# Disease-modifying anti-rheumatic drug use in pregnant women with rheumatic diseases: a systematic review of the risk of congenital malformations

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## Abstract

### Objective

*Despite the high incidence of rheumatic diseases during the reproductive years, little is known about the impact of disease-modifying anti-rheumatic drug (DMARD) use during pregnancy. Our objective was to systematically review and appraise evidence in women with rheumatic disease on the use of traditional and biologic DMARDs during pregnancy and the risk of congenital malformation outcomes.*

### Methods

*We conducted a systematic search of MEDLINE, EMBASE, and INTERNATIONAL PHARMACEUTICAL ABSTRACTS databases. Inclusion criteria were: 1) study sample including women with rheumatic disease; 2) use of traditional and/or biologic DMARDs during pregnancy; and 3) congenital malformation outcome(s) reported. We extracted information on study design, data source, number of exposed pregnancies, type of DMARD, number of live births, and number of congenital malformations.*

### Results

*Altogether, we included 79 studies; the majority were based on designs that did not involve a comparison group, including 26 case reports, 17 case series, 20 cross-sectional studies, and 4 surveys. Studies that had a comparator group included 1 case control, 10 cohort studies, and 1 controlled trial. Hydroxychloroquine and azathioprine represent the most studied traditional DMARD exposures and, among biologics, most of the reports were on infliximab and etanercept.*

### Conclusion

*This is the first systematic review on the use of both traditional and biologic DMARDs during pregnancy among women with rheumatic diseases and congenital malformation outcomes, with a focus on study design and quality. Findings confirm the limited number of studies, as well as the need to improve study designs.*

**Key words**

rheumatic disease, pregnancy, disease-modifying anti-rheumatic drugs, biologic agents, congenital malformations

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## Introduction

Autoimmune rheumatic diseases, including systemic lupus erythematosus (SLE) (1), rheumatoid arthritis (RA) (2), and juvenile idiopathic arthritis (JIA) (3), are more prevalent among women than among men (4), often striking during reproductive years (5). With improved remission rates, more women with rheumatic disease consider pregnancy (6). Although some diseases show improvement during pregnancy, particularly RA (7), treatment is often required throughout pregnancy (8). A study among pregnant women with RA reported that use of traditional and biologic disease-modifying antirheumatic drugs (DMARDs) occurred in 23% and 12.5% of pregnancies, respectively (9), which underscores the importance of understanding their perinatal impacts.

Occurring in approximately 3% of the general population, congenital malformations are conditions present at birth that cause structural changes in one or more parts of the body and associated with adverse effects on health, development, or function (10). They represent a perinatal outcome that most women fear when considering drugs during pregnancy (11). Since pregnant women are largely excluded from clinical trials (12), much of the data on the impact of medications, including DMARDs, on congenital malformations are largely based on observational studies (13). Our objective was to systematically review and describe studies reporting use of DMARDs during pregnancy in women with rheumatic disease and the risk of congenital malformation outcomes. Throughout this paper, the acronym "DMARDs" refers both to traditional and biologic DMARDs.

## Methods

*Literature search strategy*

We conducted database searches of MEDLINE (1946–2013), EMBASE (1974–2013), and International Pharmaceutical Abstracts (1970–2013). Where search concepts were well-indexed, subject headings were used. Where concepts were less well-indexed or had not yet been assigned subject headings, key words were used. These were database dependent, but analogous to Medical Subject Headings in Medline. An information scientist conducted all searches. Search concepts, corresponding subject headings, and key words are provided as supplementary material (Appendix 1, on line).

*Study selection*

Inclusion criteria were: original study; population that included women with rheumatic disease (*e.g.* RA, SLE, JIA); women of childbearing age (15–45 years); reporting of DMARD use during pregnancy, whether as a single exposure or in combination; reporting of birth outcomes including congenital malformations and; publication in English, French, or Spanish. We did not exclude studies based on design. Where a subsequent article provides an update or larger sample, we included only the most recent article.

