and immunosuppressive drugs in clinical practice in pregnant and lactating patients

| Drug | Pregnancy | | | Breast feeding | | |
|---|--|--|---|---|--|--|
| | Statement on compatibility of drug with pregnancy based on evidence | Percentage of agreement with statement | Expert opinion on use of drug in clinical practice* | Statement on compatibility of drug with breast feeding based on evidence | Percentage of agreement with statement | Expert opinion on use of drug during breast feeding† |
| Non-selective COX inhibitors (classical NSAIDs) | Current evidence indicates no increased rate of congenital malformations Non-selective COX inhibitors can be continued during the first and second trimesters | 92 | | Non-selective COX inhibitors are compatible with breast feeding | 88 | |
| Selective COX II inhibitors | Current evidence is insufficient Selective COX II inhibitors should be avoided in pregnancy | 100 | | Among COX II inhibitors only celecoxib has been sufficiently studied; celecoxib is compatible with breast feeding, other COX II inhibitors should be avoided during lactation | 94 | |
| Prednisone | Current evidence indicates no increased rate of congenital malformations Prednisolone/prednisone can be continued at the lowest effective dose throughout pregnancy | 100 | | Glucocorticoids are compatible with breast feeding | 100 | |
| Intra-articular/ intramuscular glucocorticoids | Current evidence indicates no increased rate of congenital malformations Intra-articular/ intramuscular glucocorticoids can be given, when required, throughout pregnancy | 100 | | | | |
| Intravenous glucocorticoids | Current evidence indicates no increased rate of congenital malformations Intravenous glucocorticoids can be given, when required, throughout pregnancy | 100 | | | | |
| Fluorinated glucocorticoids | Current evidence indicates that fluorinated glucocorticoids should be used with caution because they are less metabolised by the placenta They should only be used to treat fetal problems | 100 | | | | |
| Hydroxychloroquine | Current evidence indicates no increased rate of congenital malformations Hydroxychloroquine can be continued throughout pregnancy | 100 | | Hydroxychloroquine is compatible with breast feeding | 100 | |
| Chloroquine | Current evidence indicates no increased rate of congenital malformations Chloroquine can be continued throughout pregnancy | 100 | | Chloroquine is compatible with breast feeding | 88 | |

Continued

Table 4 Continued

| Drug | Pregnancy | | | Breast feeding | | |
|------------------------|---|--|---|--|--|--|
| | Statement on compatibility of drug with pregnancy based on evidence | Percentage of agreement with statement | Expert opinion on use of drug in clinical practice* | Statement on compatibility of drug with breast feeding based on evidence | Percentage of agreement with statement | Expert opinion on use of drug during breast feeding† |
| Mepacrine (quinacrine) | Current evidence is insufficientMepacrine should be avoided in pregnancy | 100 | | No data exist regarding mepacrine in breast milk, therefore mepacrine should be avoided in breast feeding | 100 | |
| Sulfasalazine | Current evidence indicates no increased rate of congenital malformations Sulfasalazine can be continued at doses up to 2 g/day with concomitant folate supplementation throughout pregnancy | 100 | | Sulfasalazine is compatible with breast feeding in the healthy, full-term infant | 94 | |
| Leflunomide | Current evidence is insufficientIn a planned pregnancy, a washout procedure should be completed before pregnancy Leflunomide should be avoided in pregnancy | 100 | | No data exist regarding leflunomide in breast milk, therefore leflunomide should be avoided in breast feeding | 100 | |
| Azathioprine | Current evidence indicates no increased rate of congenital malformations Azathioprine can be continued at doses up to 2 mg/kg/day throughout pregnancy | 100 | | Azathioprine is compatible with breast feeding | 94 | |
| Methotrexate | Current evidence indicates an increased rate of congenital malformationsIn a planned pregnancy, methotrexate should be withdrawn 1-3 months before pregnancy | 100 | | Only small amounts of methotrexate appear in breast milk, but data are limited, therefore methotrexate should be avoided in breast feeding | 100 | |
| Cyclophosphamide | Current evidence indicates an increased rate of congenital malformations Cyclophosphamide must be withdrawn before a planned pregnancy | 100 | | There are limited data regarding cyclophosphamide in breast milk, therefore cyclophosphamide should be avoided in breast feeding | 94 | |
| Cyclophosphamide | The use of cyclophosphamide might be justified to treat life-threatening conditions in the second and third trimesters | 100 | | | | |
| Ciclosporin | Current evidence indicates no increased rate of congenital malformations Ciclosporin can be continued throughout pregnancy at the lowest effective dose | 100 | | Ciclosporin is compatible with breast feeding | 100 | |

