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Epidemiology

Antirheumatic drugs in reproduction, pregnancy, and lactation: a systematic literature review informing the 2024 update of the EULAR recommendations

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ARTICLE INFO

ABSTRACT

Objectives: This study aimed to summarise and update evidence to inform the 2024 update of the European Alliance of Associations for Rheumatology recommendations for the use of antirheumatic drugs in reproduction, pregnancy, and lactation.
Methods: A systematic literature review (SLR) was performed, including keywords on reproduction, adverse pregnancy outcomes (APOs), and lactation. Two appraised SLRs were the basis for the SLR on drug safety in men. If sufficient data were available, a meta-analysis was performed on maternal drug exposure and the risk of APOs.
Results: Of 6680 screened articles, 255 were included in the final analysis. In pregnancy, most evidence was available for biologic disease-modifying antirheumatic drugs (bDMARDs). Meta-analyses with adjusted risk estimates did not reveal APOs or serious infant infections to be associated with tumour necrosis factor inhibitor (TNFi) use. Data on non-TNFi bDMARDs did not raise concerns. In bDMARD-exposed infants, no serious adverse effects to rotavirus live

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vaccination were reported. Safety of Bacille Calmette–Guérin vaccination in TNFi-exposed infants could be a concern in the first 6 months of life. Regarding oral glucocorticoids, the SLR and meta-analysis using adjusted risk estimates found a dose-dependent association with an increased risk of preterm birth. Nonsteroidal anti-inflammatory drug use could reversibly reduce fecundability. Concerning lactation, available data on various bDMARDs was reassuring. In male patients, available evidence on methotrexate and most other drugs did not reveal adverse effects on sperm quality or birth outcomes. Cyclophosphamide remains the only drug that causes a dose-dependent irreversible infertility.

Conclusions: This SLR provides up-to-date evidence to guide the 2024 update of the European Alliance of Associations for Rheumatology recommendations for the use of antirheumatic drugs in reproduction, pregnancy, and lactation.

WHAT IS ALREADY KNOWN ON THIS TOPIC

- The safety of antirheumatic drugs (ARDs) is of important relevance for patients with rheumatic and musculoskeletal disorders who are planning to start a family. A reevaluation of the literature was necessary since new studies and treatment options are available since the publication of the 2016 guidelines.

WHAT THIS STUDY ADDS

- This systematic literature review (SLR) provides the following results:
  - An update of the 2016 SLR with regard of the effect of ARDs on miscarriage and congenital malformations.
  - An update of the 2016 SLR regarding lactating women and the effect of ARDs on adverse outcomes of the child.
  - A new search focusing on the effect of ARDs on adverse pregnancy outcomes (APOs) (eg, stillbirth, preterm birth, low birth weight, and small-for-gestational age born infants), maternal outcomes (eg, gestational diabetes), and infant outcomes (eg, serious infant infections after *in utero* exposure).
  - An additional search on the effect of ARDs on reproductive safety in male patients.
  - A new search on the effect of nonsteroidal anti-inflammatory drugs on fertility and fetal health issues.
  - Meta-analyses were performed to investigate the risk of different APOs related to tumour necrosis factor inhibitor treatment during pregnancy and the risk of preterm birth associated with glucocorticoid use during pregnancy.

HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE OR POLICY

- This SLR informed the European Alliance of Associations for Rheumatology task force of the 2024 update on ARDs in reproduction, pregnancy, and lactation including all available evidence.

INTRODUCTION

Rheumatic and musculoskeletal disorders (RMDs) encompass a diverse group of medical conditions, which often require the continuous use of antirheumatic drugs (ARDs) to manage symptoms and prevent disease progression. The safety of these medications for women planning a pregnancy and during pregnancy and breastfeeding, and for men, who want to father a child, remains a major concern for both clinicians and patients. Conversely, active inflammatory RMDs are known for being a relevant risk factor for fertility and adverse pregnancy outcomes (APOs) [1–4].

The first European Alliance of Associations for Rheumatology (EULAR) points to consider (PtC) for the use of ARDs before pregnancy, and during pregnancy and lactation published in 2016, gave guidance for clinicians and healthcare professionals [4]. Since then, a growing body of literature has emerged, and new treatment options have entered the market, necessitating a reevaluation of the available evidence.

Therefore, the objective of this systematic literature review (SLR) was to update the 2016 SLR on the safety of ARDs in pregnant and breastfeeding women with RMDs reflecting the most recent scientific literature. Moreover, this SLR includes additional relevant pregnancy outcomes, such as stillbirth, preterm birth (PTB), neonates born small-for-gestational age (SGA) or of low birth weight (LBW), and serious infant infections (SII). The review also investigated drug safety for male patients planning a family. A further objective was to investigate the association between maternal drug exposure and the risk of APOs in a meta-analysis if sufficient data were available. Results of this SLR served as a basis to inform the EULAR Task Force (TF) on ARDs in pregnancy and lactation. Of note, this SLR and the update of the 2016 EULAR PtC form an integral and should be read as such.

METHODS

For the update of the 2016 EULAR SLR, we followed the standardised operating procedures for EULAR-endorsed recommendations [5]. The Cochrane Handbook was used to conduct this SLR [6], and for the reporting, we adhered to the Preferred Reporting Items for Systematic reviews and Meta-Analyses (PRISMA) guidelines [7]. Review questions were developed by the TF steering group (FF, AF, and YM) and fellows (SH, AP, and LR) following the population–intervention–outcome (PIO) framework (details in the Supplementary Material):

(1) In women planning a pregnancy or currently pregnant (P) with an indication for the given drug (I), what is the effect of the drug on congenital malformations and miscarriages (O)?
(2) In lactating women (P) with an indication for the given drug (I), what is the effect of the drug on any adverse child's outcomes (O)?
(3) In pregnant women with an indication for the given drug (P), what is the effect of the drug (I) on adverse pregnancy and maternal outcomes and adverse infant outcomes (O)?
(4) In male patients with an indication for the given drug trying to conceive or with periconceptional drug exposure (P), what is the effect of the drug (I) on fertility issues and adverse pregnancy outcomes (O)?
(5) In pregnant women using nonsteroidal anti-inflammatory

drugs (NSAIDs) (P), what is the effect of NSAIDs (I) on fetal health issues (O)?
(6) In women on NSAIDs planning to conceive (P), what is the effect of continuing NSAIDs(I) on fertility issues (O)?

PIO 1 and 2 questions represent the update of the earlier EULAR SLR and encompass a search period starting from April 1, 2015, until April 30, 2023 (in the case of included abstracts, available published full-text articles were considered for data extraction). Additional searches were performed for research questions addressing new populations and outcomes (PIO 3-6). The search was not limited to RMDs, but to all indications for the given drug. Search starting point was from January 1, 2000 (era of broader treatment option), for PIO 3, 5, and 6. The search for PIO 4 started from September 1, 2019, as 2 SLRs were used as the base for PIO 4. Included SLRs were critically reviewed and appraised according to the AMSTAR2 guidelines [8] (Supplementary Table S1). At the first TF meeting, all members approved the review questions. The detailed SLR protocol was published in PROSPERO (CRD42022357689). No comparisons between ARDs on the review questions were requested to obtain broader search results.

Search strategy and eligibility criteria

An experienced librarian (TR) translated the main elements of the research questions into search terms by using controlled vocabulary and free text, and the initial search strategy was supported by analysing key studies. The search was conducted in the databases MEDLINE ALL (Ovid), Embase (Elsevier) and Cochrane Library (Wiley). The detailed search strategy for each database is provided in the supplement. As further information sources, abstracts from the EULAR and the American College of Rheumatology (ACR) congresses of the years 2022 and 2023 were screened, and reference lists of included studies and LactMed database were handsearched.

Studies were eligible for inclusion if they reported (I) the population of adult female or male patients with an indication for a drug defined by 1 of the PIO questions who planned to conceive (exposure time before conception < 5 half-lives) or with periconceptional drug exposure, or (II) the population of pregnant or lactating/breastfeeding women with an indication for a drug defined by PIO 2, and if they reported at least 1 outcome from the 6 PIO questions in at least 1 of the investigated treatment exposure groups. The SLR also included studies of newborns/infants with *in utero* exposure to 1 of the drugs listed for PIO 3 and reporting of the infant's outcome during the first year of life. Eligible study types comprised original prospective and retrospective studies including randomised or non-randomised studies, observational cohorts, case-control or cross-sectional studies, case series or reports, short reports, or letters including original data. Publications in English, Spanish, French, or German language were included. Exclusion criteria for the SLR search comprised animal studies, *in vitro* studies, editorials, literature reviews, non–peer-reviewed publications, publications describing cancer chemotherapy, and publications in other than the above-described languages.

Selection of studies, data extraction, and assessment of risk of bias

Screening and study selection of search results were performed by using the web-based SLR tool Rayyan (https://www.rayyan.ai/). Before the formal screening, a pilot was performed. Two reviewers each (FF, SH, AP, LR, LFP-G, and IC) independently screened a subset (20%) of titles and abstracts by applying inclusion and exclusion criteria. Agreement between reviewers was sufficient (>80%), and consequently remaining results were screened by 1 reviewer. The same procedure was applied for full-text screening. Any discrepancies were resolved through discussions between reviewers or by involving the convenor and/or methodologists. Data were extracted into a standardised excel spreadsheet with a pilot extraction to ensure consistency across reviewers. Risk of bias and study quality of individual studies was assessed by the risk-of-bias tool for randomised trials (RoB2), the Newcastle–Ottawa Scale for observational studies, and JBI appraisal for case reports/case series [9–11]. The details on quality scoring of each study are provided in Supplementary Table S2. For each drug, the level of evidence was assigned according to the evidence retrieved in the SLR of EULAR PtC 2016, the present SLR, and other SLRs when relevant [4,5,12].

Meta-analysis

A meta-analysis was conducted as part of this SLR, with sufficient data available to investigate 2 key topics: the risk of APOs (miscarriages, congenital malformations, stillbirth, PTB, LBW, SGA, and SII) associated with tumour necrosis factor inhibitor (TNFi) treatment versus no TNFi treatment during pregnancy, and the risk of PTB associated with glucocorticoid (GC) use versus no GC use during pregnancy. The meta-analysis used 2 different approaches to estimate the risks: model (a) calculated pooled unadjusted odds ratios (ORs) for exposed versus unexposed groups per outcome, while model (b) pooled risk estimates adjusted for confounding factors for exposed versus unexposed groups. Methodologic details are provided in the Supplementary Material.

RESULTS

The combined search yielded 6680 results, of which 255 were eligible for inclusion (Supplementary Fig S1). The study quality overall was classified as good for 30% of studies, fair for 8%, and poor for 62%. Information on study quality for individual studies and by drug are provided in Supplementary Figs S2 and S3 and Supplementary Table S2. Notably, the number of published studies on drug exposure during pregnancy and associated APOs has increased over the past 2 decades, with a growing number of prospective cohort and national registry studies (Supplementary Fig S4). Of the included studies, 37 were incorporated in at least 1 of the meta-analyses (Supplementary Tables S3 and S4).

Effects of ARDs on congenital malformation, miscarriage, and other APOs

An overview of the crude results of the PIO questions 1 and 3 (only maternal/pregnancy outcomes) are provided in Table 1.

Glucocorticoids

Previously, EULAR recommended that GC could be considered for use in pregnancy if needed to control active disease symptoms. This recommendation was based on 24 studies (including 17 case reports/series) [4]. Since then, we identified additional evidence from 19 studies (including 8439 pregnancies). No increased risk of congenital malformation was found in adjusted analyses [13,14]. Rates of LBW and PTB were notably high at 22.2% and 17.9%, respectively. Our meta-analysis based on adjusted risk estimates from 11 cohorts confirmed an association between oral GC use and PTB (pooled adjusted odds ratio

Table 1

Outcomes of pregnancy exposure to antirheumatic drugs: summary of results stratified by drug

Drug/EULAR SLR	No. of studies per study type [Ref][a]	Total exposed pregnancies (per time points); total live births[b]	Pregnancy loss (per total pregnancies): MC,[c] SB, ND, ET	Pregnancy outcomes (per total pregnancies): PTB, LBW, SGA	CM[c] (per total live birth)[d]	Maternal outcomes: SMI, GH, GD	Comments[e]	Evidence: LoE[f] and study quality[g]
Glucocorticoids		11,717[h]						
EULAR 2016	24 [s216]	3500	MC: 70/331		CM: 34/3180			
EULAR update 2024: **prednisone/prednisolone, methylprednisolone pulse (IV)**	17 CS [s1–s17] 1 CCS [s18] 1 CSE [s19]	8439 Preg (PRE ≥349; T1 ≥1200; T2 ≥1301; T3 ≥774) 4454 LB	MC: 103/1094 SB: 13/569 ND: 2/258 ET: 25/380	PTB: 931/5212 LBW: 152/685 SGA: 106/2049	CM: 89/1457	SMI: NA GH: no increased prevalence GD: NA	No excess risk of CM, MC, and SGA compared with unexposed controls in studies adjusted for confounders. Higher risk of PTB and LBW compared with nonexposed controls was confirmed by several studies with adjustment for disease severity/activity. Higher risk of PTB for both, early and late, glucocorticoid exposures. Lowest risk of PTB for low prednisolone doses (average daily dose < 5.0 mg/d)	**2b** 8 good 7 fair 4 poor
NSAIDs								
Nonselective NSAIDs		157,561[h]						
EULAR 2016	6 [s216]	17,992	MC: 530/5609		CM: 457/12,354			
EULAR update 2024	11 CS [s4,s8,s20–s28] 1 CSE [s29]	145,889 Preg (PRE ≥133; T1 ≥130,627; T2 ≥3317; T3 ≥1564) 14,663 LB	MC: 152/1740 SB: 61/12,551 ND: 27/11,053 ET: 132/1631	PTB: 1504/21,234 LBW: 7581/141,333 SGA: 7/125	CM: 4754/118,954	SMI: NA GH: no increased prevalence GD: no increased prevalence	No excess risk of CM and MC compared with nonexposed controls in studies with adjustment for confounders	**2a** 7 good 5 poor
Selective COX-2 inhibitors		1038						
EULAR 2016	3 [s216]	215	MC: 11/71		CM: 9/114			
EULAR update 2024	2 CS [s25,s30]	823 Preg (PRE NA; T1 823; T2 ≥7; T3 ≥3) 139 LB	MC: 16/174 SB: 0/174 ND: NA ET: 19/174	PTB: 15/139 LBW: 47/649 SGA: NA	CM: 40/726	SMI: NA GH: NA GD: NA	No excess risk of CM and MC compared with unexposed controls in the prospective cohort study with adjustment for confounders	**2b** 1 good 1 poor
csDMARDs, immunosuppressives, and other drugs								
Antimalarials (HCQ, CQ)		5823[h]						
EULAR 2016	6 [s216]	492	MC: 20/170		CM: 23/492			
EULAR update 2024	20 CS [s10,s31–s49]	5331 Preg (exposure: NA) 854 LB	MC: 99/889 SB: 15/858 ND: 1/161 ET: 7/549	PTB: 437/3023[i] LBW: 110/771[i] SGA: 226/1709	CM: 204/4009	SMI: NA GH: no increased prevalence GD: no increased prevalence	Most data available for HCQ. No study reported a significantly higher risk of APO, except for 1 study based on claims data, which reported aRR of 1.33 (95% CI: 1.08, 1.65) for CM with HCQ ≥ 400.0 mg/d. No CM pattern was observed. A subsequent prospective cohort study did not confirm this risk (OR: 1.08, 95% CI: 0.51, 2.29)	**2a (HCQ)** **2c (CQ)** 16 good 3 fair 1 poor
Azathioprine/6-mercaptopurine		5619[h]						
EULAR 2016	18 [s216]	1327	MC: 40/559		CM: 65/1327			
EULAR update 2024	14 CS [s7,s10,s18,s33, s48,s50–s58] 4 CCS [s59–s62] 1 CSS [s63]	4985 Preg (exposure NA) 3597 LB	MC: 69/698 SB: 6/313 ND: 2/308 ET: 3/197	PTB: 781/4957[i] LBW: 137/1099[i] SGA: 360/4416	CM: 69/1453	SMI: NA GH: no increased prevalence GD: no increased prevalence	Most studies reported no increased risk of APO, except for a slight increase in prematurity in a single nationwide cohort study of children born to women with Crohn disease, confounded by disease severity.	**2a** 10 good 2 fair 7 poor
Bosentan		1						
EULAR 2016	—							
EULAR update 2024	1 CR [s64]	1 Preg (PRE NA; T1 1; T2 1; T3 0) 1 LB	MC: 0/1 SB: 0/1 ND: 0/1 ET: 0/1	PTB: 1/1 LBW: 1/1 SGA: NA	CM: 0/1	SMI: NA GH: NA GD: NA	Too limited data to draw conclusions	**4** 1 poor