*Data extraction and synthesis*

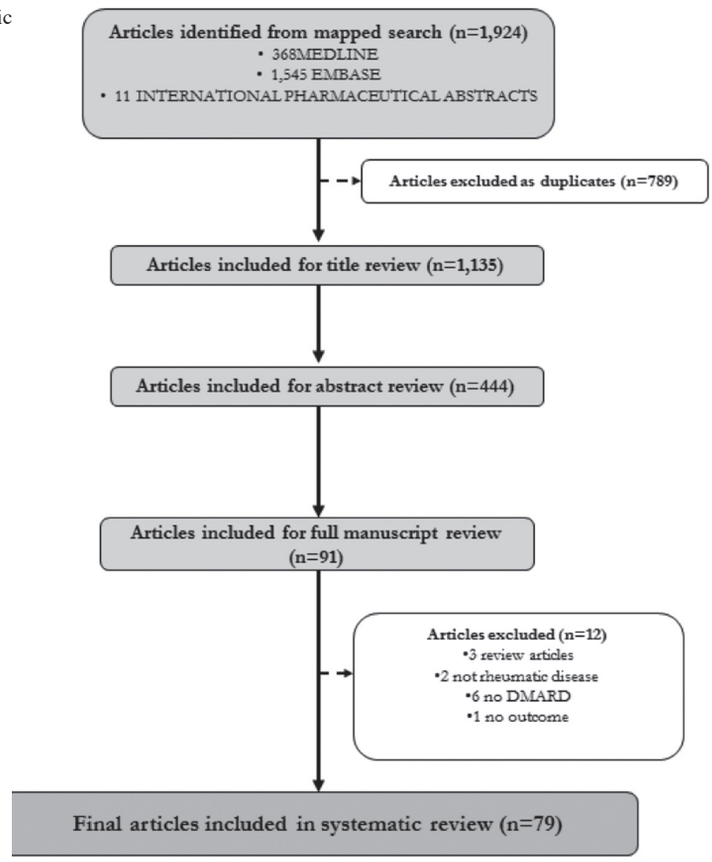
We considered study design and distinguished whether studies used a comparator group of women with rheumatic disease who were not exposed to DMARDs during pregnancy. Studies without a comparator group were defined as: case report (detailed report on 1 pregnancy); case series (detailed reports on >1 pregnancy allowing case-specific extraction of drug exposure and outcome); cross-sectional study (aggregate reporting on >1 pregnancy), and survey (information/data obtained from surveys of physicians or patients). Studies with a comparator group were classified according to established definitions for case control and cohort designs (14). Where possible, extraction of case-specific information on rheumatic disease, DMARD(s) exposure, including type, time, and duration, whether used singly or in combination, and congenital malformation outcome(s) was completed. As studies may report on one or more drug exposures, we noted whether a study is reporting a primary drug of interest (D1), reporting a concomitant drug to a primary drug studied (D2), studying multiple drugs (DM), or studying a disease primarily but with reporting of exposure to a particular drug (DD).

## Results

*Literature search*

Of 1,824 articles identified, 79 were ultimately included (Fig. 1). Figures 2 and 3 summarise study designs according to specific traditional DMARD and biologic. Tables I and II list all included studies for specific DMARDs. Studies without a comparison group included 26 case reports, 17 case series, 25 cross-sectional studies, and 4 surveys. Studies with a comparator group included 1 case control, 10 cohort studies, and 1 controlled trial (additionally summarised in Table III). Detailed information (*e.g.* dosage, timing of exposure) for case reports and case series is included as supplementary material (Appendices 2 and 3, on line).

**Fig. 1.** Systematic review study flow




## DMARDs

*Chloroquine/hydroxychloroquine*

Among 3 chloroquine studies, there was 1 case report of a patient with SLE (15) and 2 case series involving patients with SLE (16), and SLE and RA (17). Of 27 pregnancy exposures, 24 were singly and 3 were in combination with another DMARD (1 hydroxychloroquine, 1 azathioprine, and 1 D-Penicillamine). Pregnancies resulted in 19 live births including 2 infants with abnormalities – hearing loss and Wilm's tumour – born to the same mother with separate pregnancies exposed to chloroquine (15).