Continued

Table 4 Continued

| Drug | Pregnancy | | | Breast feeding | | |
|-----------------------------|--|--|---|---|--|--|
| | Statement on compatibility of drug with pregnancy based on evidence | Percentage of agreement with statement | Expert opinion on use of drug in clinical practice* | Statement on compatibility of drug with breast feeding based on evidence | Percentage of agreement with statement | Expert opinion on use of drug during breast feeding† |
| Tacrolimus | Current evidence indicates no increased rate of congenital malformations Tacrolimus can be continued throughout pregnancy at the lowest effective dose using trough levels | 100 | | Tacrolimus is compatible with breast feeding | 94 | |
| Mycophenolate mofetil (MMF) | Current evidence indicates an increased rate of congenital malformations In a planned pregnancy, MMF should be withdrawn 1.5 months before pregnancy | 100 | | No data exist regarding MMF in breast milk, therefore MMF should be avoided in breast feeding | 100 | |
| Colchicine | Current evidence indicates no increased rate of congenital malformations Colchicine can be continued at doses up to 1 mg/day throughout pregnancy | 100 | | Colchicine is compatible with breast feeding | 100 | |
| Intravenous immunoglobulin | Intravenous immunoglobulin can be used throughout pregnancy | 100 | | Intravenous immunoglobulin is compatible with breast feeding | 100 | |
| Tofacitinib | Current evidence is insufficient In a planned pregnancy treatment with tofacitinib should be stopped 2 months before conception | 100 | | No data exist regarding tofacitinib in breast milk, therefore tofacitinib should be avoided in breast feeding | 100 | |

*As an expert in the field.

- I would recommend the drug in the same way as if the patient was not pregnant.
- I would only recommend the drug if I feared at least moderate disease activity in its absence.
- I would only recommend the drug if I feared at least severe disease activity in its absence.
- I would never recommend the drug in pregnancy.

†As an expert in the field.

- I would recommend the drug in the same way as if the patient did not breastfeed.
- I would only recommend the drug if I feared at least moderate disease activity in its absence.
- I would only recommend the drug if I feared at least severe disease activity in its absence.
- I would never recommend the drug while the woman was breast feeding.

Table 5 Consensus on statements and expert opinion on use of biologic drugs in clinical practice in pregnant and lactating patients

| Drug | Pregnancy | | | Breast feeding | | |
|--------------|--|--|---|---|--|--|
| | Statement on compatibility of drug with pregnancy based on evidence | Percentage of agreement with statement | Expert opinion on use of drug in clinical practice (%)* | Statement on compatibility of drug with breast feeding based on evidence | Percentage of agreement with statement | Expert opinion on breast feeding and medication (%)† |
| Infliximab | Current evidence indicates no increased rate of congenital malformations; infliximab can be continued up to gestational week 20; if indicated, it can be used throughout pregnancy | 100 | | Infliximab is compatible with breast feeding | 100 | |
| Adalimumab | Current evidence indicates no increased rate of congenital malformations; adalimumab can be continued up to gestational week 20; if indicated, it can be used throughout pregnancy | 100 | | Adalimumab is compatible with breast feeding | 100 | |
| Golimumab | Current evidence does not indicate an increased rate of congenital malformations; because of limited evidence, alternative medications should be considered for treatment throughout pregnancy | 100 | | Golimumab is compatible with breast feeding | 94 | |
| Etanercept | Current evidence indicates no increased rate of congenital malformations; etanercept can be continued up to gestational week 30–32; if indicated, it can be used throughout pregnancy | 100 | | Etanercept is compatible with breast feeding | 100 | |
| Certolizumab | Current evidence indicates no increased rate of congenital malformations; certolizumab can be continued throughout pregnancy | 100 | | Certolizumab is compatible with breast feeding | 94 | |
| Rituximab | Current evidence indicates no increased rate of congenital malformations; in exceptional cases it can be used early in gestation; with use at later stages of pregnancy clinicians should be aware of the risk of B cell depletion and other cytopenias in the neonate | 100 | | No data exist regarding rituximab in breast milk, therefore rituximab should be avoided in breast feeding | 80 | |
| Anakinra | Current evidence does not indicate an increased rate of congenital malformations; anakinra can be used before and during pregnancy when there are no other well studied options available for treatment | 100 | | No data exist regarding anakinra in breast milk, therefore anakinra should be avoided in breast feeding | 88 | |
| Ustekinumab | Current evidence does not indicate an increased rate of congenital malformations; because of limited evidence, alternative medications should be considered for treatment throughout pregnancy | 100 | | No data exist regarding ustekinumab in breast milk, therefore ustekinumab should be avoided in breast feeding | 75 | |
| Tocilizumab | No statement can be made in regard to safety during pregnancy due to scarce documentation; treatment with tocilizumab is therefore best avoided | 100 | | No data exist regarding tocilizumab in breast milk, therefore tocilizumab should be avoided in breast feeding | 69 | |
| Abatacept | No statement can be made in regard to safety during pregnancy due to scarce documentation; treatment with abatacept is therefore best avoided | 94 | | No data exist regarding abatacept in breast milk, therefore abatacept should be avoided in breast feeding | 75 | |
| Belimumab | Current evidence does not indicate an increased rate of congenital malformations; because of limited evidence, alternative medications should be considered for treatment throughout pregnancy | 100 | | No data exist regarding belimumab in breast milk, therefore belimumab should be avoided in breast feeding | 82 | |