(*continued on next page*)

Table 1 (*Continued*)

Drug/EULAR SLR	No. of studies per study type [Ref][a]	Total exposed pregnancies (per time points); total live births[b]	Pregnancy loss (per total pregnancies): MC,[c] SB, ND, ET	Pregnancy outcomes (per total pregnancies): PTB, LBW, SGA	CM[c] (per total live birth)[d]	Maternal outcomes: SMI, GH, GD	Comments[e]	Evidence: LoE[f] and study quality[g]
Colchicine		564[h]						
EULAR 2016	3 [s216]	460	MC: 30/417		CM: 11/460			
EULAR update 2024	2 CS [s65,s66] 1 CSS [s67]	342 Preg (exposure NA) 217 LB	MC: 25/300 SB: 0/300 ND: NA ET: NA	PTB: 44/276[i] LBW: NA SGA: NA	CM: 12/321	SMI: NA GH: NA GD: NA	No adverse drug-related effect on pregnancy outcomes compared with unexposed controls.	**2b** 1 good 2 fair
Cyclophosphamide		433						
EULAR 2016	30 [s216]	276	MC: —		CM: 23/86			
EULAR update 2024	4 CS [s10,s14,s18, s68] 3 CR/CSE [s9,s69,s70]	157 Preg (PRE ≥146; T1 ≥1; T2 ≥3; T3 ≥2) 103 LB	MC: 35/151 SB: 7/114 ND: 1/94 ET: 8/61	PTB: 38/136 LBW: 4/8 SGA: 2/8	CM: 0/28	SMI: NA GH: NA GD: NA	Known teratogenic and embryotoxic risk if exposure occurs in the first trimester, which explains the high rate of MC. Few data of exposed patients vs unexposed controls, no studies with adjusted risk analyses available.	**2b** 2 fair 5 poor
Cyclosporine		1163[h]						
EULAR 2016	14 [s216]	1126	MC: 137/953		CM: 9/261			
EULAR update 2024	1 CS [s71] 1 CSE [s72]	37 Preg (exposure NA) 33 LB	MC: 3/34 SB: 1/8[i] ND: 0/7 ET: 1/29	PTB: 4/7[i] LBW: 1/7[i] SGA: 2/26[i]	CM: 0/33	SMI: NA GH: no increased prevalence GD: NA	No adverse drug-related effects on pregnancy outcomes compared with unexposed controls.	**2a** 2 poor
IV immunoglobulin		100[h]						
EULAR 2016	3 [s216]	96	MC: 24/93		CM: 0/96			
EULAR update 2024	1 CSE [s73] 1 CR [s74]	4 Preg (exposure NA) 4 LB	MC: 0/4 SB: 0/4 ND: 0/4 ET: NA	PTB: 1/3[i] LBW: NA SGA: NA	CM: 0/4	SMI: NA GH: NA GD: NA	No adverse drug-related effects on pregnancy outcomes compared with unexposed controls.	**3b** 2 poor
Leflunomide/teriflunomide		1285[h]						
EULAR 2016	7 [s216]	129	MC: 12/122		CM: 5/129			
EULAR update 2024	9 CS [s75–s83] 1 CCS [s84] 1 CR [s85]	1219 Preg (PRE ≥299; T1 ≥321; T2 ≥35; T3 ≥49) 653 LB	MC: 182/1160 SB: 7/1043 ND: 0/290 ET: 312/1160	PTB: 37/235 LBW: 10/53 SGA: 19/125	CM: 20/655	SMI: NA GH: no increased prevalence GD: no increased prevalence	No excess risk of CM, MC, LBW and PTB in studies with controls. The average rate of drug washout was 49%. Data on leflunomide/teriflunomide exposure in pregnancy without drug washout procedure remains insufficient.	**2b** 2 good 9 poor
Methotrexate		595						
EULAR 2016	12 [s216]	372	MC: 140/329		CM: 15/143			
EULAR update 2024	1 CS [s86]	223 Preg (exposure NA) 153 LB	MC: 70/223 SB: 49/223 ND: NA ET: 21/223	PTB: NA LBW: NA SGA: NA	CM: 1/153	SMI: NA GH: NA GD: NA	Known teratogenic and embryotoxic risk if exposure occurs in the first trimester, which explains the high rate of MC and stillbirth.	**2b** 1 poor
Mycophenolate mofetil		337						
EULAR 2016	23 [s216]	333	MC: 119/318		CM: 48/174			
EULAR update 2024	1 CSE[s9]	4 Preg (exposure NA) 4 LB	MC: 0/4 SB: 0/4 ND: 0/4 ET: 0/4	PTB: 2/4 LBW: 3/4 SGA: 1/4	CM: 0/4	SMI: NA GH: no increased prevalence GD: NA	Known teratogenic and embryotoxic risk if exposure occurs in first trimester, which explains the high rate of MC.	**2b** 1 poor
Sildenafil		166						
EULAR 2016	—							
EULAR update 2024	SLR [s251]	165 Preg	MC: NA SB: 3/69 ND: 5/129 ET: NA	PTB: NA LBW: NA SGA: NA	CM: 0/35	SMI: NA GH: NA GD: NA	Limited evidence available in patients with RMD. Most evidence was available from studies with control groups investigating whether sildenafil improves perinatal outcome in pregnancies with severe placental dysfunction.	**4** 1 poor
	1CR [s64]	1 Preg (exposure NA) 1 LB	MC: NA SB: NA ND: NA ET: NA	PTB: 1/1 LBW: NA SGA: NA	CM: NA	SMI: NA GH: NA GD: NA		

(*continued on next page*)

Table 1 (*Continued*)

Drug/EULAR SLR	No. of studies per study type [Ref][a]	Total exposed pregnancies (per time points); total live births[b]	Pregnancy loss (per total pregnancies): MC,[c] SB, ND, ET	Pregnancy outcomes (per total pregnancies): PTB, LBW, SGA	CM[c] (per total live birth)[d]	Maternal outcomes: SMI, GH, GD	Comments[e]	Evidence: LoE[f] and study quality[g]
Sulfasalazine/mesalazine (5-ASA)		623[h]						
EULAR 2016	4 [s216]	525	MC: 12/186		CM: 16/339			
EULAR update 2024	5 CS [s4,s5,s48,s87,s88]	98 Preg (exposure NA) 3618 LB	MC: 10/54 SB: NA ND: NA ET: NA	PTB: 296/3849 LBW: NA SGA: 108/3599	CM: 145/3618	SMI: NA GH: NA GD: NA	No adverse drug-related effects on pregnancy outcomes compared with unexposed controls, including studies with adjustment for confounders.	**2a** 4 good 1 poor
Tacrolimus		540[h]						
EULAR 2016	12 [s216]	505	MC: 91/344		CM: 3/107			
EULAR update 2024	2 CS [s89,s90]	35 Preg (exposure NA) 32 LB	MC: 3/35 SB: 0/35 ND: NA ET: NA	PTB: 3/20[i] LBW: NA SGA: 3/20[i]	CM: 1/35	SMI: NA GH: NA GD: NA	No adverse drug-related effects on pregnancy outcomes compared with unexposed controls, including 1 study with adjustment for confounders.	**2b** 1 good 1 fair
Avacopan, mepacrin, voclosporin, and iloprost/ilomedin: No studies available								
tsDMARDs								
Tofacitinib		85						
EULAR 2016	1 [s216]	27	MC: 7/27		CM: 1/15			
EULAR update 2024	1 CS [s91]	58 Preg (PRE NA; T1 ≥47; T2 NA; T3 NA) 33 LB	MC: 14/58 SB: 0/58 ND: 0/58 ET: 9/58	PTB: 7/33 LBW: NA SGA: NA	CM: 2/58	SMI: NA GH: NA GD: NA	No comparison with a control group. High rate of MC (but no data on comedication). Limited data indicate no increased risk of CM. No studies with control group available.	**2b** 1 poor
Apremilast, baricitinib, filgotinib, and upadacitinib: No studies available								
bDMARDs								
TNFi bDMARDs								
TNFi total[j]		12,817[h]						
EULAR 2016	49 [s216]	2492	MC: 265/2258		CM: 75/2110			
EULAR update 2024	50 CS [s2,s22,s23,s53,s55, s57,s58,s61,s62, s92–s132] 3 CSS [s63,s133,s134] 2 CCS [s15,s135] 3 CR [s136–s138] 5 CSE [s139–s143]	11,194 Preg (PRE ≥1471; T1 ≥5009; T2 ≥1801; T3 ≥2190) 11,826 LB	MC: 900/7540 SB: 53/7135 ND: 6/448 ET: 215/5683	PTB: 1488/14,343 LBW: 533/7330 SGA: 729/9250	CM: 277/7479	SMI: data insufficient GH: no increased prevalence GD: no increased prevalence	No adverse drug-related effects on pregnancy outcomes based on studies with control groups and adjustment for confounders.	**2a** 26 good 4 fair 33 poor
Adalimumab		1148						
EULAR 2016	23 [s216]	524	MC: 23/191		CM: 24/350			
EULAR update 2024	3 CS [s94–s96]	624 Preg (PRE ≥12; T1 ≥138; T2 ≥52; T3 ≥20) 502 LB	MC: 60/610 SB: 2/610 ND: NA ET: 17/610	PTB: 58/558 LBW: 7/45 SGA: 17/206	CM: 23/502	SMI: NA GH: no increased prevalence GD: NA	No adverse drug-related effects on pregnancy outcomes compared with unexposed controls. Analyses with adjustment for confounders available.	**2b** 1 good 2 poor
Certolizumab		1798						
EULAR 2016	6 [s216]	362	MC: 52/339		CM: 12/267			
EULAR update 2024	2 CS [s98,s99] 1 CR [s138] 2 CSE [s139,s140]	1436 Preg (PRE ≥13; T1 ≥1035; T2 ≥23; T3 ≥44) 1304 LB	MC: 111/1468 SB: 11/1454 ND: 0/29 ET: 39/1454	PTB: 125/1304 LBW: 103/1287 SGA: NA	CM: 44/1304	SMI: data insufficient GH: no increased prevalence GD: no increased prevalence	No adverse drug-related effects on pregnancy outcomes. No studies with control group available.	**2b** 1 good 4 poor
Etanercept		588						
EULAR 2016	19 [s216]	332	MC: 12/74		CM: 9/251			
EULAR update 2024	1 CS [s97]	256 Preg (PRE ≥233; T1 NA; T2 NA; T3 NA) 177 LB	MC: 56/256 SB: 2/256 ND: NA ET: 23/256	PTB: 32/166 LBW: 25/166 SGA: NA	CM: 10/165	SMI: NA GH: NA GD: NA	No adverse drug-related effects on pregnancy outcomes compared with unexposed controls.	**2b** 1 good

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Table 1 (*Continued*)

Drug/EULAR SLR	No. of studies per study type [Ref][a]	Total exposed pregnancies (per time points); total live births[b]	Pregnancy loss (per total pregnancies): MC,[c] SB, ND, ET	Pregnancy outcomes (per total pregnancies): PTB, LBW, SGA	CM[c] (per total live birth)[d]	Maternal outcomes: SMI, GH, GD	Comments[e]	Evidence: LoE[f] and study quality[g]
Golimumab		≥89[k]						
EULAR 2016	2 [s216]	50	MC: 13/47		CM: 0/26			
EULAR update 2024	No studies available[k]	≥39 Preg[k]					No adverse drug-related effects on pregnancy outcomes. No studies with control group available.	**4**
Infliximab		3127						
EULAR 2016	31 [s216]	1161	MC: 64/676		CM: 20/756			
EULAR update 2024	2 CS [s92,s93] 2 CR [s136,s137] 2 CSE [s141,s142]	1966 Preg (PRE ≥91; T1 ≥1315; T2 ≥109; T3 ≥554) 1640 LB	MC: 242/1989 SB: 2/1883 ND: 0/8 ET: 83/1989	PTB: 149/1990 LBW: 72/1879 SGA: 10/1875	CM: 27/1640	SMI: NA GH: NA GD: NA	No adverse drug-related effects on pregnancy outcomes compared with unexposed controls.	**2b** 4 poor
Mixed TNFi[l]		6912						
EULAR 2016	—							
EULAR update 2024	42 CS [s2,s22,s23,s53,s55, s57,s58,s61,s62,s100 −s132] 3 CSS [s63,s133,s134] 2 CCS [s15,s135] 1 CSE [s143]	6912 Preg (PRE ≥1122; T1 ≥2521; T2 ≥1617; T3 ≥1572) 8203 LB	MC: 431/3217 SB: 36/2932 ND: 6/411 ET: 53/1374	PTB: 1124/10,325 LBW: 326/3953 SGA: 702/7169	CM: 173/3868	SMI: data insufficient GH: no increased prevalence GD: no increased prevalence	No adverse drug-related effects on pregnancy outcomes compared with unexposed controls with adjustment for confounders	**2a** 23 good 4 fair 21 poor
Non-TNFi bDMARD								
B cell-targeted therapy								
Belimumab		410[h]						
EULAR 2016	2 [s216]	153	MC: 41/153	CM: 7/71				
EULAR update 2024	2 CS (1 abstract) [s144, s145] 6 CR [s146−s151] 2 CSE [s152,s153]	410 Preg (PRE ≥24; T1 ≥26; T2 ≥14; T3 ≥18) 255 LB	MC: 82/409[i] SB: 4/408 ND: 1/40 ET: 74/388	PTB: 14/410 LBW: 9/18[i] SGA: 8/16[i]	CM: 12/247	SMI: data insufficient GH: no increased prevalence GD: no increased prevalence	No adverse drug-related effects on pregnancy outcomes. No studies with control group available.	**4** 10 poor
Rituximab		484[h]						
EULAR 2016	21 [s216]	256	MC: 48/210		CM: 6/172			
EULAR update 2024	4 CS [s54,s154−s156] 5 CR [s157−s164] 6 CSE [s165−s170]	393 Preg (PRE ≥216 |T1 ≥19; T2 ≥24; T3 ≥11) 255 LB	MC: 43/296 SB: 3/242 ND: 2/162 ET: 35/277	PTB: 35/232[i] LBW: 6/53[i] SGA: 4/60	CM: 8/235	SMI: data insufficient GH: no increased prevalence GD: no increased prevalence	No adverse drug-related effects on pregnancy outcomes. No studies with control group available.	**4** 15 poor
T cell costimulation inhibitor								
Abatacept		170[h]						
EULAR 2016	2 [s216]	152	MC: 40/151		CM: 7/87			
EULAR update 2024	2 CS (one abstract) [s171, s172] 2 CR [s161,s173]	169 Preg (PRE ≥2 |T1 ≥2; T2 ≥0; T3 ≥0) 101 LB	MC: 42/169[i] SB: 2/169 ND: 2/104 ET: 19/168	PTB: 2/15[i] LBW: 0/2 SGA: 1/13	CM: 8/100 (not increased compared with overall rates for CM: in the thoroughly collected OTIS data)	SMI: NA GH: NA GD: no increased prevalence	Overall, 2 cohort studies with prospective data indicated no adverse drug-related effect on pregnancy outcomes. No studies with control group available.	**4** 4 poor
Interleukin inhibitors								
Anakinra		70[h]						
EULAR 2016	4 [s216]	40	MC: 4/40		CM: 2/34			
EULAR update 2024	3 CS [s174−s176] 1 CR [s177] 1 CSE [s178]	39 Preg (PRE ≥19; T1 ≥6; T2 ≥5; T3 ≥5) 37 LB	MC: 3/39 SB: 0/29 ND: 0/29 ET: 0/4	PTB: 2/32 LBW: 0/14 SGA: 1/18	CM: 2/36	SMI: no increased prevalence GH: no increased prevalence GD: no increased prevalence	No increased risk for adverse pregnancy outcomes compared with unexposed controls. No studies with control group available.	**4** 5 poor