Of 31 hydroxychloroquine studies, there were 5 case reports (18-22), 8 case series (16-17, 23-28), 12 cross-sectional studies (29-40), 1 patient-survey (41), 1 case control (42), 3 cohort studies (43-45), and 1 controlled study (46). We extracted case-specific information from 21 studies, which represent 359 pregnancies exposed to hydroxychloroquine, of which 311 were single exposures. The remaining 48 exposures occurred in combination with another DMARD, including cyclophosphamide in 5 cases (18, 28), azathioprine in 13 cases (44-45), methotrexate in 10 cases (23-24), mycophenolate mofetil (MMF) in 13 cases (20, 39), gold in 6 cases (27) and gold and etanercept in 1 case (27). Altogether, there were 294 live births with 10 congenital abnormalities reported, including 3 infants with multiple severe abnormalities following exposure to hydroxychloroquine in combination with MMF (20, 39), and one case each of transposition of the great arteries, Down syndrome, cleft lip, hypospadias, craniostenosis, Duane's syndrome, and minor unspecified malformation. Among the remaining 10 reports for which we could not extract case-specific data, there were at least 234 pregnancies exposed to hydroxychloroquine, which may or may not have occurred in combination with other DMARDs. From these there were 3 reported malformations, including one infant each with scaphocephaly and microcephaly (34). One neonatal death was reported in an infant with Down syndrome and multiple cardiac defects; however, it was unclear if this infant had been exposed to other DMARDs (35). Hydroxychloroquine was the only drug for which there is a published controlled trial – with 20 pregnant patients with SLE randomised to hydroxychloroquine or placebo (46). No malformations were reported in either study group (46).

*Gold*

Four studies, mostly in women with RA, represented 24 pregnancy exposures to gold including one each of case report (47), case series (27), cross-sectional study (29) and cohort study (48). In 14 pregnancies, exposure occurred singly and in 8, in combination with other DMARDs including hydroxychloroquine (27), sulfasalazine (27), and etanercept and hydroxychloroquine (27). At least 17 live births resulted from these exposures including 3 infants with congenital abnormalities – 1 infant with multiple severe anomalies described as hypertelorism, occipital encephalocele, cleft lip and palate, short neck and abnormal ears (47), 1 infant with mild abnormalities including a blocked tear duct (27), and 1 infant with mild Duane's syndrome (27). Although Verstappen *et al.'s* cohort study, using data from the British Society for Rheumatology Biologics Register (BSRBR), primarily investigated anti-tumour necrosis factor (TNFs), it warrants mention as some were reported to have concomitant exposures to other DMARDs including gold, sul-

