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

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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 2006[1] 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 2004[3] 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

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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 publication[2] 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 childrens' 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, preeclampsia, 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 technique[6] 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

Overarching principles		
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.	
*Points to consider for use of antirheumatic drugs in pregnancy**		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
*Points to consider for use of antirheumatic drugs during lactation**		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 hydoxychloroquine, 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.

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 indicationNo 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) *16case 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) *11case 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 CMNo 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 CMNo 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 CMNo 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 confounderNo 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 days[73] 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‡, theurapeutic 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)	LipophilicTitres 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)	LipophilicTitres 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‡, theurapeutic 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 diarrhoeaDue 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

	Pregnancy			Breast feeding		
Drug	**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 malformationsNon-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 insufficientSelective 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 malformationsIntra-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 placentaThey 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

	Pregnancy			Breast feeding		
Drug	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: Statement on compatibility of drug with pregnancy based on evidence	Pregnancy: Percentage of agreement with statement	Pregnancy: Expert opinion on use of drug in clinical practice*	Breast feeding: Statement on compatibility of drug with breast feeding based on evidence	Breast feeding: Percentage of agreement with statement	Breast feeding: 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 malformationsIn 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 insufficientIn 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

	Pregnancy			Breast feeding		
Drug	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 childbearing 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.

4. 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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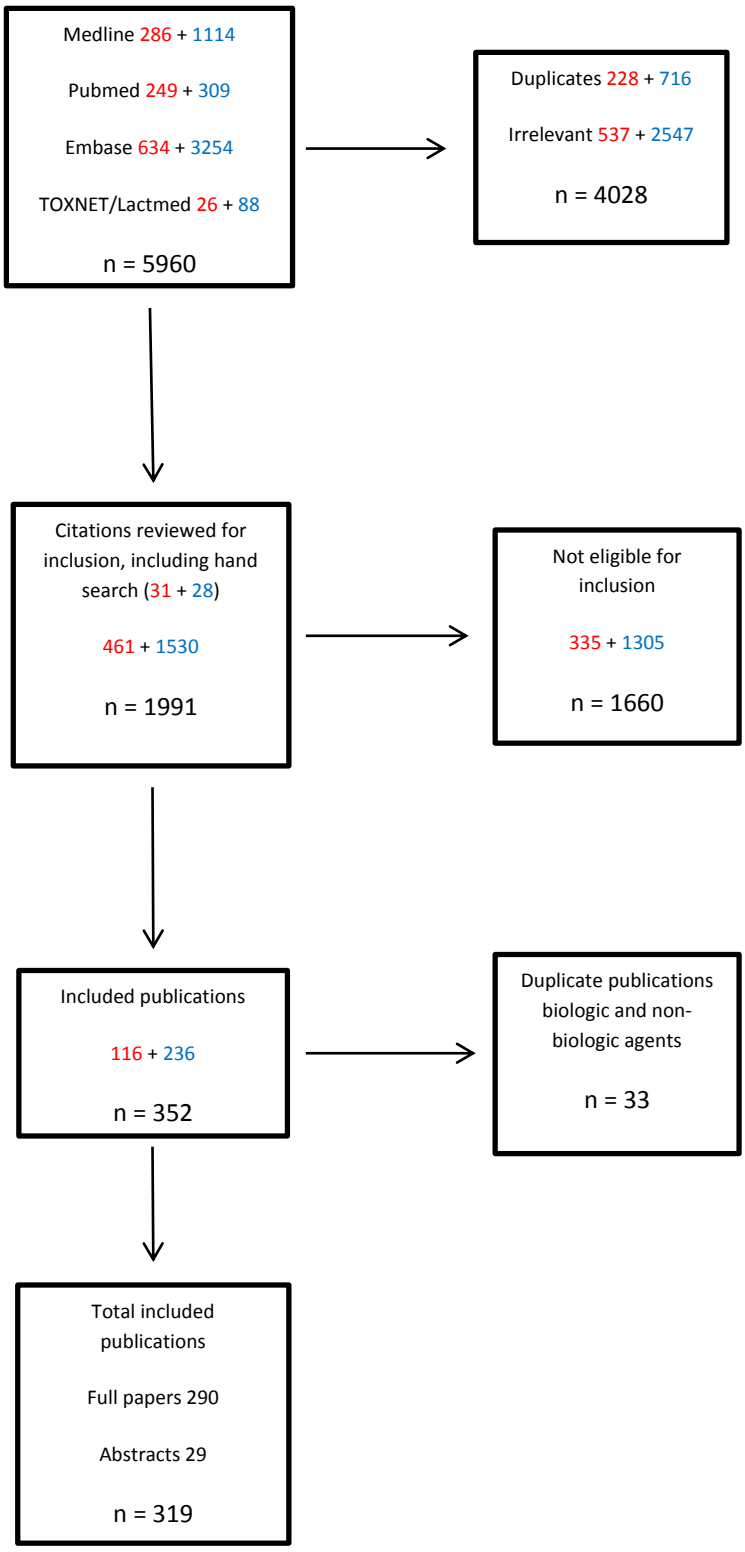
Supplementary Figure S1.