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Table 1 (*Continued*)

Drug/EULAR SLR	No. of studies per study type [Ref][a]	Total exposed pregnancies (per time points); total live births[b]	Pregnancy loss (per total pregnancies): MC,[c] SB, ND, ET	Pregnancy outcomes (per total pregnancies): PTB, LBW, SGA	CM[c] (per total live birth)[d]	Maternal outcomes: SMI, GH, GD	Comments[e]	Evidence: LoE[f] and study quality[g]
Canakinumab		16						
EULAR 2016	—							
EULAR update 2024	2 CS [s174,s175] 1 CR [s179] 1 CSE [s175]	16 Preg (PRE ≥14 |T1 ≥7; T2 ≥2; T3 ≥3) 13 LB	MC: 2/16 SB: 1/13 ND: 0/13 ET: 0/1	PTB: 0/7 LBW: 0/7 SGA: 0/7	CM: 0/10	SMI: no increased prevalence GH: NA GD: NA	Limited evidence showed no increased risk for adverse pregnancy outcomes. No studies with control group available.	**4** 4 poor
Mepolizumab		3						
EULAR 2016	—							
EULAR update 2024	2 CR [s180,s181]	3 Preg (exposure NA) 2 LB	MC: 0/3 SB: NA ND: NA ET: 1/3	PTB: NA LBW: NA SGA: NA	CM: 0/2	SMI: NA GH: NA GD: NA	Limited evidence showed no increased risk for adverse pregnancy outcomes. No studies with control group available.	**4** 2 poor
Sarilumab		1						
EULAR 2016	—							
EULAR update 2024	1 CR [s182]	1 Preg (exposure NA) 1 LB	MC: 0/1 SB: 0/1 ND: 0/1 ET: 0/1	PTB: 0/1 LBW: 0/1 SGA: 0/1	CM: 0/1	SMI: NA GH: NA GD: NA	Limited evidence from 1 case report showed no adverse pregnancy outcome. No studies with control group available.	**4** 1 poor
Tocilizumab		401[h]						
EULAR 2016	3 [s216]	218	MC: 47/218		CM: 5/128			
EULAR update 2024	2 CS [s183,s184] 1 CSS [s14] 4 CR [s185–s188] 2 CSE [s189,s190]	363 Preg (PRE ≥84; T1 ≥216; T2 ≥10; T3 ≥6) 221 LB	MC: 84/360 SB: 1/294 ND: 2/294 ET: 59/359	PTB: 33/190[i] LBW: 20/75[i] SGA: 0/3	CM: 6/219	SMI: no increased prevalence GH: no increased prevalence GD: no increased prevalence	No adverse drug-related effects on pregnancy outcomes. No studies with control group available.	**4** 9 poor
Ixekizumab		99						
EULAR 2016	—							
EULAR update 2024	1 CS [s191]	99 Preg (PRE NA; T1 77; T2 NA; T3 NA) 39 LB	MC: 14/99 SB: 0/99 ND: 0/39 ET: 17/99	PTB: 6/39 LBW: NA SGA: NA	CM: 1/39	SMI: NA GH: NA GD: NA	No adverse drug-related effects on pregnancy outcomes. No studies with control group available.	**4** 1 poor
Secukinumab		119						
EULAR 2016	—							
EULAR update 2024	1 CS [s192]	119 Preg (exposure NA) 54 LB	MC: 26/119[i] SB: NA ND: NA ET: 39/119	PTB: 6/119 LBW: NA SGA: NA	CM: 2/54	SMI: NA GH: NA GD: NA	No adverse drug-related effects on pregnancy outcomes. No studies with control group available.	**4** 1 poor
Ustekinumab		598[h]						
EULAR 2016	5 [s216]	108	MC: 15/108		CM: 1/58			
EULAR update 2024	7 CS [s105,s106,s193–s197] 6 CR [s141,s198–s202] 1 CSE [s203]	571 Preg (PRE ≥487; T1 ≥125; T2 ≥73; T3 ≥153) 473 LB	MC: 71/576 SB: 3/487 ND: 0/28 ET: 31/574	PTB: 40/438 LBW: 21/429 SGA: 2/18[i]	CM: 12/468	SMI: NA GH: no increased prevalence GD: no increased prevalence	No adverse drug-related effects on pregnancy outcomes compared with unexposed controls.	**2b** 1 good 13 poor

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Table 1 (*Continued*)

Drug/EULAR SLR	No. of studies per study type [Ref][a]	Total exposed pregnancies (per time points); total live births[b]	Pregnancy loss (per total pregnancies): MC,[c] SB, ND, ET	Pregnancy outcomes (per total pregnancies): PTB, LBW, SGA	CM[c] (per total live birth)[d]	Maternal outcomes: SMI, GH, GD	Comments[e]	Evidence: LoE[f] and study quality[g]
Anifrolumab, guselkumab, risankizumab: No studies available							Due to the molecular structure analogous to most other biologics, a similar risk profile is expected.	**5**
Others								
Eculizumab		14						
EULAR 2016	—							
EULAR update 2024	4 CR [s204–s207] 2 CSE [s208,s209]	14 Preg (exposure NA) 13 LB	MC: 0/14 SB: NA ND: NA ET: 1/14	PTB: 7/13[i] LBW: NA SGA: NA	CM: 0/13	SMI: NA GH: NA GD: NA	Limited evidence showed no increased risk for the pregnancy outcomes MC and CM. No studies with control group available.	**4** 6 poor

APO, adverse pregnancy outcome; bDMARD, biologic disease-modifying antirheumatic drug; C5i, complement protein C5 inhibitor; CCS, case-control study; CM, congenital malformation; COX, cyclooxygenase; CQ, chloroquine; CR, case report; CS, cohort study; csDMARD, conventional synthetic disease-modifying antirheumatic drug; CSE, case series; CSS, cross-sectional study; ET, elective termination; GD, gestational diabetes; GH, gestational hypertension; HCQ, hydroxychloroquine; IFNAR1, interferon α/β receptor subunit 1 inhibitor; ILi, interleukin inhibitor; IV, intravenous; IVIG, intravenous immunoglobulin; LB, live birth; LBW, low birth weight; LoE, level of evidence; MC, miscarriage; NA, not available; ND, neonatal death; NSAID, nonsteroidal anti-inflammatory drug; OTIS, Organization of Teratology Information Specialists; PDE4i, phosphodiesterase-4 inhibitor; PRE, exposure prepregnancy; Preg, pregnancies; PTB, preterm birth; RMD, rheumatic and musculoskeletal disorder; SB, stillbirth; SGA, small-for-gestational age; SLR, systematic literature review; SMI, serious maternal infection; SSZ, sulfasalazine; T1, exposure in first trimester; T2, exposure in second trimester; T3, exposure in third trimester; TNFi, tumour necrosis factor inhibitor; tsDMARD, targeted synthetic disease-modifying antirheumatic drug.

[a] The complete list of references is available in the Supplementary Material.

[b] The number of pregnancies and live births may vary due to different data reporting in the different studies. The same applies to the number of reported outcomes, where the number of pregnancies or live births may differ compared with the reported denominator. The same applies to the number of exposed pregnancies during the various exposure periods, which may differ from the total number of reported pregnancies. As the exposure period was not recorded in all studies, the number of pregnancies that were exposed during at least this period is used.

[c] Due to the methodology of the SLR for the outcome MC and CM, some additional studies before 2015 may be included.

[d] If number of live birth was not available as denominator, the number of pregnancies was used as denominator.

[e] Summary on pregnancy exposure related to antirheumatic drugs including evidence of both previous and present SLRs. Where available, only high-quality studies were considered.

[f] Level of evidence according to studies retrieved in the SLR of EULAR points to consider 2016 and the 2024 SLR Update as well as additional studies (including additional SLRs and MA).

[g] Study quality rated as good, fair, and poor based on the Newcastle–Ottawa Scale; CR and CSE were rated as poor.

[h] Total number of exposed cases including present EULAR SLR and previous EULAR SLR without data overlap.

[i] Increased rate (considering all studies regardless of quality) due to potential confounding by disease severity, disease activity, or concomitant medication.

[j] All studies with different TNFi (monotherapy) and studies not differentiating between the different TNFi.

[k] No separate studies with golimumab. In studies with different TNFi, >39 pregnancies with golimumab described.

[l] Studies not differentiating between the different TNFi (if different bDMARD including >80%TNFi).

Table 2
Meta-analysis estimates of the risk of preterm birth with glucocorticoid use vs no use

Exposure	Unadjusted meta-analysis results					Adjusted meta-analysis results				
	No. of studies	Pooled odds ratio (95% CI)	Type of CI	I^2	τ^2	No. of studies	Pooled adjusted risk estimates (95% CI)	Type of CI	I^2	τ^2
GC vs no GC	8	2.02 (1.56, 2.62)	HKSJ	58.01	0.05	1	aHR: 1.12 (0.45, 2.78)	—	—	—
						5	aOR: 2.24 (1.84, 2.71)	HKSJ	0	0
						6	aRR: 1.78 (1.06, 3.00)	HKSJ	64.48	0.14
GC high dose vs no GC	3	[a]	—	—	—	3	[a]	—	—	—
GC low dose vs no GC	3	[a]	—	—	—	3	aRR: 1.03 (0.56, 1.87)	HKSJ	41.4	0.02

aHR, adjusted hazard ratio; aOR, adjusted odds ratio; aRR, adjusted risk ratio; GC, glucocorticoid; HKSJ, CIs based on Hartung–Knapp–Sidik–Jonkman.
[a] Estimate is not informative (ie, lower and/or upper confidence bounds fall outside the range of combined study estimates) and is therefore not reported.

[aOR]: 2.24; 95% CI: 1.84, 2.71 and pooled adjusted risk ratio [aRR]: 1.78; 95% CI: 1.06, 3.00) (Table 2 and Supplementary Fig S5). In the subanalysis stratified by dose, the association with PTB was particularly found for higher GC doses (≥5.0-10.0 mg daily or a cumulative dose of >300.0 mg within the first 20 weeks of gestation), but not for low doses (lowest risk with daily doses <5.0 mg) (Table 1 and Supplementary Table S5).

Nonsteroidal anti-inflammatory drugs

Based on the earlier EULAR SLR, which included 17,992 pregnancies exposed to nonselective NSAIDs, NSAIDs were considered compatible with the first and second trimesters of pregnancy. Regarding selective cyclooxygenase (COX) 2 inhibitors, it was recommended to avoid them during pregnancy, given the insufficient evidence (215 pregnancies from 3 studies) [4]. In this SLR update, we found an additional evidence from 12 studies of 145,889 pregnancy exposures to nonselective NSAIDs, most of which (58%) were of good quality. No increased risk of congenital malformation or miscarriage was reported in confounder-adjusted studies [15–18]. For selective COX-2 inhibitors, exposure in the first trimester was not associated with congenital malformations or miscarriages in 823 additional pregnancies [19]. Data on other outcomes were insufficient to draw conclusions.

Conventional synthetic disease-modifying ARDs, immunosuppresives, and other drugs

Antimalarials (hydroxychloroquine/chloroquine). The antimalarials hydroxychloroquine and chloroquine were previously considered safe for use during pregnancy according to the 2016 EULAR PtC [4], based on data from 492 pregnancy exposures. Our SLR identified 5331 new cases of antimalarial exposure (mainly hydroxychloroquine in systemic lupus erythematosus [SLE]). The majority of the studies were of good quality (80%). No congenital malformation risk was reported for ≤400.0 mg hydroxychloroquine per day, and no association with miscarriage, PTB, or SGA. One large study using claims data showed a slight increase of congenital malformation with hydroxychloroquine of ≥400.0 mg/d, without a specific pattern (aRR: 1.33; 95% CI: 1.08, 1.65) [20]. This finding was not confirmed by a subsequent prospective cohort study, neither in comparison with disease-matched nor with healthy subjects (OR: 1.08; 95% CI: 0.51, 2.29; and aOR: 0.76; 95% CI: 0.28, 2.05, respectively) [21]. Data remain insufficient for mepacrine.

Azathioprine/6-mercaptopurine (thiopurines). Based on the earlier EULAR SLR [4] with 1327 pregnancies exposures, azathioprine was considered compatible with pregnancy. In our updated SLR, thiopurine exposure was reported for 4985 pregnancies (mostly SLE and inflammatory bowel disease [IBD]) by 19 studies (quality 53% good, 11% fair, and 37% poor). No significant increased risk of congenital malformation or miscarriage was identified. An increased rate of prematurity was observed by 1 study (aRR: 4.2; 95% CI: 1.4, 12.5) [22], which was not confirmed by others [23–25].

Bosentan. One case of bosentan exposure during the first and second trimester of pregnancy was reported, resulting in a live premature birth without congenital malformation [26].

Colchicine. Based on previous consensus and evidence [4] from 460 exposed pregnancies, colchicine was considered compatible with pregnancy. This SLR included 342 pregnancies with colchicine exposure, primarily patients with familial Mediterranean fever, with 1 study of good and 2 of fair quality. No increased rates of miscarriage and congenital malformation were observed, but there was an increase in PTB, which may have been confounded by disease severity [27].