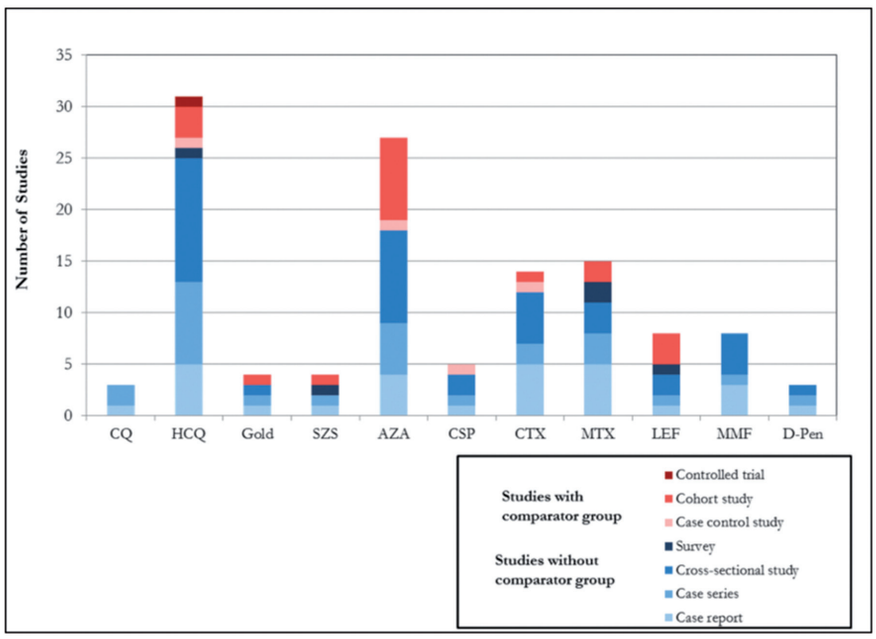



**Fig. 2.** Number of included studies according to design for traditional DMARDs.

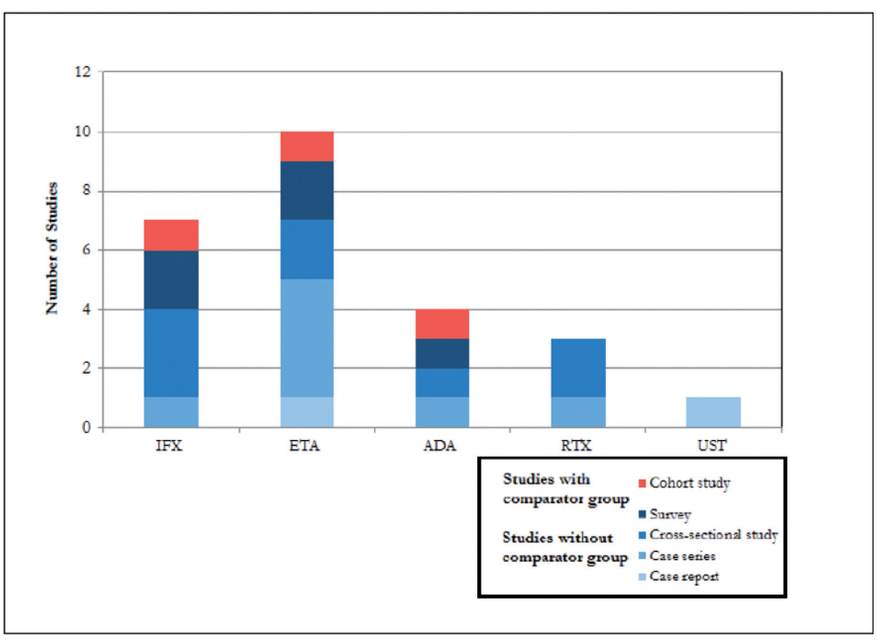



**Fig. 3.** Number of included studies according to design for biologics.

fasalazine, azathioprine, methotrexate, and leflunomide (Table III) (48). However, it was not possible to link these exposures to underlying rheumatic disease or extract outcomes for these patients (48).

*Sulfasalazine*

We identified 4 studies reporting pregnancy exposure to sulfasalazine including 1 case report (49) and 1 case series in RA (27), and 1 survey (to Teratology Information Services [TIS]) (50) and 1 cohort study which both included women with various rheumatic diseases (48). None of the included papers reported on sulfasalazine primarily (*i.e.* assigned "D1" in Table I), however, we synthesised three pregnancies with exposure to sulfasalazine in women with RA (27, 49-50), with two exposures occurring in combination with another DMARD including methotrexate (50) and gold (27). All 3 pregnancies resulted in live births with minor congenital malformations reported in 2 infants – 1 with bilateral metatarsus varus and 1 with eyelid haemangioma (50).

*Azathioprine*

We identified 27 studies reporting pregnancies exposed to azathioprine, including 4 case reports (22, 51-53), 5 case series (17, 28, 54-56), 9 cross-sectional (29, 33, 35-39, 57-58), 1 case control (42), and 8 cohort studies (43-45, 48, 59-62). We were able to extract complete data from 13 (17, 22, 28, 29, 33, 35-39, 42, 51-59), which represent 42 pregnancies exposed to azathioprine, with SLE as the most common indication. One exposure occurred in combination with phenytoin (17) and at least 10 exposures in combination with other DMARDs including chloroquine, hydroxychloroquine, cyclosporine, MMF, cyclophosphamide, and infliximab. Of the 33 live births there were 3 infants with abnormalities, including 1 with preaxial polydactyly (51) and 2 with multiple severe abnormalities (52-53), 1 of which followed from a pregnancy that was also exposed to MMF (53). There was 1 neonatal death in a premature infant with Down syndrome and associated multiple severe cardiac abnormalities (35). In 14 studies representing at least 144 pregnancy exposures to azathioprine and 43 reported abnormalities, extraction of case-specific data was not possible. Thirty of these congenital malformations were reported, along with an increased risk of congenital malformations associated with azathioprine use in early pregnancy (odds ratio 2.82; 95%CI 1.13–5.82), in a cohort study by Cleary *et al*. (62) that primarily included women with other indications, particularly inflammatory bowel disease (Table III).