*As an expert in the field.
 I would recommend the drug in the same way as if the patient was not pregnant.
 I would only recommend the drug if I feared at least moderate disease activity in its absence.
 I would only recommend the drug if I feared at least severe disease activity in its absence.
 I would never recommend the drug in pregnancy.

†As an expert in the field.
 I would recommend the drug in the same way as if the patient did not breastfeed.
 I would only recommend the drug if I feared at least moderate disease activity in its absence.
 I would only recommend the drug if I feared at least severe disease activity in its absence.
 I would never recommend the drug while the woman was breast feeding.

There was 90–100% agreement between experts of the task force with the statements on compatibility of antirheumatic drugs during pregnancy. However, much less agreement was achieved for the use of each drug in clinical practice. In the statements, emphasis was placed on congenital malformations whereas in the propositions for clinical use other considerations come into play including personal experience with a given drug, pharmacological properties of drugs, national preferences, availability of drugs in certain countries and legal issues. Statements on lactation were restricted to compatibility, and included no detailed advice on timing, short-term discontinuation of breast feeding or discarding milk on days of drug administration. As a consequence, great heterogeneity in regard to clinical practice among experts was observed (tables 4 and 5). This reflects the insufficient documentation in the field as well as the propensity to discourage patients in need of therapy from breast feeding although a flexible schedule would allow more women to breast-feed. Lactating mothers may have the opposite view, and would rather breast-feed than receive medications for active disease. Faced with a paucity of studies, pharmacological properties of drugs may act as a guide for decision to allow breast feeding even when there is scarce or no documentation (table 3). Non-ionised and lipophilic agents with a low molecular weight are the most likely to be transferred into breast milk. Highly protein-bound drugs or agents with high molecular weight are unlikely to cross extensively into breast milk.⁷⁴ Term neonates, older or partially breastfed babies are usually at low risk for side effects of drugs in breast milk. Breast feeding is particularly important for premature and very low birthweight babies, however, no studies on this subgroup and the risks they may encounter by exposure to drugs in breast milk are available.

Studies on the long-term effects of drugs administered during pregnancy and/or breast feeding on child health and development are scarce, and often of low quality (see online supplementary table S7). The data available for azathioprine, ciclosporin and dexamethasone do not indicate immunosuppression in exposed children or raise special concern in regard to physical or neurological development (see online supplementary table S7). By contrast, biologics with extensive placental transfer achieving high serum levels in the child when administered after gestational week 30, might increase the risk of postnatal infection. Children exposed to biologics only before week 22 can receive vaccinations according to standard protocols including live vaccines. Children exposed at the late second and during the third trimester can follow vaccination programmes, but should not receive live vaccines in the first 6 months of life. When available, measurement of child serum levels of the biologic in question could guide the decision for or against a live vaccine.

The strengths of this study include the extensive SLR, inclusion of until now unpublished pharmacovigilance and registry data, and evaluation of data by experts from different specialties. Limitations of the study are the great variability in quality of reports in the literature and in registries. There is variety in disease indications and drug dosage. Assignment of an adverse pregnancy outcome to a particular drug can be influenced by confounders. Disease type, disease activity during pregnancy, extent of systemic inflammation and organ involvement, comorbidities, and concomitant drug therapy may all contribute to negative outcomes. When combinations of immunosuppressive and cytotoxic drugs are used defined pregnancy outcomes cannot be assigned to each of these classes of drugs separately. For recently approved biologics the adverse effect of concomitant use of MTX confounds the rate of miscarriages and of

congenital malformations occurring after first trimester exposure in unintended pregnancies (table 5). In studies without carefully matched non-exposed control groups it is difficult to separate adverse drug effects from the above-mentioned confounders. Control groups are lacking in a majority of reports. The malformation rate is nearly always reported for live birth but does not include information on miscarriages or terminations. Therefore malformation rates are best derived from studies that include comparator groups of women with the same disease unexposed to the drug under consideration as well as non-exposed healthy pregnant women.