Cyclophosphamide. Owing to its teratogenic properties, the previous EULAR PtC recommended that cyclophosphamide should be discontinued before pregnancy; however, it may be considered during the second or third trimester in case of severe, refractory maternal disease [4]. This recommendation was based on data from 276 pregnancies. Seven additional studies involving 157 pregnancies (in women with SLE and vasculitis) were reviewed in this SLR update. Study quality was low, with 29% being fair and 71% being poor. High overall rates of miscarriage (23.2%) and PTB (27.9%) were observed. Comedication was reported in only 3 studies (case series/reports): all patients were exposed to high doses of GC. No congenital malformations were reported in the more recent studies; however, of the 5 studies reporting the timing of exposure during pregnancy, only 1 pregnancy was exposed during the first trimester.

Cyclosporine. In addition to the 1126 exposed pregnancies described in the previous EULAR SLR [4], we identified 37 new cases of cyclosporine exposure during gestation (mostly SLE and IBD patients) from 2 studies of poor quality. The data did not raise concerns about miscarriages and congenital malformations. Increased rates of stillbirth, PTB, and LBW were likely confounded by elevated disease activity and GC use [28,29].

Intravenous immunoglobulins. The previous EULAR SLR identified 96 exposed pregnancies and considered intravenous immunoglobulins (IVIGs) compatible with pregnancy [4]. Four additional pregnancies with IVIG exposure were included in this SLR (patients with adult-onset Still disease and vasculitis). Although limited, evidence did not raise concerns about miscarriages or congenital

malformations. The high rate of PTB cannot be interpreted due to the small sample size, the severity of the underlying disease, and comedication [30].

Leflunomide/teriflunomide. The previous EULAR 2016 consensus stated that leflunomide should be avoided in pregnancy given the limited data available [4]. A total of 1219 additional pregnancies exposed to leflunomide or teriflunomide (the active metabolite of leflunomide) were reviewed in this SLR. However, the quality of the studies was mostly poor (82%). A drug washout procedure was performed in 49% of cases where information was available (307/627 pregnancies) [31–37]. In 4 comparative studies, no increased risk of miscarriage, congenital malformations, LBW, or PTB was found, yet the drug washout rate ranged from unknown to 95% [36,38–40].

Methotrexate. The EULAR 2016 PtC concluded that methotrexate is teratogenic and should therefore be discontinued before pregnancy, based on data from 372 pregnancies [4]. Since then, 1 single retrospective cohort of poor quality investigated 223 pregnancies in patients with rheumatoid arthritis (RA) and reported an increased risk of miscarriage, congenital malformations, and stillbirth compared with controls [41].

Mycophenolate. The EULAR 2016 PtC included 333 pregnancies, leading to the conclusion that mycophenolate is teratogenic and should be withdrawn before pregnancy. In this review, we found an additional case series of 4 SLE pregnancies resulting in live births without malformations [42], providing little new evidence.

Sildenafil. Sildenafil was not included in the earlier EULAR SLR [4]. Three SLRs analysed the safety of sildenafil use for treatment of foetoplacental insufficiency, recurrent miscarriage, or maternal pulmonary hypertension, finding mild maternal side effects, no teratogenicity, and no increased rate of stillbirths or perinatal deaths [43–45]. In addition, we identified 1 case report [26] of sildenafil use for pulmonary hypertension in a patient with mixed connective tissue disease, which resulted in PTB. Of note, 1 SLR (10 studies, 1090 participants) concluded that a prolonged use of sildenafil for the treatment of severe fetal growth restriction may increase the risk of persistent pulmonary hypertension of the neonate [43].

Sulfasalazine/5-aminosalicylates. The earlier EULAR SLR considered sulfasalazine compatible with pregnancy based on 525 pregnancy exposures [4]. We identified additional 98 pregnancy exposures in patients with IBD and RA. Data quality was 67% good, 17% fair, and 17% poor. In line with the previous SLR, no adverse drug-related effects on miscarriage, congenital malformations, PTB, or SGA were described [46].

Tacrolimus. Tacrolimus was considered compatible with pregnancy in the previous consensus based on 505 exposures [4]. We found additional evidence from 2 studies of 35 pregnancies in women with SLE exposed to tacrolimus (1 good and 1 fair quality). Consistent with the earlier SLR, rates of miscarriage, and congenital malformations were not elevated. In addition, tacrolimus was not associated with PTB in 1 adjusted analysis (aOR: 0.76; 95% CI: 0.10, 4.99) [47].

Targeted synthetic disease-modifying ARDs. The previous consensus was based on a case series of 27 pregnancies exposed to tofacitinib and therefore advised avoiding tofacitinib in pregnancy due to insufficient data. We found additional evidence from 58 pregnancies exposed to tofacitinib. One cohort study of poor quality reported a 24.1% miscarriage and a 21.2% PTB rate, but no increased rate of congenital malformations [48]. Data on other outcomes were lacking.

Biologic disease-modifying ARDs

TNFi biologic disease-modifying ARDs. The previous EULAR consensus was that TNFi biologic disease-modifying ARDs (bDMARDs) are compatible during the first part of pregnancy, and etanercept and certolizumab may be used throughout pregnancy due to low transplacental passage [4]. This consensus was based on data of 2492 pregnancy exposures to TNFi bDMARDs. We found additional evidence from 63 studies of 11,194 pregnancy exposures to TNFi bDMARDs (Table 1). The underlying diagnoses were mixed (inflammatory rheumatic diseases, psoriasis, and IBD) [49–51], with more than half of the studies including only patients with IBD [24,51–53]. Study quality was diverse, with 50% rated as good and 50% rated as poor. Overall, no increased risk for any APO was apparent. A total of 28 studies including 11,282 pregnancy exposures to TNFi were eligible for meta-analyses (Supplementary Table S3). The pooled unadjusted OR showed increased risks for TNFi-exposed vs TNFi-unexposed pregnancies for the outcomes congenital malformations (1.37; 95% CI: 1.02, 1.84) and SGA (1.16; 95% CI: 1.01, 1.32) (Supplementary Figs S6A and S7A, Table 3). No significant increased risk was observed for miscarriage, stillbirth, PTB, and LBW (Supplementary Figs 8A, 9A, 10A, and 11A, Table 3). However, the meta-analysis of adjusted pooled estimates did no longer show an increased risk for TNFi-exposed vs TNFi-unexposed pregnancies for congenital malformations and SGA, and all other outcomes (Supplementary Figs 6B–11B, Table 3). Overall, the available evidence for the use of TNFi during pregnancy is reassuring.

Table 3
Meta-analysis estimates of the risk of adverse pregnancy and infant outcomes with tumour necrosis factor inhibitor use vs no use

	Unadjusted meta-analysis results					Adjusted meta-analysis results				
Outcome	No. of studies	Pooled odds ratio (95% CI)	Type of CI	I^2	τ^2	No. of studies	Pooled adjusted risk estimates (95% CI)	Type of CI	I^2	τ^2
Miscarriage	8	1.32 (0.99, 1.76)	HKSJ	0	0	1	aHR 2.22 (0.67, 7.29)	—	—	—
						1	aOR 1.30 (0.50, 3.30)			
Stillbirth	8	0.92 (0.37, 2.25)	mKH	0	0		—	—	—	—
Congenital malformation	13	1.37 (1.02, 1.84)	mKH	0	0	4	aOR 1.24 (0.71, 2.16)	mKH	0	0
Preterm birth	25	1.23 (0.98, 1.54)	HKSJ	63.49	0.13	1	aHR 0.82 (0.66, 7.20)	—	—	—
						6	aOR 1.18 (0.83, 1.68)	HKSJ	29.6	0.03
Small-for-gestational age	12	1.16 (1.01, 1.32)	mKH	6.58	0	3	aOR 1.06 (0.60, 1.87)	HKSJ	0	0
Low birth weight	12	0.89 (0.45, 1.77)	HKSJ	84.14	0.86	2	aOR 1.16 (0.67, 2.00)	Z	—	—

aHR, adjusted hazard ratio; aOR, adjusted odds ratio; HKSJ, CIs based on Hartung–Knapp–Sidik–Jonkman; mKH, CIs based on modified Knapp–Hartung; Z, CI based on fixed-effects normal-normal model.

Non-TNFi bDMARDs. The earlier EULAR PtC recommended replacing rituximab, anakinra, tocilizumab, abatacept, belimumab, and ustekinumab with other ARDs before conception, mainly due to the limited data available, although there was no evidence of an increased rate of congenital malformations [4].

For the B cell-targeted therapies using belimumab and rituximab, the previous consensus was based on 153 and 256 exposed pregnancies; we identified further 410 and 393 pregnancy exposures from 6 cohort studies with poor quality (SLE and other immune-mediated inflammatory diseases). The studies did not report higher rates for miscarriage or congenital malformation. However, 1 cohort study investigating rituximab showed an increased miscarriage rate of 21.6%, which was confounded by potentially teratogenic comedication (eg, methotrexate and mycophenoate) in more than half of the exposed pregnancies [54]. Crude rates showed an increase of PTB in pregnancies exposed to anti-B cell agents, which may have been confounded by disease severity [55]. For belimumab, rates of LBW and SGA were high, but sample size was small (Table 1).

Regarding abatacept, 152 pregnancy exposures were reported in the previous EULAR SLR [4]. We identified additional 169 pregnancies in RA with exposure to abatacept, but study quality was poor. The studies mainly investigated miscarriages and congenital malformations, and no increased miscarriage rates were reported. The 8% rate of congenital malformations is higher than the typically reported malformation rate, which was due to methodological aspects of the Organization of Teratology Information Specialists (OTIS) register with thorough analysis by dysmorphology specialists and long follow-up period, but was in line with the rates of unexposed controls [49,56]. Other APOs were only investigated in a limited number of pregnancies.

For interleukin (IL) inhibitors (ILi), most new evidence was available for ustekinumab (IL12/23i) with 571 exposed pregnancies that were added to the previously reviewed 152 cases [4]. The study quality was 14% good and 86% poor. Regarding crude rates, no increase in APOs was apparent. This finding is consistent with the results of a prospective cohort, which found no increase in APOs in 27 ustekinumab-exposed pregnancies compared with TNFi- or non-bDMARD-exposed pregnancies [57].

Previously, evidence on IL1i was limited to 40 pregnancy exposures to anakinra and no data on canakinumab [4]. In our SLR update, we found additional evidence of 39 pregnancy exposures to anakinra and 16 to canakinumab (all studies of poor quality). Data did not show higher rates of any APO.

In the previous EULAR SLR, evidence on tocilizumab (IL6i) exposure in pregnancy was based on 218 cases [4]. We identified 363 additional pregnancies exposed to tocilizumab (IL6i). All studies were of poor quality and did not show increased rates of pregnancy loss or congenital malformations. One cohort study of RA pregnancies reported increased rates for PTB and LBW [58] but did not account for disease activity, which is a risk factor for PTB and LBW. Only 1 pregnancy exposed to sarilumab was included (IL6i) in this SLR [59].

The SLR identified 119 pregnancies exposed to the IL17i secukinumab and 99 to ixekizumab, all from studies of poor quality. No increased risk of miscarriage or congenital malformation was reported. One study analysed a pharmaceutical safety database of secukinumab-exposed pregnancies, showing a miscarriage rate of 21.8%. However, the number of unknown pregnancy outcomes due to lost to follow-up and ongoing pregnancies was high [60].

For mepolizumab and eculizumab, only case reports/series were available including 3 mepolizumab-exposed and 14 eculizumab-exposed pregnancies. No events of miscarriage or congenital malformation were reported.

Effect of ARDs on adverse infant outcomes

bDMARDs

A total of 4521 TNFi-exposed pregnancies and 7665 live births with *in utero* exposure to TNFi were investigated for the different infant outcomes within the first year of life. Less information was available for non-TNFi-exposed pregnancies. An overview of the results is given in Tables 2–4.

SIIs

In our meta-analysis (Table 3), the pooled unadjusted OR of SII in TNFi-exposed pregnancies showed an increased risk of SII (OR: 1.26; 95% CI: 1.14, 1.40); however, the association was attenuated when adjusted estimates were used (Fig A, B). Restricting the meta-analysis to studies that reported exposure in the third trimester did not show an increased risk for SII associated with maternal TNFi treatment (adjusted incidence rate ratio: 1.02; 95% CI: 0.79, 1.33; aOR: 0.88: 95% CI: 0.67, 1.16) (Fig C). The evidence regarding SII after *in utero* exposure to non-TNFi bDMARDs is scarce, but overall reassuring for rituximab, belimumab, ustekinumab, anakinra, and canakinumab. Limited data are available for sarilumab, tocilizumab, and abatacept, and no data for other non-TNFi bDMARDs. For rituximab, treatment in the second part of pregnancy resulted in haematologic alterations in up to 12% of the newborns without evidence of an increased risk of SII, and B cell counts normalised within 6 months [61]. In a belimumab cohort of 13 pregnancies, no haematologic changes in the infants were reported [62].

Vaccinations

In infants with *in utero* exposure to bDMARDs, no serious adverse events were reported after the application of nonlive vaccines according to standard vaccination schedules (Table 4). Most studies on this outcome addressed infants born at term, data on premature infants are sparse or missing. An adequate serologic response after *in utero* exposure to TNFi compared with that to non-TNFi was reported even if TNFi drug levels were detectable in the newborn at birth [53,63,64].

In our SLR, we found evidence for the safety of live rotavirus vaccination in 72 infants with *in utero* exposure to TNFi. In addition, no adverse events were observed after rotavirus vaccination in 1295 infants with *in utero* exposure to any bDMARD (60%-70% TNFi), with 28% to 93% exposed during the third trimester (1 SLR article and 1 study published after our search date) [65–68]. For the vaccination with Bacillus Calmette–Guérin (BCG), 1 case report described a fatal outcome of an infant who was exposed to infliximab *in utero* and vaccinated with BCG at 3 months of age [69]. No other serious adverse events related to BCG vaccination occurred in 192 infants with exposure to TNFi (>50% infliximab) (Table 4), with more than half exposed in the third trimester [68]. For non-TNFi bDMARDs, case reports described no serious adverse events after BCG vaccination, with most vaccines administrated in children older than 6 months of age [70].