*Cyclosporine*

Five studies reported outcomes in pregnancies exposed to cyclosporine, including 1 case report (18), 1 case series (63), 2 cross-sectional studies (29, 58), and 1 case control study (42). Altogether, these represent 19 pregnancy exposures to cyclosporine across indications of SLE (29, 42, 58, 63), scleroderma (58), PsA (58), JIA (18), and mixed connective tissue

**Table I.** Included studies for synthetic DMARDs according to design.

| ID | Study | Design | Rheumatic disease* | Case-specific data extracted§ |
|---|---|---|---|---|
| | | **Chloroquine (CQ)** | | |
| 1 | Matz 1968 (15) | Case report[D1] | SLE | Y |
| 2 | Parke 1988 (16) | Case series[D1] | SLE | Y |
| 3 | Levy 1991 (17) | Case series[D1] | SLE, RA | Y |
| | | **Hydroxychloroquine (HCQ)** | | |
| 4 | Airo 2002 (18) | Case report[D2] | SLE | Y |
| 5 | Stirnemann 2002 (19) | Case report[D1] | SLE | Y |
| 6 | Anderka 2009 (20) | Case report[D2] | SLEn | Y |
| 7 | Keeling 2009 (21) | Case report[D1] | SLE | Y |
| 8 | Streit 2009 (22) | Case report[D2] | SLE | Y |
| (2)‡ | Parke 1988 (16) | Case series[D1] | SLE | Y |
| 9 | Kozlowski 1990 (23) | Case series[D2] | RA, JIA | Y |
| (3) | Levy 1991 (17) | Case series[D1] | SLE, RA | Y |
| 10 | Donnenfeld 1994 (24) | Case series[D2] | RA | Y |
| 11 | Parke 1996 (25) | Case series[D2] | SLE | Y |
| 12 | Mok 2004 (26) | Case series[D1] | AOSD | Y |
| 13 | Almarzouqi 2007 (27) | Case series[D2] | RA | Y |
| 14 | Lannes 2011 (28) | Case series[D2] | SLE | Y |
| 15 | Ostensen 1992 (29) | Cross-sectional study[DD] | JIA | Y |
| 16 | Huong 1994 (30) | Cross-sectional study[D2] | SLE | Y |
| 17 | Buchanan 1992 (31) | Cross-sectional study[DD] | SLE | N |
| 18 | Huong 2001 (32) | Cross-sectional study[DD] | SLEn | N |
| 19 | Carmona 2005 (33) | Cross-sectional study[DM] | SLEn | N |
| 20 | Renaud 2006 (34) | Cross-sectional study[D1] | SLE | N |
| 21 | Silva 2008 (35) | Cross-sectional study[DM] | SLE | N |
| 22 | Ambrosio 2010 (36) | Cross-sectional study[DM] | SLE | N |
| 23 | Carvalheiras 2010 (37) | Cross-sectional study[DM] | SLE | N |
| 24 | Teh 2011 (38) | Cross-sectional study[DM] | SLE | N |
| 25 | Hoeltzenbein 2012 (39) | Cross-sectional study (T)[D2] | SLE | Y |
| 26 | Mekinian 2013 (40) | Cross-sectional study (R)[DD] | SLE | N |
| 27 | Bonaminio 2006 (41) | Survey (patient)[DD] | SLE | Y |
| 28 | Andrade 2008 (42) | Case control study[DD] | SLE | N |
| 29 | Buchanan 1996 (43) | Cohort study[D1] | SLE | Y |
| 30 | Costedoat 2003 (44) | Cohort study[D1] | SLE | Y |
| 31 | Clowse 2006 (45) | Cohort study[D1] | SLEn | Y |
| 32 | Levy 2001 (46) | Controlled trial[D1] | SLE | Y |
| | | **Cyclosporine (CSP)** | | |
| (4) | Airo 2002 (18) | Case report[D1] | SLE | Y |
| 49 | Hussein 1993 (63) | Case series[D1] | SLEn | Y |
| (15) | Ostensen 1992 (29) | Cross-sectional study[DD] | JIA | Y |