Treating a pregnant woman with RDs during pregnancy and lactation is a challenge since the well-being of two individuals, the mother and her child, has to be considered. Decisions on therapy during pregnancy and lactation have often been confounded by medical and legal concerns.⁷⁵ The general cautious attitude to drug treatment during pregnancy and lactation has resulted in the withholding of necessary therapy, often at considerable risk for mother and child.⁷⁵ Updating of knowledge in the field and dissemination of new insights is therefore of great importance in order to ensure implementation into daily practice and counselling. A publication based on SLR and available registry data is a first step that must be followed by dissemination of the new data through congresses, conferences, workshops and educational courses that include all types of healthcare providers (HCPs). Dissemination should target national societies of specialists in rheumatology, internal medicine, gynaecology and obstetrics, family medicine, paediatrics and pharmacology as well as national teratology information services. Disseminating the data through internet accessible websites would reach a large audience of the different HCPs who care for patients with RDs. Ideally the new insights should also be communicated to the patients at congresses, conferences and via national patient associations. Information needs on child-bearing issues are great in women with RDs.⁷⁶ There is a considerable gap in written material and educational resources that could meet this need. Development of evidence-based information on drugs in pregnancy/lactation, tailored for the lay public and accessible on the internet, would help patients make informed decisions.

RECOMMENDATIONS FOR FUTURE RESEARCH

Despite various international efforts, there is still limited evidence on the safety of a substantial number of drugs in pregnancy and lactation. The following are points for a research agenda:

1. All pharmaceutical companies should give academic institutions access to data on drug exposure during pregnancy and lactation from long-term extension studies of randomised trials and from registries. Independent assessment of the available data would be crucial.
2. Current initiatives for establishing pregnancy registers should be continued on a long-term and international basis. Specifically for the more recently licensed drugs, data collection should be intensified. Individual pregnancy registers are not likely to yield enough exposure and observation time to draw valid conclusions. Therefore, joint approaches among several countries which enable collaborative data analyses are recommended. EULAR could be an umbrella organisation for the harmonisation of approaches in establishing pregnancy registries.
3. Data collection should follow a protocol and be prospective, starting in early pregnancy or preferably when a pregnancy is planned and with high follow-up rates throughout

pregnancy, lactation and during at least the 1st year of life of the child. Studies should include comparator groups of disease-matched women and their children unexposed to the drug under consideration as well as non-exposed healthy pregnant women.

- The major gap in the documentation of transfer of drugs into human breast milk and the effect of drugs in breastfed children, including risk groups of premature and very low birthweight children, requires new and detailed studies.

CONCLUSION

Management of female patients with RDs during pregnancy and lactation requires weighing risks of withholding treatment from the mother against any risk to the fetus/child via exposure to drugs during pregnancy or breast feeding. Restrictions in use apply for the few proven teratogenic drugs and the large proportion of medications for which insufficient safety data for the fetus/child are available. The points to consider presented in this review show that, in spite of limitations, effective drug treatment of active RD is possible with reasonable safety for the fetus/child during pregnancy and lactation.

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Acknowledgements The authors thank Solveig Isabel Taylor; Medicine and Health Library, NTNU University Library Knowledge Center, St Olavs Hospital, Trondheim, Norway for help with the literature search; Ane S Simensen; The Norwegian Medicines Agency, Pharmacovigilance, Oslo, Norway for access to pregnancy reports; May Ching Soh; Division of Women's Health, Women's Health Academic Centre, King's College London, King's Health Partners, London, UK, for collecting data on lactation; Cecilia Nalli, Department of Clinical and Experimental Science Rheumatology and Clinical Immunology Unit, Spedali Civili and University of Brescia, Italy for collecting data on child outcome.

Contributors Each author has contributed to one or more of the following aspects of the manuscript—literature search, access to registry data, analysis and

interpretation of data, drafting and revising the article. All authors approved the final version.

Funding EULAR.