Effect of NSAID use on adverse fetal health outcomes

This update of the 2016 SLR encompassed a new PIO question about fetal health issues related to NSAID use during pregnancy. Two recent studies (1 good and 1 poor quality) evaluated 127,203 pregnancies exposed to NSAIDs (657 to COX-2

Table 4

Data on adverse infant outcomes following *in utero* exposure to bDMARDs: summary of results stratified by drug

Drug	No. of studies per study type [Ref][a]	Total exposed pregnancies (n) (per time points); total live births (n)[b]	Serious infant infections with hospitalisation during first year of life (per total pregnancies)	Serious adverse events after nonlive vaccination within first year of life (per total infants vaccinated)	Serious adverse events after live vaccination within first year of life (per total infants vaccinated)	Comment[c]	Evidence: LoE[d] and study quality[e]
bDMARDs							
TNFi bDMARD							
TNFi total[f]	22 CS [s53,s57,s58, s61,s93,s94,s100, s101,s103,s106,s108 −s110,s112−s115, s119,s127,s130 −s132] 2 CSS [s133,s134] 2 CR [s136,s137] 3 CSE [s139,s141, s142]	4521 Preg (PRE ≥461; T1 ≥2638; T2 ≥1183; T3 ≥1549) 7665 LB	SII: 813/8506	SAE: 0/144	RV: 0/72 BCG: 1/193	No increased risk of SII compared with controls. No increased risk of SII in the subanalysis with T3 exposure. Adequate serologic response for nonlive vaccines according to normal immunisation schedule is demonstrated in infants after *in utero* exposure to TNFi. No increased risk for SAEs in infants in the first year of life after vaccination with nonlive vaccines and with live RV vaccines. Regarding BCG vaccination during the first year of life in infants after *in utero* exposure to TNFi, there was 1 case (*in utero* infliximab exposure) of fatal disseminated BCGitis after BCG vaccinated at 3 mo of age, but no other report of SAEs in the majority of cases (n = 192). For TNFi with transplacental transfer, there was no evidence of an increased risk of SAEs in infants with *in utero* exposure and vaccination with BCG after the age of 6 mo.	**2b** 13 good 2 fair 14 poor
Adalimumab	1 CS [s94]	257 Preg (PRE NA; T1 ≥55; T2 ≥27; T3 ≥3) 221 LB	SII: 10/229	SAE: NA	RV: NA BCG: NA	No increased risk for SII.	**2b** 1 good
Certolizumab	1 CSE [s139]	14 Preg (PRE ≥10; T1 ≥10; T2 ≥14; T3 ≥14) 15 LB	SII: 0/15	SAE: 0/15	RV: 0/1 BCG: NA	Limited evidence showed no increased risk for SII or SAEs to nonlive vaccines. Regarding live vaccines 1 case with RV vaccination showed no SAE.	**4** 1 poor
Infliximab	1 CS [s93] 2 CR [s136,s137] 2 CSE [s141,s142]	1860 Preg (PRE ≥91; T1 ≥1216; T2 ≥10; T3 ≥515) 1559 LB	SII: 16/1558	SAE: 0/4	RV: NA BCG: 1/3	No increased risk for SII. No increased risk for SAEs to nonlive vaccines. Regarding live vaccines, 1 fatal event after BCG vaccination at 3 mo of age.	**4** 5 poor
Etanercept and golimumab: No studies available						Several studies with mixed TNFi containing etanercept and golimumab with no evidence of increased risk for any adverse infant outcome.	**4**
Mixed TNFi[g]	20 CS [s53,s57,s58, s61,s100,s101,s103, s106,s108−s110, s112−s115,s119, s127,s130−s132] 2 CSS [s133,s134]	2390 Preg (PRE ≥360; T1 ≥1357; T2 ≥1132; T3 ≥1017) 5870 LB	SII: 787/6704	SAE: 0/125	RV: 0/71 BCG: 0/190	No increased risk of SII compared with controls. No increased risk of SII in the subanalysis with T3 exposure. Regarding nonlive and live vaccines with RV and BCG, no SAEs after vaccination reported. Adequate serologic response for nonlive vaccines according to normal immunisation schedule is shown.	**2b** 12 good 2 fair 8 poor

(*continued on next page*)

Table 4 (*Continued*)

Drug	No. of studies per study type [Ref][a]	Total exposed pregnancies (n) (per time points); total live births (n)[b]	Serious infant infections with hospitalisation during first year of life (per total pregnancies)	Serious adverse events after nonlive vaccination within first year of life (per total infants vaccinated)	Serious adverse events after live vaccination within first year of life (per total infants vaccinated)	Comment[c]	Evidence: LoE[d] and study quality[e]
Non-TNFi bDMARD							
B cell–targeted therapy							
Belimumab	1 CS (abstract) [s152] 1 CR [s148]	14 Preg (exposure NA) 14 LB	SII: 1/14	SAE: 0/1	RV: 0/1 BCG: NA	The limited evidence did not show increased risk of SII. Most pregnancies were exposed during T3. No studies with control group available. One case report without any adverse event to vaccination with RV and with adequate serologic vaccination response. Very limited evidence showed possible B cell depletion in neonates exposed to belimumab *in utero* (exposure time late T2). No SII in 1 infant with B cell depletion occurred.	**4** 2 poor
Rituximab	3 CS [s54,s154,s156] 4 CR [s158,s162–s164] 2 CSE [s165,s166]	280 Preg (PRE ≥111 T1 ≥9; T2 ≥21; T3 ≥10) 187 LB	SII: 4/194	SAE: 0/2	RV: NA BCG: NA	Three cohort studies showed that most *in utero* exposed infants did not develop SII. Regarding the exposure time, more than half of the pregnancies were exposed to rituximab before conception. No studies with control group available. Very limited evidence did not show a SAE to nonlive vaccines. One cohort study without controls reports haematologic alterations in 12% of the neonates. Most haematologic changes occurred with treatment in the second half of pregnancy. The haematologic changes normalised within weeks to 4 mo. No increased evidence of SII in neonates with B cell depletion or other haematologic changes.	**4** 9 poor
T cell costimulation inhibitor							
Abatacept	1 CR [s188]	1 Preg (exposure NA) 1 LB	SII: 0/1	SAE: 0/1	RV: 0/1 BCG: 0/1	One case report with *in utero* exposure in T1 without SII. Very limited evidence without any adverse events to nonlive or live vaccines (RV and BCG after the age of 6 mo).	**4** 1 poor
Interleukin inhibitors							
Anakinra	1 CS [s174] 1 CR [s177]	24 Preg (exposure NA) 23 LB	SII: 0/23	SAE: 0/1	RV: NA BCG: NA	Limited evidence did not show increased rates for SII. One case report without any adverse events to nonlive vaccines.	**4** 2 poor
Canakinumab	1 CS [s174] 1 CSE (abstract) [s210]	11 Preg (exposure NA) 9 LB	SII: 0/9	SAE: 0/1	RV: NA BCG: NA	Very limited evidence without increased rates for SII. Very limited evidence showing no adverse events to nonlive vaccines and reporting adequate serologic vaccination response.	**4** 2 poor
Sarilumab	1 CR [s182]	1 Preg (exposure NA) 1 LB	SII: NA	SAE: NA	RV: NA BCG: 0/1	Very limited evidence showing no adverse events to live vaccines including BCG (time of administration of BCG after the age of 6 mo).	**4** 1 poor

(*continued on next page*)

Table 4 (*Continued*)

Drug	No. of studies per study type [Ref][a]	Total exposed pregnancies (n) (per time points); total live births (n)[b]	Serious infant infections with hospitalisation during first year of life (per total pregnancies)	Serious adverse events after nonlive vaccination within first year of life (per total infants vaccinated)	Serious adverse events after live vaccination within first year of life (per total infants vaccinated)	Comment[c]	Evidence: LoE[d] and study quality[e]
Tocilizumab	2 CR [s186,s187] 1 CSE [s190]	4 Preg (exposure NA) 4 LB	SII: 0/4	SAE: 0/4	RV: 0/1 BCG: 0/2	Very limited evidence without increased rates for SII. Very limited evidence without any adverse events to nonlive vaccines. One small case series without any adverse events to live vaccines (time of administration of BCG not documented).	**4** 3 poor
Ustekinumab	3 CS [s106,s195,s197] 2 CR [s141,s198]	50 Preg (PRE 1; T1 ≥46; T2 ≥46; T3≥40) 45 LB	SII: 3/45	SAE: 0/1	RV: NA BCG: 0/1	One cohort study with control group did not show an increased risk of SII. Very limited evidence without any adverse events to nonlive vaccines. Very limited evidence without any adverse events to BCG vaccination after the age of 6 mo.	**2b** 1 good 4 poor
Others							
Anifrolumab, eculizumab, guselkumab, risankizumab, secukinumab, ixekizumab, and mepolizumab: No studies available						Due to the molecular structure analogous to most other biologics, a similar risk profile is expected.	**5**

BCG, Bacillus Calmette–Guérin; bDMARD, biologic disease-modifying antirheumatic drug; CCS, case-control study; C5i, complement protein C5 inhibitor; CR, case report; CS, cohort study; CSE, case series; CSS, cross-sectional study; IFNAR1, interferon α/β receptor subunit 1 inhibitor; ILi, interleukin inhibitor; LoE, level of evidence; NA, not available; PRE, exposure prepregnancy; RV, rotavirus; SAE, serious adverse event; SII, serious infant infection; SLR, systematic literature review; T1, exposure in first trimester; T2, exposure in second trimester; T3, exposure in third trimester; TNFi, tumour necrosis factor inhibitor.

[a] The complete list of references is available in the Supplementary Material.

[b] The number of pregnancies and live births may vary due to different data reporting in the different studies. The same applies to the number of reported outcomes, where the number of pregnancies or live births may differ compared with the reported denominator. The same applies to the number of exposed pregnancies during the various exposure periods, which may differ from the total number of reported pregnancies. As the exposure period was not recorded in all studies, the number of pregnancies that were exposed during at least this period is used.

[c] Summary including evidence of the present SLR of all adverse infant outcomes. Where available, only high-quality studies were considered.

[d] Level of evidence according to studies retrieved in the SLR of EULAR points to consider 2016 and the 2024 SLR Update as well as additional studies (including additional SLRs and MA).

[e] Study quality rated as good, fair, and poor based on the Newcastle–Ottawa Scale; CR and CSE were rated as poor.

[f] All studies with different TNFi and studies not differentiating between the different TNFi.

[g] Studies not differentiating between the different TNFi (if different bDMARD including >80%TNFi).

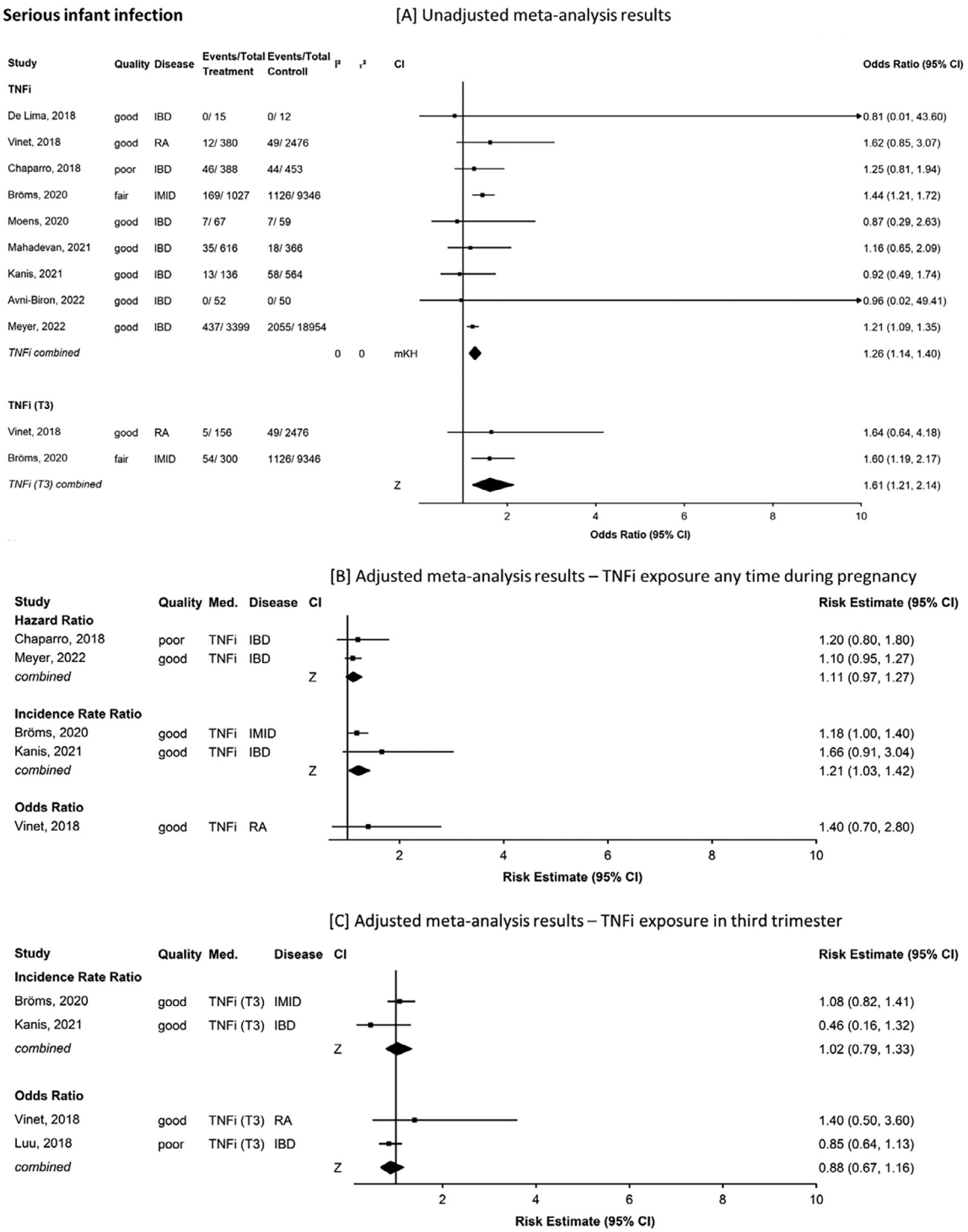

Figure. Serious infant infection risk associated with TNFi use during pregnancy investigated (A) unadjusted meta-analysis, (B) adjusted meta-analysis using TNFi exposure any time during pregnancy and (C) adjusted meta-analysis using TNFi exposure during third trimester. A fixed-effects normal-normal model with CIs based on normal approximation was used. Since no heterogeneity was estimated and the normal approximation was used, the results must be treated with caution. Combined effects of at least 3 studies: A random-effects normal-normal model, Paule Mandel estimates for τ, and Hartung–Knapp–Sidik–Jonkman (HKSJ) CIs were used. It was evaluated if the interval resulting from the HKSJ interval was shorter than an interval based on the DerSimonian–Laird method. If so, the variance correction method was used. If the resulting lower and/or upper bound from the CI of an estimate was smaller or larger, respectively, than the union of the combined study estimates, the resulting estimate was deemed uninformative and therefore removed. IBD, inflammatory bowel disease; IMID, immune-mediated inflammatory disease; mKH, modified Knapp–Hartung; RA, rheumatoid arthritis; TNFi, tumour necrosis factor inhibitors; Z, CI based on fixed-effects normal-normal model.

inhibitors) but did not specify population or NSAID dosage (Table 5). One study reported comedication, noting corticosteroid use in 57.9% of cases [71].