| (44) | Ostensen 2008 (58) | Cross-sectional study[DM] | SLE, RA | Y |
| (28) | Andrade 2008 (42) | Case control study[DD] | SLE | N |
| | | **Cyclophosphamide (CTX)** | | |
| 50 | Kirshon 1988 (64) | Case report[D1] | SLE | Y |
| 51 | Enns 1999 (65) | Case report[D1] | SLEn | Y |
| 52 | Aslan 2005 (66) | Case report[DD] | SJS | Y |
| 53 | Escobar 2011 (67) | Case report[D1] | SLEn | Y |
| 54 | Lazalde 2012 (68) | Case report[D1] | SLEn | Y |
| (41) | Clowse 2005 (55) | Case series[D1] | SLEn | Y |
| (14) | Lannes 2011 (28) | Case series[D1] | SLE | Y |
| (18) | Huong 2001 (32) | Cross-sectional study[DD] | SLEn | N |
| 55 | Huong 2002 (69) | Cross-sectional study[D1] | SLE | Y |
| 56 | Park 2004 (70) | Cross-sectional study[D1] | SLEn | N |
| (21) | Silva 2008 (35) | Cross-sectional study[DM] | SLE | N |
| 57 | Whitelaw 2008 (71) | Cross-sectional study[DD] | SLE | Y |
| (28) | Andrade 2008 (42) | Case control study[DD] | SLE | N |
| (45) | Ramsey 1993 (59) | Cohort study[DM] | SLE | Y |
| | | **Methotrexate (MTX)** | | |
| 58 | Feldkamp 1993 (72) | Case report[D1] | RA | Y |
| 59 | Buckley 1997 (73) | Case report[D1] | JIA | Y |
| 60 | Delatycki 2005 (74) | Case report[D1] | RA | Y |
| 61 | Corona 2010 (75) | Case report[D1] | SLE | Y |
| 62 | Piggott 2011 (76) | Case report[D1] | SLE | Y |
| (9) | Kozlowski 1990 (23) | Case series[D1] | RA, JIA | Y |
| (10) | Donnenfeld 1994 (24) | Case series[D1] | RA | Y |
| 63 | Ostensen 2000 (77) | Case series[D1] | RA | Y |
| 64 | Hyrich 2006 (78) | Cross-sectional study (R)[D2] | RA | Y |
| (44) | Ostensen 2008 (58) | Cross-sectional study[DM] | SLE, RA | Y |
| 65 | Chakravarty 2011 (79) | Cross-sectional study (R)[D2] | RA, SLE | N |
| 66 | Chakravarty 2003 (80) | Survey (rheumatologist)[DD] | RA | Y |
| (36) | Lewden 2004 (50) | Survey (TIS)[D1] | RA, PsA | Y |
| (34) | Verstappen 2011 (48) | Cohort study (R)[D2] | RA, JIA | N |
| 67 | Cassina 2012 (81) | Cohort study (T)[D2] | RA, JIA | Y |
| | | **Gold** | | |
| 33 | Rogers 1980 (47) | Case report[D1] | RA | Y |
| (13) | Almarzouqi 2007 (27) | Case series[D1] | RA | Y |
| (15) | Ostensen 1992 (29) | Cross-sectional study[DD] | JIA | Y |
| 34 | Verstappen 2011 (48) | Cohort study (R)[D2] | RA, JIA | N |
| | | **Sulfasalazine (SZS)** | | |
| 35 | Ostensen 2005 (49) | Case report[DD] | RA | Y |
| (13) | Almarzouqi 2007 (27) | Case series[D2] | RA | Y |
| 36 | Lewden 2004 (50) | Survey (TIS)[D2] | RA, PsA | Y |
| (34) | Verstappen 2011 (48) | Cohort study (R)[D2] | RA, JIA | N |
| | | **Azathioprine (AZA)** | | |
| 37 | Williamson 1982 (51) | Case report[D1] | SLE | Y |
| 38 | Ostrer 1984 (52) | Case report[D1] | SLE | Y |
| 39 | Schoner 2008 (53) | Case report[D2] | SLE | Y |
| (8) | Streit 2009 (22) | Case report[D2] | SLE | Y |
| 40 | Sharon 1974 (54) | Case series[D1] | SLE | Y |
| (3) | Levy 1991 (17) | Case series[D2] | SLE, RA | Y |
| 41 | Clowse 2005 (55) | Case series[D2] | SLEn | Y |