Competing interests These are summarised below as remuneration for consultation and/or speaking engagements ('R'), research funding ('F') or 'none'. AT—R: GSK, UCB, Pfizer, Abbott/Abbvie, IL; F: MSD, Pfizer, Roche, Abbott/Abbvie, BMS, Actelion; RF—B—R: Abbott/Abbvie, Chugai, GSK, MSD, Pfizer, Roche, SOBI, UCB; F:GSK, UCB; EE—R: Abbott/Abbvie; CC—F: AbbVie, Amgen, Apotex, Bristol Myers Squibb, Celgene, CSL, GSK, Janssen, Lilly, Pfizer, Roche-Genentech, Sandoz, Sanofi-Genzyme, Teva; JdS—R: Abbott/Abbvie, MSD, Pfizer, Roche, BIAL; CN—P—R LEO Pharma, Sanofi, UCB; IC—R: Bayer, Nestle, Pierre Fabre, Zambon; NC—C—none; RD—F: UCB; FF—R: Mepha, Roche, UCB; MK—R: Inova Diagnostics, Medimmune/Astrazeneca, GSK, UCB, Menarini; F: Bayer; GR—I—none; AZ—R: AbbVie, BMS, MSD, Pfizer, Roche, Sanofi, UCB—F: AbbVie, BMS, GSK, Medac, MSD, Novartis, Pfizer, Roche, UCB; JV—R: UCB, Pfizer, MSD; MC—R: Actelion, BMS, Horizon, Abbvie, Novartis, Celltrion; MØ—R: Abbott/Abbvie, Mepha, MSD, New Bridge, Pfizer, Roche, UCB.

Provenance and peer review Not commissioned; externally peer reviewed.

REFERENCES

- Østensen M, Khamashta M, Lockshin M, *et al*. Anti-inflammatory and immunosuppressive drugs and reproduction. *Arthritis Res Ther* 2006;8:209.
- Ostensen M, Lockshin M, Doria A, *et al*. Update on safety during pregnancy of biological agents and some immunosuppressive anti-rheumatic drugs. *Rheumatology (Oxford)* 2008;47(Suppl 3):iii28–31.
- Dougados M, Betteridge N, Burmester GR, *et al*. EULAR standardised operating procedures for the elaboration, evaluation, dissemination, and implementation of recommendations endorsed by the EULAR standing committees. *Ann Rheum Dis* 2004;63:1172–6.
- van der Heijde D, Aletaha D, Carmona L, *et al*. 2014 Update of the EULAR standardised operating procedures for EULAR-endorsed recommendations. *Ann Rheum Dis* 2015;74:8–13.
- Ghogomu EA, Maxwell LJ, Buchbinder R, *et al*. Updated method guidelines for cochrane musculoskeletal group systematic reviews and metaanalyses. *J Rheumatol* 2014;41:194–205.
- Hsu C-C, Sandford BA. The Delphi technique: making sense of consensus. *Pract Asses Res Eval* 2007;12:1–8.
- Burns PB, Rohrich RJ, Chung KC. The levels of evidence and their role in evidence-based medicine. *Plast Reconstr Surg* 2011;128:305–10.
- Goldet G, Howick J. Understanding GRADE: an introduction. *J Evid Based Med* 2013;6:50–4.
- Jeremy H, Iain C, Paul G. Explanation of the 2011 Oxford Centre for Evidence-Based Medicine (OCEBM) table of evidence. Background document. <http://www.cebm.net/index.aspx?o=5653>. (accessed Jan 2014).
- Phillips B, Ball C, Sackett D, *et al*. Oxford Centre for Evidence-based Medicine—levels of evidence (March 2009). Centre for Evidence Based Medicine Web site. <http://www.cebm.net/index.aspx?o=5653> (accessed Jan 2014).
- Nezvalová-Henriksen K, Spigset O, Nordeng H. Effects of ibuprofen, diclofenac, naproxen, and piroxicam on the course of pregnancy and pregnancy outcome: a prospective cohort study. *BJOG* 2013;120:948–59.
- Edwards DR, Aldridge T, Baird DD, *et al*. Periconceptional over-the-counter nonsteroidal anti-inflammatory drug exposure and risk for spontaneous abortion. *Obstet Gynecol* 2012;120:113–22.
- van Gelder MM, Roeleveld N, Nordeng H. Exposure to non-steroidal anti-inflammatory drugs during pregnancy and the risk of selected birth defects: a prospective cohort study. *PLoS ONE* 2011;6:e22174.
- Daniel S, Koren G, Lunenfeld E, *et al*. Fetal exposure to nonsteroidal anti-inflammatory drugs and spontaneous abortions. *CMAJ* 2014;186:E177–82.
- Daniel S, Matok I, Gorodischer R, *et al*. Major malformations following exposure to nonsteroidal anti-inflammatory drugs during the first trimester of pregnancy. *J Rheumatol* 2012;39:2163–9.
- Viktik KK, Engeland A, Furu K. Outcomes after anti-rheumatic drug use before and during pregnancy: a cohort study among 150,000 pregnant women and expectant fathers. *Scand J Rheumatol* 2012;41:196–201.
- Nakhai-Pour HR, Broy P, Sheehy O, *et al*. Use of nonaspirin nonsteroidal anti-inflammatory drugs during pregnancy and the risk of spontaneous abortion. *CMAJ* 2011;183:1713–20.
- Al Arfaj AS, Khalil N. Pregnancy outcome in 396 pregnancies in patients with SLE in Saudi Arabia. *Lupus* 2010;19:1665–73.
- Bay Bjørn AM, Ehrenstein V, Hundborg HH, *et al*. Use of corticosteroids in early pregnancy is not associated with risk of oral clefts and other congenital malformations in offspring. *Am J Ther* 2014;21:73–80.
- Gomaa MF, Elkholy AG, El-Said MM, *et al*. Combined oral prednisolone and heparin versus heparin: the effect on peripheral NK cells and clinical outcome in patients with unexplained recurrent miscarriage. A double-blind placebo randomized controlled trial. *Arch Gynecol Obstet* 2014;290:757–62.