Analysis of national health insurance data from South Korea revealed a 9% increased risk of oligohydramnios in women exposed to NSAIDs compared with unexposed women during the first 19 weeks of gestation (relative risk: 1.09; 95% CI: 1.01, 1.19) [71]. Further stratification into nonselective NSAIDs and selective COX-2 inhibitors showed aRRs of 1.08 (95% CI: 1.00, 1.18) and of 2.98 (95% CI: 1.70, 5.22), respectively. Despite a low overall rate, treatment duration had a significant impact, with evident risk after >10 days of exposure (aRR: 1.19; 95% CI: 1.00, 1.42). Data of the German teratology information service showed an increase in oligohydramnios risk with NSAID use in

Table 5
Effect of NSAID use on adverse fetal health outcomes: summary of results

Author, year [Ref][a]	Study type	No. of pregnancies	NSAID type	Outcomes and results	Conclusions	Study quality[b]
Choi et al, 2023 [s25]	CS	n = 124,957	Both nonselective and COX-2 selective NSAIDs	Oligohydramnios 884/124,957 (0.7%), in comparison with unexposed women (aOR: 1.09; 95% CI: 1.01, 1.19)	Higher risk of oligohydramnios in women exposed to NSAIDs during pregnancy, especially with longer exposure times (>10 d). Increased risk with coxibs in comparison with nonselective NSAIDs.	Poor
Dathe et al, 2022 [s26]	CS	n = 1154 (T1 exposure) n = 1092 (T2/T3 exposure)	Both nonselective and COX-2 selective NSAIDs	Oligohydramnios T1: 29/1154 (2.5%) T2/T3: 41/1092 (3.8%) Limited to T2 exposure: 8/904 (0.9%) PDA T1: 10/1133 (0.9%) T2/T3: 15/1098 (1.4%) CDA T1: 0/1154 (0%) T2/T3: 5/1092 (0.5%) Risk estimates comparing T1 with T2/T3 exposure: no difference except for oligohydramnios in T2—RR: 5.1 (95% CI: 1.1, 24.0)	NSAIDs use in the second trimester limited to a few days is not associated with fetal health issues. Prolonged use in the advanced second trimester is associated with oligohydramnios.	Good

aOR, adjusted odds ratio; CDA, constriction of ductus arteriosus; CS, cohort study, COX, cyclooxygenase; NSAID, nonsteroidal anti-inflammatory drug; PDA, patent ductus arteriosus; RR, relative risk; T1, exposure in first trimester; T2, exposure in second trimester; T3, exposure in third trimester.
[a] The complete list of references is available in the Supplementary Material.
[b] Study quality rated as good, fair, and poor based on the Newcastle–Ottawa Scale.

the advanced second trimester (0.9% in exposed vs 0.2% in controls), but short-term use (few days) in the second trimester did not appear to increase the risk [72]. In this database, constriction of ductus arteriosus occurred in 0.5% of NSAIDs exposed women and patent ductus arteriosus in 1.4%. For the latter outcome, frequency was higher in PTB infants (6.8%).

Effect of NSAID use on maternal fertility

The PIO question regarding the impact of NSAIDs on fertility was added to this SLR. Five prospective cohort studies (3 in RMD, 2 in pain, and 1 in mixed RMD and pain; study quality 60% good, 40% poor) addressed a variety of outcomes including luteinised unruptured follicle syndrome, subfertility (absence of ongoing pregnancy or time-to-pregnancy >12 months), adjusted fecundability ratio, and ovarian reserve markers (antral follicle count, ovarian volume, and circulating hormone levels) (Table 6).

Luteinised unruptured follicle syndrome was more frequent in NSAID-exposed women. An independent subfertility risk with NSAID exposure was demonstrated for women with RA (adjusted hazard ratio for pregnancy: 0.66; 95% CI: 0.46, 0.94), after adjustment for disease activity and comedication [73]. One study showed a reduced adjusted fecundability ratio for naproxen with a dose-response effect [74]. No differences were revealed for ovarian reserve markers in juvenile idiopathic arthritis women versus controls [75]. In summary, the evidence indicated a negative impact of NSAIDs, especially naproxen, ibuprofen, and etoricoxib, on fertility, primarily affecting ovulation, not ovarian reserve.

ARDs in breastfeeding women

This SLR identified 42 articles, most of which addressed pharmacokinetic aspects with drug levels in breast milk in small number of cases and follow-up of exposed infants. The cumulative evidence on ARDs in breastfeeding women summarises previous EULAR SLR data and new data, (Table 7) [4].

bDMARDs

Based upon the previous EULAR consensus, TNFi are considered compatible with breastfeeding, whereas non-TNFi bDMARDs with no data should be avoided if other therapy is available [4]. Most new data were available on bDMARDs, 245 cases with exposure to TNFi bDMARDs [4,57,63,76–82], and 69 cases with exposure to non-TNFi bDMARDs [59,83–98]. All reports showed that bDMARDs are undetectable or appear in minimal amounts (<0.5 μg/mL) in breast milk [76,78,81–83,86–89,91–98]. Limited data on bDMARDs (tocilizumab) in colostrum, the low volume of protein-rich milk produced during the first 5 days postpartum, revealed marginally higher levels compared with mature milk [92–94,99]. In infants of mothers starting treatment during lactation, bDMARDs (rituximab) were undetectable in the serum [87,89]. During follow-up of breastfed infants of mothers on various bDMARDs, no serious infections, serious adverse effects to vaccinations, or cytopenias were reported [57,59,63,76–80,83,85–91,93–98].

Traditional lactation-compatible conventional synthetic disease-modifying ARDs and anti-inflammatory drugs

The previously EULAR PtC lists lactation-compatible conventional synthetic disease-modifying ARDs (csDMARDs) [4], for which we found new data on hydroxychloroquine, tacrolimus, and mesalamine (active metabolite of sulfasalazine) revealing very low levels in human milk; 102 breastfed infants of mother on thiopurines showed no increased rate of infection in the first 12 months of life [76,100,101]. No new data have emerged on NSAIDs, IVIG, and colchicine [4].

Table 6
Effect of NSAID exposure on fertility: summary of results

Author, year [Ref][a]	Study type	Population; No. of patients	NSAID type	Outcomes	Results	Conclusions	Study quality[b]
Tomioka et al, 2018 [s211]	CS	JIA n = 8 (n = 26 controls)	NA	LUF syndrome Antral follicule count Ovarian volume Hormones levels	LUF syndrome: 25% vs 0% in JIA and healthy controls Antral follicule count, ovarian volume, and hormones levels similar to controls	More LUF syndrome in patients with JIA on NSAIDs compared with controls (patients with JIA but without NSAIDs and HC), cofounded by disease activity. Ovarian reserve unaffected.	Good
Micu et al, 2011 [s212]	CS	RA and r-axSpA n = 14 (59 cycles) Low back pain n = 29 (29 cycles) (n = 446 controls)	Both nonselective NSAIDs and selective COX-2 inhibitors	LUF syndrome	LUF syndrome: 35.6% in patients with RMD (etoricoxib: 75% vs. diclofenac: 15%) 24.1% in patients with low back pain (etoricoxib: 56% vs. diclofenac: 14.3%) 3.4% in controls No LUF syndrome on ketoprofen, ibuprofen, celecoxib, and nimesulide	Higher frequency of LUF syndrome in patients on NSAIDs compared with unexposed women. LUF only occurred in cases with etoricoxib and diclofenac exposure.	Good
Brouwer et al, 2015 [s213]	CS	RA n = 60 (n = 185 unexposed)	Both nonselective NSAIDs and selective COX-2 inhibitors	Subfertility (no pregnancy or TTP >12 mo)	Subfertility: 58.3% and 37.2% in patients with RA on NSAIDs vs unexposed patients aHR for occurrence of pregnancy 0.66; 95% CI: 0.46, 0.94	Higher risk of subfertility in patients with RA on NSAIDs compared with unexposed patients	Good
McInerney et al, 2017 [s214]	CS	Pain n = 523 acetaminophen n = 884 ibuprofen n = 156 naproxen	Acetaminophen, aspirin, ibuprofen, and naproxen	aFR	Acetaminophen aFR: 1.04; 95% CI: 0.92, 1.18 Ibuprofen aFR: 1.00; 95% CI: 0.89, 1.11 Naproxen aFR: 0.78; 95% CI: 0.64, 0.97	Reduced fecundability with naproxen, with a dose-dependent effect	Poor
Jukic et al, 2020 [s215]	CS	Pain n = 150 acetaminophen n = 33 ibuprofen and naproxen	Acetaminophen, aspirin, ibuprofen, and naproxen	aFR	Acetaminophen aFR: 1.02; 95% CI: 0.73, 1.44 Ibuprofen and naproxen aFR: 1.00; 95% CI: 0.73, 1.46	No impact of acetaminophen, ibuprofen, and naproxen on fecundability.	Poor

aFR, adjusted fecundability ratio; aHR, adjusted hazard ratio; COX, cyclooxygenase; CS, cohort study; HC, healthy control; JIA, juvenile idiopathic arthritis; LUF syndrome, luteinised unruptured follicle syndrome; NA, not available; NSAID, nonsteroidal anti-inflammatory drugs; RA, rheumatoid arthritis; r-axSpA, radiographic axial spondyloarthritis; RMD, rheumatic and musculoskeletal disease; TTP, time-to-pregnancy.
[a] The complete list of references is available in the Supplementary Material.
[b] Study quality rated as good, fair, and poor based on the Newcastle–Ottawa Scale.

Glucocorticoids

In the previous EULAR consensus, GCs were considered compatible with breastfeeding [4]. We added data on both oral prednisone/prednisolone (4.0-15.0 mg/d) and intravenous methylprednisolone pulses (1000 mg) that appeared at very low concentrations in breast milk [102–106]. The maximum methylprednisolone levels occurred 1 to 2 hours after the application [103,104].

Drugs with limited data in lactation

We added new data on ARD in lactation. Case reports showed very low levels of sildenafil and bosentan in breast milk, and no harmful effects in breastfed infants [107,108]. The 2016 EULAR SLR and LactMed indicated that methotrexate is unlikely to be excreted into breast milk due to its lipid insoluble form at physiologic pH [4]. In 6 cases, methotrexate appeared at undetectable or very low levels in breast milk after both, high dose (given for malignancy) and low dose (≤25.0 mg weekly), and no evidence of harm during 9 months follow-up [109]. Very few cases have emerged on the use of the Janus kinase inhibitor (JAKi) tofacitinib in lactating women, showing low maximum drug concentration in breast milk samples (<0.1 μg/mL) and no severe adverse events in exposed infants [110–112]. Regarding mycophenolate, data on breast milk were insufficient, and values of the estimated relative infant dose showed unacceptable variations [113,114]. As for cyclophosphamide, no new data have emerged [4,109].

Reproductive safety of ARDs in male patients

Two recent SLRs on this topic [115,116] were appraised, and an updated search from 2019 to 2023 identified 16 new articles (Table 8). Most of the new data came from 4 studies that evaluated the effect of methotrexate on male fertility. The study quality ranged from fair to good, with most new studies graded as good quality.

General findings

Treatment with various ARD, including azathioprine, mercaptopurine, colchicine, cyclosporine, hydroxychloroquine, chloroquine, filgotinib, IVIG, leflunomide, methotrexate ≤25.0 mg/wk, mycophenolate, NSAIDs, prednisone, prednisolone, sildenafil, sulfasalazine, tacrolimus, TNFi bDMARDs, and non-TNFi bDMARDs did not show a clinically relevant impact on fertility (semen parameters) or pregnancy outcomes.

Table 7
Lactation data on antirheumatic drugs: summary of results stratified by drug

Drug	No. of exposed cases	No. of studies per study type [Ref][a]	Drug detected in breast milk	Dose	Drug detected in infant blood	Reported side effects in breastfed children	Evidence: LoE[b] and study quality[c]
Glucocorticoids							
Prednisone/prednisolone MP pulse	56 P 26 MP 30	SLR [s216] 3 CS [s217−s219] 2 CR [s220,s221]	Detected at low levels MP pulse: Cavg: 0.032-1.382 μg/mL levels drop exponentially	Prednisone/prednisolone (4.0-15.0 mg) RID: 0.35-0.58/0.09-0.18 Milk:plasma ratio$_{AUC\ 24h}$: 0.5-0.6/0.02-0.03 MP pulse (1000 mg) RID 0.1-0.71 Milk:serum ratio$_{AUC\ 24h}$: 0.27	No data	No adverse events	**2a** 3 good 2 poor
NSAIDs							
Nonselective: e.g. ibuprofen Selective: e.g. celecoxib	53	SLR [s216]	Detected at very low levels, most reassuring data for short-half life agents, eg, ibuprofen	RID: <0.1-1.2	Not detected (celecoxib)	3-12 mo FU: no adverse events.	**2a** ibuprofen **4** celecoxib **5** etoricoxib poor
csDMARDs, immunosuppressive, and other drugs							
Antimalarials: HCQ and CQ	112 HCQ: 51 CQ: 61	SLR [s216] 1 CS [s222]	Detected at low levels Cavg: 0.4-1.4 μg/mL (HCQ)	RID: 1.9-3.2 (HCQ) RID: 0.6-14 (CQ)	No data	No adverse events	**2a** HCQ **4** CQ poor
Azathioprine and active metabolite (6-mercaptopurine)	241	SLR [s216] 1 CS [s223]	Not detected (n = 14) detected (n = 11)	RID: <1 Dose: <0.1% of paediatric transplant dose	Not detected (n = 16); detected at low level (n = 1)	No adverse events (n = 225), 12 mo FU: no increased infection rate with thiopurines + TNFi vs controls (n = 67); neutropenia (n = 1, possibly due to reduced TPMT activity).	2a good
Bosentan	2	2 CR [s224]	Detected at very low concentrations Cavg 0.05 μg/ml	RID 0.24-0.33	No data	No adverse events (n = 2).	**4** poor
Colchicine	154	SLR [s216]	Detected (n = 6)	RID <10	Not detected (n = 1)	No adverse events (n = 149).	**2a** poor
Cyclophosphamide	3	SLR [s216]	Detected (n = 1)	No data	No data	Neutropenia and bone marrow suppression (n = 2).	**4** poor
Cyclosporine	76	SLR [s216]	Variable titres depending on fat content in sampled milk	RID: <2 Dose: <2% of paediatric transplant dose	Not detected (n = 12); detected (n = 2)	No adverse events	**2a** poor
IVIG	149	SLR [s216]	Expected to be poorly transferred into breast milk	No data	No data	No adverse events (n = 146) Transient rash (n = 1)	**2a** poor
Leflunomide	No studies available	SLR [s216]					**5**
Methotrexate	3	SLR [s216]	Very low transfer into breast milk due to lipid insoluble nature, MTX 25.0 mg/wk: below quantifiable limits	RID about 1	No data	9 mo FU: no adverse events [s216] (n = 1)	**4** MTX ≤25 mg/wk poor
Mycophenolic acid products	10	SLR [s216] 1 CSE [s225] 1 CR [s226]	Detectable at variable levels: MPA (n = 2): undetectable to Cmax of 0.08 μg/mL MMF (n = 1): Cmax of 0.13 μg/mL	Very heterogeneous data: RID: 0-83 (MPA), 0.02 (MMF)	No data	No adverse events (n = 7)	**5** poor

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Table 7 (*Continued*)