Systematic literature search for anti-rheumatic drugs in pregnancy (2008 – 2015) and lactation (1970 – 2015). Biologic and non-biologic agents



Supplementary Table S1. Characteristics of registry data included in the study.

Name of Registry	Time period	Number of prospective cases with known outcome	Number of ongoing pregnancies or lost to follow up	Comment
French Regional Centers of Pharmacovigilance (FRCP)	1990 through August 2009 (17/31 centers)	31	Not reported	Cases exposed to adalimumab (3), etanercept (13) or infliximab (15)
The Norwegian Medicines Agency (NOMA)	2002 through May 2014	17[1]	5	Cases exposed to adalimumab (8), etanercept (2) or infliximab (7)
GlaxoSmithKline (GSK)	Cumulative through March 2015	153[2]	74	Cases exposed to belimumab
Janssen Pharmaceutical Companies of Johnson & Johnson	Cumulative through December 2012	81	85	Cases exposed to ustekinumab
Roche	December 2009 through December 2014	449[3]	712	Cases exposed to mycophenolate mofetil (202), rituximab (67) or tocilizumab (180)
Swedish Orphan Biovitrum (Sobi)	Cumulative through December 2014	26	22	Cases exposed to anakinra

[1] Spontaneous reports, not stated whether prospective or retrospective

[2] 1 retrospective case

[3] 48 retrospective cases with exposure to rituximab

Supplementary Table S2. Expert opinion on use of antirheumatic drugs during pregnancy and breastfeeding

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 a woman was breastfeeding

Supplementary Table S3. GRADE – rating the quality of evidence (8)

High quality of evidence (++++)	We are very confident that the true effect lies close to that of the estimate of the effect
Moderate quality of evidence (+++)	We are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different
Low quality of evidence (++)	Our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect
Very low quality of evidence (+)	We have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect

Supplementary Table S4. Oxford Centre for Evidence-based Medicine – Levels of Evidence (9)

1a	Systematic review (with homogeneity) of randomised controlled trials (RCT)
1b	Individual RCT (with narrow Confidence Interval)
1c	All or none
2a	Systematic review (with homogeneity) of cohort studies
2b	Individual cohort study (including low quality RCT; e.g., <80% follow-up)
2c	"Outcomes" Research; Ecological studies
3a	Systematic review (with homogeneity) of case-control studies
3b	Individual Case-Control Study
4	Case-series (and poor quality cohort and case-control studies)
5	Expert opinion without explicit critical appraisal, or based on physiology, bench research or "first principles"

Supplementary Table S5. References for case-reports and case-series concerning nonsteroidal anti-inflammatory drugs (NSAIDs), non-biologic and biologic drugs used to treat rheumatic diseases, SLR-period 2008– 2015[1].

Drug	Type of publication in numbers	References on Case-reports/case-series
Non selective COX-inhibitors (classical NSAIDs)	**3 Cohorts** 3 Case-controls	------
Selective COX – II Inhibitors (rofecoxib,celecoxib, etoricoxib)	3 Case-controls	------
Glucocorticoids (any route/formulation)	**2 Cohorts** 5 Case-controls *17 Case-reports/series* *(1 abstract)*	[1-17]
Antimalarials	**2 Cohorts** 4 Case-controls	------
Sulfasalazine	**2 Cohorts** 2 Case-controls	------
Leflunomide	**2 Cohorts** **(1 abstract)** 1 Case-control *4 Case-reports/series*	[18-21]
Azathioprine	**4 Cohorts** **(1 abstract)** 7 Case-controls *7 Case-reports/series* *(1 abstract)*	[22-28]
Methotrexate	**2 Cohorts** 2 Case-controls *8 Case-reports/series*	[29-36]
Cyclo phosphamide	**2 Cohorts** *28 Case-reports/series* *(2 abstracts)*	[37-64]
Ciclosporin	**2 Cohorts** 1 case-control *11 Case-reports/series* *(1 abstract)*	[28 ,65-74]
Tacrolimus	**1 Cohort** 1 Case-control *10 Case-reports/series*	[5 ,69 ,75-82]
Mycophenolate mofetil	**2 Cohorts** 1 Register data *20 Case-reports/series* *(2 abstracts)*	[66 ,83-101]
Colchicine	**1 Cohort** 1 Case-control *1 Case-series*	[102]
IVIG	**3 Cohorts** *3 Case-reports/series*	[103-105]
Tofacitinib	*1 Case-series* *(abstract)*	[106]
Infliximab	**9 Cohorts** **(1 abstract)** 4 Case-controls (1 abstract) 2 Register data (1 abstract) *16 Case-reports/series* *(3 abstracts)*	[107-123]
Adalimumab	**10 Cohorts** **(2 abstracts)** 5 Case-controls (1 abstract) 2 Register data (1 abstract) *6 Case-reports/series*	[111 ,118 ,121 ,124-127]