- 21 Hviid A, Mølgaard-Nielsen D. Corticosteroid use during pregnancy and risk of orofacial clefts. *CMAJ* 2011;183:796–804.
- 22 Reddy D, Murphy SJ, Kane SV, et al. Relapses of inflammatory bowel disease during pregnancy: in-hospital management and birth outcomes. *Am J Gastroenterol* 2008;103:1203–9.
- 23 Tang AW, Alfrevic Z, Turner MA, et al. A feasibility trial of screening women with idiopathic recurrent miscarriage for high uterine natural killer cell density and randomizing to prednisolone or placebo when pregnant. *Hum Reprod* 2013;28:1743–52.
- 24 Diav-Citrin O, Blyakhman S, Shechtman S, et al. Pregnancy outcome following in utero exposure to hydroxychloroquine: a prospective comparative observational study. *Reprod Toxicol* 2013;39:58–62.
- 25 Clowse ME, Magder L, Witter F, et al. Hydroxychloroquine in lupus pregnancy. *Arthritis Rheum* 2006;54:3640–7.
- 26 Koh JH, Ko HS, Kwok SK, et al. Hydroxychloroquine and pregnancy on lupus flares in Korean patients with systemic lupus erythematosus. *Lupus* 2015;24:210–7.
- 27 Cooper WO, Cheetham TC, Li DK, et al. Brief report: risk of adverse fetal outcomes associated with immunosuppressive medications for chronic immune-mediated diseases in pregnancy. *Lupus* 2014;66:444–50.
- 28 Izmirly PM, Costedoat-Chalumeau N, Pisoni CN, et al. Maternal use of hydroxychloroquine is associated with a reduced risk of recurrent anti-SSA/Ro-antibody-associated cardiac manifestations of neonatal lupus. *Circulation* 2012;126:76–82.
- 29 de Man YA, Hazes JM, van der Heide H, et al. Association of higher rheumatoid arthritis disease activity during pregnancy with lower birth weight: results of a national prospective study. *Arthritis Rheum* 2009;60:3196–206.
- 30 Rahimi R, Nikfar S, Rezaie A, et al. Pregnancy outcome in women with inflammatory bowel disease following exposure to 5-aminosalicylic acid drugs: a meta-analysis. *Reprod Toxicol* 2008;25:271–5.
- 31 Nørgård B, Pedersen L, Christensen LA, et al. Therapeutic drug use in women with Crohn's disease and birth outcomes: a Danish nationwide cohort study. *Am J Gastroenterol* 2007;102:1406–13.
- 32 Chambers CD, Johnson DL, Robinson LK, et al. Birth outcomes in women who have taken leflunomide during pregnancy. *Arthritis Rheum* 2010;62:1494–503.
- 33 Karadag O, Kilic L, Erbil AA, et al. Pregnancy outcomes of rheumatic patients with pre/perigestational leflunomide exposure. *Ann Rheum Dis* 2013;72(Suppl 3):A896–7.
- 34 Alami Z, Cissoko H, Ahid S, et al. Pregnancy outcomes after maternal use of azathioprine: a French cohort Study. *Fundam Clin Pharmacol* 2013;27:43.
- 35 Ban L, Tata LJ, Fiaschi L, et al. Limited risks of major congenital anomalies in children of mothers with IBD and effects of medications. *Gastroenterology* 2014;146:76–84.
- 36 Casanova MJ, Chaparro M, Domènech E, et al. Safety of thiopurines and anti-TNF- α drugs during pregnancy in patients with inflammatory bowel disease. *Am J Gastroenterol* 2013;108:433–40.
- 37 Cleary BJ, Kallen B. Early pregnancy azathioprine use and pregnancy outcomes. *Birth Defects Res Part A Clin Mol Teratol* 2009;85:647–54.
- 38 Coelho J, Beaugerie L, Colombel JF, et al. Pregnancy outcome in patients with inflammatory bowel disease treated with thiopurines: cohort from the CESAME Study. *Gut* 2011;60:198–203.
- 39 Goldstein LH, Dolinsky G, Greenberg R, et al. Pregnancy outcome of women exposed to azathioprine during pregnancy. *Birth Defects Res Part A Clin Mol Teratol* 2007;79:696–701.
- 40 Julsgaard M, Norgaard M, Hvas CL, et al. Influence of medical treatment, smoking and disease activity on pregnancy outcomes in Crohn's disease. *Scand J Gastroenterol* 2014;49:302–8.