Drug	No. of exposed cases	No. of studies per study type [Ref][a]	Drug detected in breast milk	Dose	Drug detected in infant blood	Reported side effects in breastfed children	Evidence: LoE[b] and study quality[c]
Sildenafil	2	2 CR [s224,s227]	Detected at low concentrations (20.0 mg, 3×/d)—Cavg: 0.003 μg/mL; Cmax: 0.006 μg/mL)	RID 0.06-0.08	No data	No adverse events (n = 2)	**4** poor
Sulfasalazine and active metabolite mesalamine	39	SLR [s216] 1 CS [s228]	Low levels (mesalamine) Cavg: 0.11 μg/mL Cmax: 1.7 μg/mL	RID: 0.003-0.09	Sulfasalazine not detected (n = 5), detected (n = 2), sulfapyridine ≤10% of maternal level (n = 6)	No adverse events in majority of exposed infants. Bloody diarrhoea (n = 1)	**2a** poor
Tacrolimus	167	SLR [s216] 1 CS [s229]	Variable titres depending on fat content in sampled milk, in n = 13 Cavg: 0.0004 μg/ml Cmax 0.0012 μg/mL	RID: 0.18 (0.12-0.35) Milk:plasma ratio: 0.12 (0.08-0.24) Dose <0.1% of paediatric transplant dose	Not detected (n = 28), detected level declining with time (n = 4)	No adverse events (n = 136)	**2a** poor
Avocapan, iloprost, and voclosporin: No studies available							**5**
tsDMARDs							
Tofacitinib	4	1 CSE [s230] 2 CR [s231,s232]	Detected in all samples Cavg: 0.01 μg/mL (5.0 mg twice daily), 0.01 μg/mL (10.0 mg twice daily) Cmax: 0.03 μg/mL (5.0 mg twice daily), 0.04 μg/mL (10.0 mg twice daily)	Maximal RID: 3.4 (based on peak milk levels, probably lower average) Milk:plasma ratio: 1.07 (0.47-1.68)	No data	No adverse events, eg, serious infections or SAE to mandatory nonlive vaccination and rotavirus live vaccination, at 3 mo FU: normal complete blood count with only mild thrombocytosis, normal immunoglobulin levels	**4** poor
Apremilast, baricitinib, filgotinib, and upadacitinib: No studies available							**5**
TNFi bDMARDs							
adalimumab **certolizumab** **golimumab** **infliximab**	245 IFX: >71 ADA: >31 GOL: 1 CZP: >41	SLR [s216] 6 CS [s106,s112,s114, s115,s223,s233] 2 CR [s137,s138] 1 CSE [s140]	Detected at minimal levels: IFX—Cmax: 0.15-0.74 μg/mL ADA—Cmax: 0.45-0.71 μg/mL CZP—Cmax: 0.08-0.29 μg/mL	RID (CZP): 0.04-0.30 Milk:plasma ratio: 0.001-0.05	Not detected, serum concentration after *in utero* exposure decreased despite drug exposure during breastfeeding	No adverse events, eg, similar risks of infection and rates of milestone achievements in exposed (TNFi or TNFi + immunomodulators) vs controls	**2a** **5** good **4** poor
Non-TNFi bDMARDs							
Abatacept	1	1 CR [s234]	Detected at minimal levels—Cmax: 0.256 μg/mL	RID: 1.30 Milk:serum ratio: 0.005	No data	12 mo FU: no adverse events, eg, serious infections or SAE to vaccines including rotavirus and BCG at 6 mo of age	**4** poor
Anakinra	12	1 CS [s174] 1 CR [s177]	No data	No data	No data	9 mo FU: no adverse events, eg, serious infections or SAE to vaccines	**2a** poor
Belimumab	1	1 CR [s235]	Detected at minimal levels—Cmax: 0.17 μg/mL	RID: 3.67 Milk:serum ratio: 0.0041	No data	15 mo FU: no adverse events	**4** poor
Canakinumab	5	1 CS [s174] 1 CR [s236]	Detected at minimal levels—Cmax: 0.023 μg/mL	RID: 0.08 Milk:serum ratio: 0.015	Not detected (n = 1)	2 y FU: no adverse events	**2a** poor
Rituximab and ocrelizumab	23 RTX: 21 OCR: 2	3 CS [s237–s239] 2 CR [s165,s236]	Detected at minimal levels—Cmax: 0.004-0.6 μg/mL	RID: 0.01-0.10 Milk:serum ratio: 0.0001-0.005	Not detected (n = 7)	Normal B cell count and immunoglobulin levels (n = 6), no adverse events (n = 3)	**2a** 1 fair 4 poor

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Table 7 (*Continued*)

Drug	No. of exposed cases	No. of studies per study type [Ref][a]	Drug detected in breast milk	Dose	Drug detected in infant blood	Reported side effects in breastfed children	Evidence: LoE[b] and study quality[c]
Tocilizumab and sarilumab	6 TCZ: 5 SAR: 1	4 CR [s182,s186,s187, s240] 1 CSE [s190]	Detected at minimal levels—Cmax: 0.22-0.39 μg/mL (colostrum), 0.148 μg/mL (mature milk)	RID: 1.30 Milk:serum ratio: 0.01-0.11 (colostrum), 0.001-0.01 (mature milk)	Not detected (n = 1)	6-9 mo FU: no adverse events, eg, serious infections or SAE to vaccines: nonlive vaccines (n = 4) and live vaccine BCG (n = 1)	**4** poor
Ustekinumab	21	3 CS [s106,s195,s223] 2 CR [s198,s201]	Detected at minimal levels—Cmax: 0.014-3.2 μg/mL	Milk:serum ratio: 0.001-0.005	Infant serum concentration after *in utero* exposure decreased despite drug exposure during breastfeeding	12 mo FU: no adverse events	**2a** 4 good 1 poor
Anifrolumab, eculizumab, guselkumab, mepolizumab, secukinumab, and ixekizumab: No studies available							**5**

ADA, adalimumab; BCG, Bacillus Calmette–Guérin; bDMARD, biologic disease-modifying antirheumatic drug; Cavg, average concentration; C5i, complement protein C5 inhibitor; Cmax, maximum concentration; CQ, chloroquine; CR, case report; CS, cohort study; csDMARD, conventional synthetic disease-modifying antirheumatic drug; CSE, case series; CZP, certolizumab; FU, follow-up time; GOL, golimumab; HCQ, hydroxychloroquine; IFNAR1, interferon α/β receptor subunit 1 inhibitor; IFX, infliximab; ILi, interleukin inhibitor; IVIG, intravenous immunoglobulin; LoE, level of evidence; MMF, mycophenolate mofetil; MP, methylprednisolone pulse; MPA, mycophenolic acid; MTX, methotrexate; NSAID, nonsteroidal anti-inflammatory drugs; OCR, ocrelizumab; P, prednisone/prednisolone; RID, relative infant dose (given as %); RTX, rituximab; SAE, serious adverse event; SAR, sarilumab; SLR, systematic literature review; SSZ, sulfasalazine; TCZ, tocilizumab; TNFi, tumour necrosis factor inhibitor; TPMT, thiopurine methyltransferase.

[a] The complete list of references is available in the Supplementary Material.

[b] Level of evidence based on EULAR SLR 2016 [4], 2024 SLR Update and LactMed.

[c] Study quality rated as good, fair, and poor based on the Newcastle–Ottawa Scale; CR and CSE were categorised as poor.

Methotrexate

New evidence supports the safety of weekly methotrexate doses (≤25.0 mg/wk) on semen parameters, sperm DNA fragmentation index, and reproductive hormones [117,118]. A large retrospective cohort study involving over 171 paternal methotrexate-exposed pregnancies found no increased risk of major congenital malformations, LBW, or PTB (relative risk: 0.67; 95% CI: 0.21, 1.55) [117].

TNFi bDMARDs

Evidence from studies involving more than 1500 cases indicates that TNFi do not impair semen parameters or lead to adverse birth outcomes. Notably, some studies reported an improvement in semen parameters following TNFi exposure [115,116]. The risk for adverse birth outcomes with TNFi was not elevated (relative risk: 1.14; 95% CI: 0.81, 1.57) [117].

Non-TNFi bDMARDs

Based on very limited data, no negative effects on fertility and pregnancy outcomes were reported for non-TNFi bDMARDs such as abatacept, canakinumab, ixekizumab, ustekinumab, tocilizumab, and anakinra [116,118].

Targeted synthetic disease-modifying ARDs

A recent randomised controlled trial involving 249 patients demonstrated no measurable impact on semen parameters or sex hormones after at least 13 weeks of filgotinib (200.0 mg/d) [119]. Data on pregnancy and offspring outcomes was reported on only 3 pregnancies resulting in 3 healthy offsprings. Limited to no information is available for the other JAKi.

Other medications

Thiopurines (azathioprine and 6-mercaptopurine) and calcineurin inhibitors (cyclosporine and tacrolimus) showed no adverse effects on semen parameters or APO [115]. Limited evidence suggests that antimalarials (hydroxychloroquine and chloroquine) and mycophenolate have no negative effect on sperm quality [115,116]. Studies on teriflunomide (active metabolite of leflunomide), including 63 cases, reported no APO.

Colchicine does not negatively impact semen parameters at therapeutic doses and was not associated with an increased risk of spontaneous abortions [115]. Sildenafil improves sperm motility and morphology and is safe for use in men planning to conceive [120].

Sulfasalazine has been associated with reversible asthenozoospermia and decreased sperm counts [115,116]. Regarding pregnancy outcomes, data on sulfasalazine are reassuring [116].

Exposure to cyclophosphamide has been linked to reduced sperm counts and a dose-related risk for irreversible infertility, particularly at doses ≥4000.0 mg/m^2 [115].

DISCUSSION

This SLR provided crucial insights to the EULAR TF for the 2024 update of recommendations on ARDs in reproduction, pregnancy, and lactation. The SLR included data on the safety of ARDs concerning miscarriage, malformation, and breastfeeding from 2015 onwards, and it additionally covered additional pregnancy outcomes, newly approved drugs, other RMD drugs, and the impact of ARDs on male fertility and offspring outcomes. Among the 255 included studies, 86% focused on maternal exposure to drugs during pregnancy. The broad search strategy aimed to capture as much information as possible, including

Table 8

Male exposure to antirheumatic drugs and reproductive safety: summary of results stratified by drug

Study, year [Ref][a]	Type of study; No. total exposed cases and controls	Drug	Impact on fertility: sperm quality (sperm concentration, sperm motility, and sperm DNA fragmentation index), fecundability, and reproductive hormones	Impact on adverse pregnancy outcomes: MC, elective termination of pregnancy, SB, PTB, SGA, LBW, BDs	Evidence: LoE[b] and study quality[c]
Prednisone, prednisolone	4165				**2b**
Perez-Garcia et al, 2020 [s241]	SLR (7 studies) exp: 4165 ctr: 1,011,691	Prednisone and prednisolone	One study showed no adverse effect on human testis (after 75.0 mg cortisone, n = 4). One study reported slightly elevated FSH and LH (n = 36).	No adverse drug-related effects on pregnancy outcomes. No increased rates of MC, PTB, SGA, and BD.	Fair
NSAIDs	861				**2b**
Wesselink et al, 2020 [s242]	CS exp: 812 ctr: 944 (HC)	Ibuprofen (200.0 mg) and naproxen (220.0 mg)	Ibuprofen and naproxen used at low dose do not impair fecundability.	NA	Fair
Perez-Garcia et al, 2020 [s241]	SLR (5 studies) exp: 49 ctr: 29	Acetylsalicylic acid, ibuprofen, indomethacin, and naproxen	Limited evidence showed no adverse effect on fertility.	NA	Fair
csDMARDs, immunosuppressive, and other drugs					
Antimalarials	50				**2c**
Perez-Garcia et al, 2020 [s241]	SLR (4 studies) exp: 37	Chloroquine	No adverse effect on sperm quality. No adverse effect on reproductive hormones.	NA	Poor
Mouyis et al, 2019 [s243]	SLR (2 studies on pregnancy outcome) exp: 13	Hydroxychloroquine	NA	No adverse drug-related effects on pregnancy outcomes.	Poor
Calcineurin inhibitors	1034				**2b**
Perez-Garcia et al, 2020 [s241]	SLR (23 studies) exp: 851 ctrl: 417,793	Cyclosporine, sirolimus, and tacrolimus	Majority of data did not report relevant sperm abnormalities. No negative effect on reproductive hormones.	No adverse drug-related effects on pregnancy outcomes.	Fair
Mouyis et al, 2019 [s243]	SLR (3 studies) exp: 183	Cyclosporine	Limited evidence showed no adverse effect on fertility.	No adverse drug-related effects on pregnancy outcomes.	Fair
Colchicine	339				**2c**
Perez-Garcia et al, 2020 [s241]	SLR (11 studies) exp: 158	Colchicine	Inconsistent reports with confounding by disease activity and severity. Therapeutic doses of colchicine are not likely to affect sperm motility and production.	No increased risk of spontaneous abortions.	Fair
Cyclophosphamide	315				**2b**
Tiseo et al, 2019 [s244]	CS exp: 12	Cyclophosphamide IV (median cumulative dose: 10.5 g)	Patients with nonazoospermic SLE had increased sperm DFI without evident gonadal dysfunction, an abnormality confounded by indication.	NA	Fair
Perez-Garcia et al, 2020 [s241]	SLR (21 studies) exp: 303 ctr: 88	Cyclophosphamide	Dose-dependent negative effect on sperm quality (azoospermia and teratospermia). Negative effect on reproductive hormones.	Data confounded by treatment indication and use of comedications, especially for use in malignancies.	Fair
Leflunomide and metabolite	85				**2c**
Andersen et al, 2022 [s78]	CSS exp: 63 ctr: 364 (HC)	Teriflunomide	NA	No adverse drug-related effects on pregnancy outcomes.	Fair

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Table 8 (*Continued*)

Study, year [Ref][a]	Type of study; No. total exposed cases and controls	Drug	Impact on fertility: sperm quality (sperm concentration, sperm motility, and sperm DNA fragmentation index), fecundability, and reproductive hormones	Impact on adverse pregnancy outcomes: MC, elective termination of pregnancy, SB, PTB, SGA, LBW, BDs	Evidence: LoE[b] and study quality[c]
Kieseier and Benamor, 2014 [s82]	CS exp: 19	Teriflunomide	NA	No adverse drug-related effects on pregnancy outcomes.	Poor
Perez-Garcia et al, 2020 [s241]	SLR (1 study) exp: 1	Leflunomide	NA	No adverse drug-related effects on pregnancy outcomes.	Poor
Mouyis et al, 2019 [s243]	SLR (2 studies) exp: 2	Leflunomide	NA	No adverse drug-related effects on pregnancy outcomes.	Poor
Methotrexate	1143				**2b**
Perez-Garcia et al, 2023 [s245]	CS exp: 25 ctr: 25 (HC)	Methotrexate (16.0-18.0 mg/wk)	No adverse effect on sperm quality (SC, SM, DFI). Very low concentrations of MTX-polyglutamates in spermatozoa. No negative effect on reproductive hormones.	NA	Good
Grosen et al, 2022 [s246]	CSS exp: 14 ctr: 40 (HC)	Methotrexate (12.5 mg/wk)	No adverse effect on sperm quality (SC, SM, DFI). No negative effect on reproductive hormones.	NA	Good
Meserve et al, 2021 [s247]	CS exp: 171 ctr: 5607 (DC)	Methotrexate	NA	No adverse drug-related effects on pregnancy outcomes, adjusted risk estimates showed no increased risk of PTB, LBW, and BD.	Good
Salama et al, 2019 [s248]	CR exp: 1	Methotrexate (10.0 mg/wk)	Normal sperm quality (SC, SM, and DFI). No negative effect on reproductive hormones.	NA	Poor
Perez-Garcia et al, 2020 [s241]	SLR (14 studies) exp: 932 ctr: 2,379,668	Methotrexate	No adverse effect on sperm quality in most exposed patients. No negative effect on reproductive hormones.	No adverse drug-related effects on pregnancy outcomes; adjusted risk estimates showed no increased risk of MC, PTB, SGA, and BD.	Fair
Mycophenolate	299				**2b**
Perez-Garcia et al, 2020 [s241]	SLR (4 studies) exp: 295 ctr: >1308	Mycophenolate acid products: mycophenolate mofetil and mycophenolate sodium	NA	No adverse drug-related effects on pregnancy outcomes.	Fair
Mouyis et al, 2019 [s243]	SLR (1 study on fertility) exp: 4	Mycophenolate mofetil	Very limited evidence did not suggest an adverse effect on fertility.	NA	Poor
Sulfasalazine	>2782				**2b**
Norgard et al, 2022 [s88]	CS exp: 2168 ctr: 7732 (DC)	5-ASA drugs: mesalazine (94%), sulfasalazine (58%), olsalazine (1%-2%), and basalazide (0.3%-1%)	NA	No adverse drug-related effects on pregnancy outcomes, adjusted risk estimates showed no increased rates of PTB, SGA, and BD.	Good
Chatzimeletiou et al, 2021 [s249]	CR exp: 1	Sulfasalazine	SM, DFI normal; abnormal sperm form in 93% (1 patient, analysis of cryoconserved sperm sample)	No BD.	Poor
Perez-Garcia et al, 2020 [s241]	SLR (22 studies on fertility) exp: 329	Aminosalicylic acid and similar agents	Abnormal sperm quality reported in 40%-100% (decreased SC and SM). Sperm quality usually resolved after discontinuation of drug.	NA	Fair