	(1 abstract)	
Etanercept	**3 Cohorts** 3 Case-controls (1 abstract) 2 Register data (1 abstract) *11 Case-reports/series* *(3 abstracts)*	[111 ,117 ,118 ,121 ,128-135]
Certolizumab	**2 Cohorts** 1 Case-control *2 Case-reports/series*	[136 ,137]
Golimumab	**1 Cohort** *1 Case-series* *(abstract)*	[138]
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)*	[107-135 ,137-139]
Rituximab	1 Register data *20 Case-reports/series*	[60 ,140-158]
Anakinra	1 Register data *3 Case-reports*	[159-161]
Abatacept	*1 Case- series*[8] *1 Case-report*	[150 ,162]
Tocilizumab	1 Register-data *2 Case-series* *(2 abstracts)*	[163 ,164]
Ustekinumab	1 Register data *4 Case-reports/series* *(1 abstract)*	[165-168]
Belimumab	1 Register data *1 case-series* *(abstract)*	[169]

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Supplementary Table S6. Number of publications and references concerning 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 publications	References
Non selective COX-inhibitors (classical NSAIDs)	7	[1-6]
Selective COX II Inhibitors	4	[7-10]
Prednisone	6	[1 ,11-15]
Hydroxy-Chloroquine	5	[16-20]
Chloroquine	6	[21-26]
Mepacrine (quinacrine)	0	------
Sulfasalazine (SSZ)	7	[27-33]
Leflunomide	0	------
Azathioprine[4]	9	[34-42]
Methotrexate	3	[43-45]
Cyclo phosphamide	3	[46-48]
Ciclosporin	11	[49-59]
Tacrolimus	9	[38 ,49 ,60-66]
Mycophenolate Mofetil	1	[49]
Colchicine	5	[67-70]
IVIG	5	[71-75]
Tofacitinib	0	------
Infliximab	9	[76-84]
Adalimumab	4	[78 ,81 ,85 ,86]
Golimumab	0	------
Etanercept	4	[87-90]
Certolizumab	2	[81 ,91]
Rituximab	0	------
Anakinra	1	[92]
Ustekinumab	0	------
Tocilizumab	0	------
Abatacept	0	------
Belimumab	0	------

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Supplementary Table S7. Follow up of children* exposed to immunosuppressive medications in 2nd and/or 3rd trimester of pregnancy,

SLR period 2006-2015

Maternal medication in pregnancy	Type of publication in numbers	References	Number of children	Mean follow up time and range: years (yrs)	Number of children vaccinated[1]/ children with normal vaccination response	Rate of serious infection[2] in 1st year of life compared to non-exposed children	Physical development: Number of children normal/impaired	Cognitive development: Number of children normal /impaired	Comments
Infliximab	**2 cohorts (2 abstracts)** 2 case-controls *7 case-reports*	[1-11]	269	1.1 (4 mo.-3yrs)	49/48	Not increased	57/0	22/0	1 child died after BCG vaccination at 3 months of age
Adalimumab	**2 cohorts (2 abstracts)** 2 case-controls *3 case-reports*	[1 ,4 ,7-9 ,12 ,13]	136	1.2 (5 mo.-2.2 yrs)	3/3	Not increased	15/1	3/0	
Certolizumab	**2 cohorts (2 abstracts)**	[7 ,8]	99	1.0	Not reported	Not increased	10/0	Not studied	
Rituximab	*9 case-reports*	[1 ,14-21]	8	1.4 (6 mo.-4.5yrs)	5/5	Not reported	8/0	2/0	Transient B cell depletion in children exposed in 2nd and 3rd trimester
Ciclosporin	**1 cohort**	[22]	39	Mean not reported. (7 mo.-3 yrs)	Not reported	Not reported	Not reported	39/0	
Azathioprine	**1 cohort** 2 case-controls	[23-25]	58	4.5 yrs (6 mo-9.2 yrs)	45/45	Not increased	45/0	58/7	
Dexamethason	**2 cohorts**	[26 ,27]	27	6 (1.8-11 yrs)	Not reported	Not reported	11/0	27/0	

[*]Included only if total number of children exposed to a medication > 5

[1] According to National vaccination programs, including measles, mumps, rubella, pertussis, tetanus, diphtheria, hepatitis B, poliomyelitis. In some countries live vaccines BCG vaccine is given at 3 months and rotavirus at 2,4, and 6 months of age

[2] Serious infection defined as requiring intravenous treatment or hospitalization

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