- 41 Langagergaard V, Pedersen L, Gislum M, et al. Birth outcome in women treated with azathioprine or mercaptopurine during pregnancy: a Danish nationwide cohort study. *Aliment Pharmacol Ther* 2007;25:73–81.
- 42 Shim L, Eslick GD, Simring AA, et al. The effects of azathioprine on birth outcomes in women with inflammatory bowel disease (IBD). *J Crohns Colitis* 2011;5:234–8.
- 43 Martin MC, Barbero P, Groisman B, et al. Methotrexate embryopathy after exposure to low weekly doses in early pregnancy. *Reprod Toxicol* 2014;43:26–9.
- 44 Weber-Schoendorfer C, Chambers C, Wacker E, et al. Pregnancy outcome after methotrexate treatment for rheumatic disease prior to or during early pregnancy: a prospective multicenter cohort study. *Reprod Toxicol* 2014;66:1101–10.
- 45 Cardonick E, Usmani A, Ghaffar S. Perinatal outcomes of a pregnancy complicated by cancer, including neonatal follow-up after in utero exposure to chemotherapy: results of an international registry. *Am J Clin Oncol* 2010;33:221–8.
- 46 Silva CA, Hilario MO, Febronio MV, et al. Pregnancy outcome in juvenile systemic lupus erythematosus: a Brazilian multicenter cohort study. *J Rheumatol* 2008;35:1414–8.
- 47 Mohamed-Ahmed O, Nelson-Piercy C, Bramham K, et al. Pregnancy outcomes in liver and cardiothoracic transplant recipients: a UK national cohort study. *PLoS ONE* 2014;9:e89151.
- 48 Nulman I, Sgro M, Barrera M, et al. Long-term neurodevelopment of children exposed in utero to ciclosporin after maternal renal transplant. *Paediatr Drugs* 2010;12:113–22.
- 49 Perales-Puchalt A, Vila Vives JM, Lopez Montes J, et al. Pregnancy outcomes after kidney transplantation-immunosuppressive therapy comparison. *J Matern Fetal Neonatal Med* 2012;25:1363–6.
- 50 Hoeltzenbein M, Elefant E, Vial T, et al. Teratogenicity of mycophenolate confirmed in a prospective study of the European Network of Teratology Information Services. *Am J Med Genet A* 2012;158 A:588–96.
- 51 Ben-Chetrit E, Ben-Chetrit A, Berkun Y, et al. Pregnancy outcomes in women with familial Mediterranean fever receiving colchicine: is amniocentesis justified? *Arthritis Care Res (Hoboken)* 2010;62:143–8.
- 52 Diav-Citrin O, Shechtman S, Schwartz V, et al. Pregnancy outcome after in utero exposure to colchicine. *Am J Obstet Gynecol* 2010;203:144.e1–6.
- 53 Dendros S, Sakkas E, Makrakis E. Low-molecular-weight heparin versus intravenous immunoglobulin for recurrent abortion associated with antiphospholipid antibody syndrome. *Int J Gynaecol Obstet* 2009;104:223–5.
- 54 Heilmann L, Schorch M, Hahn T, et al. Pregnancy outcome in women with antiphospholipid antibodies: report on a retrospective study. *Semin Thromb Hemost* 2008;34:794–802.
- 55 Perricone R, De Carolis C, Kröegler B, et al. Intravenous immunoglobulin therapy in pregnant patients affected with systemic lupus erythematosus and recurrent spontaneous abortion. *Rheumatology (Oxford)* 2008;47:646–51.
- 56 Bortlik M, Machkova N, Duricova D, et al. Pregnancy and newborn outcome of mothers with inflammatory bowel diseases exposed to anti-TNF- α therapy during pregnancy: three-center study. *Scand J Gastroenterol* 2013;48:951–8.
- 57 Diav-Citrin O, Otcheretianski-Volodarsky A, Shechtman S, et al. Pregnancy outcome following gestational exposure to TNF-alpha-inhibitors: a prospective, comparative, observational study. *Reprod Toxicol* 2014;43:78–84.
- 58 Giacuzzo S, Padovan M, Capucci R, et al. Pregnancy outcome of mothers with rheumatic diseases exposed to biological agent during pregnancy: a single-centre study. *Ann Rheum Dis* 2014;73(Suppl 2):414.