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Table 8 (*Continued*)

Study, year [Ref][a]	Type of study; No. total exposed cases and controls	Drug	Impact on fertility: sperm quality (sperm concentration, sperm motility, and sperm DNA fragmentation index), fecundability, and reproductive hormones	Impact on adverse pregnancy outcomes: MC, elective termination of pregnancy, SB, PTB, SGA, LBW, BDs	Evidence: LoE[b] and study quality[c]
Mouyis et al, 2019 [s243]	SLR (12 studies on pregnancy outcome) exp: >284	Sulfasalazine	NA	No adverse drug-related effects on pregnancy outcomes.	Fair
Thiopurines	1647				**2b**
Meserve et al, 2021 [s247]	CS exp: 461 ctr: 5607 (DC)	Azathioprine and 6-mercaptopurine	NA	No adverse drug-related effects on pregnancy outcomes, adjusted risk estimates showed no increased risk of PTB, LBW, and BD.	Good
Perez-Garcia et al, 2020 [s241]	SLR (13 studies) exp: 1186 ctr: 1,013,251	Azathioprine and 6-mercaptopurine	No adverse effect on sperm quality (SC, SM, and DFI) in majority of exposed patients, including off vs on cases. No negative effect on reproductive hormones.	No adverse drug-related effects on pregnancy outcomes.	Fair
tsDMARDs	204				**1b-4**
Reinisch et al, 2023 [s250]	RCT exp: 120 ctr: 120 (DC)	Filgotinib (200.0 mg/d, 13 wk)	No adverse effect on sperm quality (SC, SM). No negative effect on reproductive hormones.	3 healthy live born infants without BD.	Good
Perez-Garcia et al, 2020 [s241]	SLR (1 study) exp: 63	Tofacitinib	NA	No adverse drug-related effects on pregnancy outcomes.	Poor
TNFi bDMARDs	1610				**1b**
Meserve et al, 2021 [s247]	CS exp: 1082 ctr: 5607 (DC)	Adalimumab, certolizumab, golimumab, etanercept, and infliximab	NA	No adverse drug-related effects on pregnancy outcomes; adjusted risk estimates showed no increased risk of PTB, LBW, and BD.	Good
Perez-Garcia et al, 2020 [s241]	SLR (23 studies) exp: 528 ctr: 412,365	Adalimumab, certolizumab, golimumab, etanercept, and infliximab	No adverse effect on sperm quality (SC, SM, and DFI). Improved sperm quality after initiation of TNFi therapy. No negative effect on reproductive hormones.	No adverse drug-related effects on pregnancy outcomes.	Fair
Non-TNFi bDMARDs					
Abatacept	10				**4**
Perez-Garcia et al, 2020 [s241]	SLR (1 study) exp: 10	Abatacept	NA	No adverse drug-related effects on pregnancy outcomes.	Poor
Anakinra	6				**4**
Perez-Garcia et al, 2020 [s241]	SLR (1 study) exp: 6	Anakinra	NA	No adverse drug-related effects on pregnancy outcomes.	Poor
Canakinumab	5				**4**
Perez-Garcia et al, 2020 [s241]	SLR (1 study) exp: 5	Canakinumab	NA	No adverse drug-related effects on pregnancy outcomes.	Poor
Ixekizumab	75				**4**
Egeberg et al, 2022 [s191]	CSE, pharmacovigilance exp: 75	Ixekizumab	NA	No adverse drug-related effects on pregnancy outcomes.	Poor
Rituximab	11				**4**
Mouyis et al, 2019 [s243]	SLR (1 study) exp: 11	Rituximab	NA	No adverse drug-related effects on pregnancy outcomes.	Poor

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Table 8 (*Continued*)

Study, year [Ref][a]	Type of study; No. total exposed cases and controls	Drug	Impact on fertility: sperm quality (sperm concentration, sperm motility, and sperm DNA fragmentation index), fecundability, and reproductive hormones	Impact on adverse pregnancy outcomes: MC, elective termination of pregnancy, SB, PTB, SGA, LBW, BDs	Evidence: LoE[b] and study quality[c]
Secukinumab	54				**4**
Perez-Garcia et al, 2020 [s241]	SLR (1 study) exp: 54	Secukinumab	NA	No adverse drug-related effects on pregnancy outcomes.	Poor
Tocilizumab	15				**4**
Hoeltzenbein et al, 2016 [s183]	CSE, pharmacovigilance exp: 13	Tocilizumab	NA	No adverse drug-related effects on pregnancy outcomes.	Poor
Perez-Garcia et al, 2020 [s241]	SLR exp: 2	Tocilizumab	NA	No adverse drug-related effects on pregnancy outcomes.	Poor
Ustekinumab	219				**2b**
Meserve et al, 2021 [s247]	CS exp: 132 ctr 5607 (DC)	Ustekinumab	NA	No adverse drug-related effects on pregnancy outcomes; adjusted risk estimates showed no increased risk of PTB, LBW, and BD.	Good
Mahadevan et al, 2021 [s194]	CSE, pharmacovigilance exp: 87	Ustekinumab	NA	No adverse drug-related effects on pregnancy outcomes.	Poor

5-ASA, 5-aminosalicylic acid; FSH, follicle-stimulating hormone; BD, birth defect; bDMARD, biologic disease-modifying antirheumatic drug; CM, congenital malformation; CR, case report; CS, cohort study; csDMARD, conventional synthetic disease-modifying antirheumatic drug; CSE, case series; CSS, cross-sectional study; ctr, control; DC, diseased control; DFI, sperm DNA fragmentation index; exp, exposed cases; HC, healthy control; LBW, low birth weight; LH, luteinising hormone; LoE, level of evidence; MC, miscarriage; NA, not available; NSAID, nonsteroidal anti-inflammatory drug; PTB, preterm birth; RCT, randomised controlled trial; SC, sperm concentration; SGA, small-for-gestation age; SLE, systemic lupus erythematosus; SLR, systematic literature review; SM, sperm motility; TNFi, tumour necrosis factor inhibitor; tsDMARD, targeted synthetic disease-modifying antirheumatic drug.

[a] The complete list of references is available in the Supplementary Material.

[b] Level of evidence according to studies retrieved in included SLR and the 2024 SLR Update.

[c] Study quality rated as good, fair, and poor based on the Newcastle–Ottawa Scale; CR and CSE were categorised as poor. Quality of studies of the SLR rated as low, fair, or good were converted into poor, fair, and good. RoB2 showing low risk of bias was converted into good.

diverse patient groups apart from RMDs, such as those with IBD or multiple sclerosis, in whom ARDs or its active metabolites (eg, teriflunomide and 6-mercaptopurine) or bDMARDs throughout pregnancy were used.

Teratogentic drugs comprise methotrexate, cyclophosphamide, and mycophenolate that should be discontinued before conception, although cyclophosphamide and mycophenolate may be used in the second or third trimester for organ-threatening or life-threatening disease, as most children exposed during these trimesters were born healthy [4,121−124]. Regarding leflunomide or teriflunomide, data suggest no major teratogenic effects, even with unknown or low washout rates [31,36,38,125], with a prospective pharmacovigilance database suggesting discontinuation 3.5 months before conception [125]. Other drugs that should be stopped before conception include those with insufficient data in pregnancy, for example, apremilast, avacopan, bosentan, all JAKi (baricitinib, tofacitinib, upadacitinib, and filgotinib), mepacrine, and voclosporine.

Current evidence remains reassuring for csDMARDs already considered compatible with pregnancy in the previous EULAR consensus [4]. These drugs include antimalarials, azathioprine, colchicine, cyclosporine, sulfasalazine, and tacrolimus, all showing favourable safety profiles without increasing the risk for APOs.

Further, bDMARDs, particularly TNFi, have a largely safe profile during pregnancy. Our meta-analyses with adjusted risk estimates did not show significant increases in malformations, PTB, SGA, LBW, or SII in pregnancies exposed to TNFi, consistent with previous meta-analyses [126]. Crude risk estimates did show an increased risk for these outcomes, highlighting the importance of considering disease activity and severity [55,127−129]. In addition, TNFi use was not associated with miscarriage and stillbirth. Data on non-TNFi biologics in pregnancy are limited and often lack comparison with unexposed diseased controls, but existing evidence does not indicate significant concerns about adverse pregnancy or infant outcomes [54,57,61,62,70,84]. Transient B cell depletion or cytopenias may occur in neonates exposed *in utero* to rituximab or belimumab, with recovery within 6 months [54,62,130,131]. Concerns about immunologic changes, including adverse vaccination effects in infants exposed *in utero* to bDMARDs, exist due to transplacental passage. However, no serious adverse events were reported with nonlive vaccines, and immunologic responses were similar to unexposed infants [54]. In addition, no serious adverse events were linked to live rotavirus vaccines, consistent with a recent larger cohort study [67]. BCG vaccination safety in bDMARDs-exposed infants is a concern in the first 6 months but is considered safe thereafter [68,70].

Regarding oral GC in pregnancy, this SLR confirmed no increased rate of major birth defects [4,13,14,62,132], but there are other relevant dose-related risks for the mother and the newborn [133−136]. A large retrospective study showed an increased risk of serious maternal infections at daily doses of 10.0 mg [133]. Our meta-analysis, including studies adjusted for disease severity, revealed an association of prednisone with PTB [109,134,135,137,138]. A cumulative dose above 300.0 mg prednisone within the first 20 weeks of gestation or an average daily dose above 5.0 to 10.0 mg was associated with increased PTB risk [134−136,139]. GC cross the placental barrier, yet the placental enzyme 11β-hydroxysteroid dehydrogenase type 2 significantly limits fetal exposure to active prednisolone [102]. Two studies indicated normal developmental milestones, but conflicting infection rates in infants exposed to maternal GC [13,14].

Data on NSAIDs showed that a continuous periovulatory use can reduce fecundability [73,74]. Data on first trimester NSAID use, including prospective studies, did not show increased risks of major birth defects or miscarriage [4,15,16,18,140]. Most reassuring data were available for ibuprofen, whereas data on COX-2 inhibitors were limited [15,16,18,19,140]. Short-term (7-10 days) NSAID use in the second trimester did not reveal substantial fetal risks [71,72,141].

Among the vasodilatory drugs used in RMDs, data in pregnancy are available for sildenafil. Sildenafil is not teratogenic and was investigated in clinical trials for various pregnancy-related conditions like fetal growth restriction, pre-eclampsia, and preterm labour [43−45]. Limited data on the use of sildenafil in maternal pulmonary hypertension showed no maternal or fetal drug-related adverse effects [142]. However, for the treatment of fetal growth restriction, sildenafil may increase the risk of persistent pulmonary hypertension [43].

Evaluations of drug safety during breastfeeding are based on pharmacokinetic studies and clinical follow-ups. Despite limitations in study size, most studies showed very low drug levels in breast milk and no reported harm to infants. The relative infant dose (RID) is used to assess risk, with a cutoff of 10% indicating breastfeeding compatibility [143]. In fact, none of the drugs analysed showed an average RID above 10%. Most studies addressed bDMARDs in breastfeeding, all showing no to minimal transfer into breast milk and no adverse events in infants [57,59,63,76−79,83−86,88−90,92−95,97,98]. Drugs with limited data, such as methotrexate, sildenafil, and bosentan, also displayed low levels in breast milk without evidence of infant harm [107−109]. Given the overall benefits of breastfeeding, these findings support a risk-benefit assessment in breastfeeding patients, especially when alternative treatments are lacking [144].

Data on the impact of ARDs on male fertility are limited and often of poor quality, with disease activity itself known to negatively affect sperm quality [145−147]. Recent studies on methotrexate and filgotinib set new standards for research in this area [119,148]. Compared with filgotinib, however, data on methotrexate are more comprehensive, both in terms of sperm parameters and birth outcomes. Sulfasalazine may temporarily impair fertility without affecting offspring outcomes. It is advisable to switch to alternative medications to prevent disease flares, which could further impact fertility. Cyclophosphamide is the only ARD known to cause irreversible infertility at high doses, necessitating fertility preservation [149]. The most reassuring evidence for male fertility and birth outcomes was available for TNFi bDMARDs [115].

There are significant limitations of this SLR that need to be mentioned, such as the heterogeneity and varying quality among the included studies, for example, small sample size, insufficient data on drug exposure time during pregnancy, or unknown outcomes. However, classical scores of study quality rather focus on efficacy of a drug than on safety [4]. In addition, most studies were lacking adequate control groups, particularly unexposed populations with the same disease, making it difficult to distinguish the effects of medication from the underlying disease. This issue is crucial, as patients with RMDs have a higher risk of APOs, and treatment may mitigate disease activity, affecting these outcomes [1−3]. Therefore, well-designed prospective studies are needed, comparing drug exposure in diseased populations with unexposed controls while adjusting for confounders like disease severity, comorbidities, maternal age, and comedication. In addition, further studies on ARDs during breastfeeding and in male patients planning a family are required.

In conclusion, the updated SLR provides valuable insights about the relative safety of ARDs in reproduction, pregnancy, and lactation and supports the update of the EULAR recommendations.

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FF, AF, YM, APS, LR, and SH developed the search strategies. FF, APS, LR, SH, IC, and LFP-G extracted the data for the SLR. MK performed the meta-analyses; FF, YM, APS, LR, SH, and LFP-G wrote the first version of the manuscript. All authors revised the manuscript critically for important intellectual content and gave final approval of the version to be published.

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All data relevant to the study are included in the article or uploaded as online supplemental information.

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Patient and/ or public were not involved in the design, conduct, reporting or disseminating of the study.

Supplementary materials

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