- 59 Kalari S, Granath F, Guo CY, et al. Pregnancy outcomes in women with rheumatologic conditions exposed to infliximab. *Ann Rheum Dis* 2014;73(Suppl 2):482–3.
- 60 Kelly O, Hartery K, Boland K, et al. TNF alpha inhibitor use in pregnancy: Experience in a European cohort. *J Crohn's Colitis* 2014;8:S204–S05.
- 61 Mahadevan U, Wolf DC, Dubinsky M, et al. Placental transfer of anti-tumor necrosis factor agents in pregnant patients with inflammatory bowel disease. *Clin Gastroenterol Hepatol* 2013;11:286–92.
- 62 Schnitzler F, Fidder H, Ferrante M, et al. Outcome of pregnancy in women with inflammatory bowel disease treated with antitumor necrosis factor therapy. *Inflamm Bowel Dis* 2011;17:1846–54.
- 63 Seirafi M, de Vroey B, Amiot A, et al. Factors associated with pregnancy outcome in anti-TNF treated women with inflammatory bowel disease. *Aliment Pharmacol Ther* 2014;40:363–73.
- 64 Verstappen SM, King Y, Watson KD, et al. Anti-TNF therapies and pregnancy: outcome of 130 pregnancies in the British Society for Rheumatology Biologics Register. *Ann Rheum Dis* 2011;70:823–6.
- 65 Weber-Schoendorfer C, Oppermann M, Wacker E, et al. Pregnancy outcome after TNF- α inhibitor therapy during the first trimester: a prospective multicentre cohort study. *Br J Clin Pharmacol* 2015;80:727–39.
- 66 Zelinkova Z, van der Ent C, Bruin KF, et al. Effects of discontinuing anti-tumor necrosis factor therapy during pregnancy on the course of inflammatory bowel disease and neonatal exposure. *Clin Gastroenterol Hepatol* 2013;11:318–21.
- 67 Chambers C, Johnson D, Luo Y, et al. Pregnancy outcome in women treated with adalimumab for the treatment of rheumatoid arthritis: An update on the otis autoimmune diseases in pregnancy project. *Am J Gastroenterol* 2014;109(Suppl):S638.
- 68 Johnson D, Luo Y, Jones KL, et al. Pregnancy outcomes in women exposed to adalimumab: an update on the autoimmune diseases in pregnancy project. *Arthritis Rheum* 2011;1(Suppl S10):1874.
- 69 Sinclair S, Cunningham M, Messenheimer J, et al. Advantages and problems with pregnancy registries: observations and surprises throughout the life of the International Lamotrigine Pregnancy Registry. *Pharmacoepidemiol Drug Saf* 2014;23:779–86.
- 70 Nordeng H, Havnen GC, Spigset O. Drug use and breastfeeding. *Tidsskr Nor Laegeforen* 2012;132:1089–93.
- 71 Mahadevan U, Martin CF, Sandler RS, et al. Piano: A 1000 patient prospective registry of pregnancy outcomes in women with ibd exposed to immunomodulators and biologic therapy. *Gastroenterology* 2012;151:149.
- 72 Suzuki T, Ishii-Watabe A, Tada M, et al. Importance of neonatal FcR in regulating the serum half-life of therapeutic proteins containing the Fc domain of human IgG1: a comparative study of the affinity of monoclonal antibodies and Fc-fusion proteins to human neonatal FcR. *J Immunol* 2010;184:1968–76.

Recommendation

- 73 Sarvas H, Seppala I, Kurikka S, *et al.* Half-life of the maternal IgG1 allotype in infants. *J Clin Immunol* 1993;13:145–51.
- 74 Begg EJ, Atkinson HC, Duffull SB. Prospective evaluation of a model for the prediction of milk: plasma drug concentrations from physicochemical characteristics. *Br J Clin Pharmacol* 1992;33:501–5.
- 75 Dewulf L. Medicines in pregnancy—women and children first? Time for a coalition to address a substantial patient need. *Ther Innov Regul Sci* 2013;47:528–32.
- 76 Cush JJ, Kavanaugh A. Editorial: pregnancy and rheumatoid arthritis—do not let the perfect become the enemy of the good. *Curr Opin Rheumatol* 2014;26:299–301.