| 42 | Rosner 2007 (56) | Case series[D2] | RA, JIA | Y |
| (14) | Lannes 2011 (28) | Case series[D2] | SLE | Y |
| (15) | Ostensen 1992 (29) | Cross-sectional study[DD] | JIA | Y |
| 43 | Tincani 1992 (57) | Cross-sectional study[DD] | SLE | N |
| (19) | Carmona 2005 (33) | Cross-sectional study[DM] | SLEn | N |
| 44 | Ostensen 2008 (58) | Cross-sectional study[DM] | SLE, RA | Y |
| (21) | Silva 2008 (35) | Cross-sectional study[DM] | SLE | Y |
| (22) | Ambrosio 2010 (36) | Cross-sectional study[DM] | SLE | N |
| (23) | Carvalheiras 2010 (37) | Cross-sectional study[DM] | SLE | N |
| (24) | Teh 2011 (38) | Cross-sectional study[DM] | SLE | N |
| (25) | Hoeltzenbein 2012 (39) | Cross-sectional study (T)[D2] | SLE | N |
| (28) | Andrade 2008 (42) | Case control study[DD] | SLE | N |
| 45 | Ramsey 1993 (59) | Cohort study[DM] | SLE | Y |
| (29) | Buchanan 1996 (43) | Cohort study[D2] | SLE | N |
| (30) | Costedoat 2003 (44) | Cohort study[D2] | SLEn | N |
| (31) | Clowse 2006 (45) | Cohort study[D2] | SLEn | N |
| 46 | Goldstein 2007 (60) | Cohort study (T)[D1] | SLEn | N |
| 47 | Langagergaard 2007 (61) | Cohort study (A)[D1] | SLE, PAN | N |
| 48 | Cleary 2009 (62) | Cohort study (A)[D1] | SLE | N |
| (34) | Verstappen 2011 (48) | Cohort study (R)[D2] | RA, JIA | N |
| | | **Leflunomide (LEF)** | | |
| 68 | Heine 2008 (82) | Case report[D1] | JIA | Y |
| 69 | Hajdyla-Banas 2009 (83) | Case series[D1] | RA | Y |
| (64) | Hyrich 2006 (78) | Cross-sectional study (R)[D2] | RA | Y |
| (44) | Ostensen 2008 (58) | Cross-sectional study[DM] | SLE, RA | Y |
| (66) | Chakravarty 2003 (80) | Survey (rheumatologist)[DD] | RA | Y |
| 70 | Chambers 2010 (84) | Cohort study (T)[D1] | RA, JIA | Y |
| (34) | Verstappen 2011 (48) | Cohort study (R)[D2] | RA, JIA | N |
| (67) | Cassina 2012 (81) | Cohort study (T)[D1] | RA, JIA | Y |
| | | **Mycophenolate mofetil (MMF)** | | |
| (6) | Anderka 2009 (20) | Case report[D1] | SLEn | Y |
| (39) | Schoner 2008 (53) | Case report[D1] | SLE | Y |
| 71 | Somalanka 2009 (85) | Case report[D1] | SLEn | Y |
| (42) | Rosner 2007 (56) | Case series[D2] | RA, JIA | Y |
| (44) | Ostensen 2008 (58) | Cross-sectional study[DM] | SLE, RA | Y |
| (65) | Chakravarty 2011 (79) | Cross-sectional study (R)[D2] | RA, SLE | N |
| (24) | Teh 2011 (38) | Cross-sectional study[DM] | SLE | Y |
| (25) | Hoeltzenbein 2012 (39) | Cross-sectional study (T)[D1] | SLE | Y |
| | | **D-Penicillamine (D-Pen)** | | |
| 72 | Solomon 1977 (86) | Case report[D1] | RA | Y |
| (3) | Levy 1991 (17) | Case series[D2] | SLE, RA | Y |
| (15) | Ostensen 1992 (29) | Cross-sectional study[DD] | JIA | Y |

*: indicates underlying rheumatic disease of women with pregnancy exposures to DMARD under study. In studies involving women with other conditions (*e.g.* inflammatory bowel disease), we listed the two most representative rheumatic conditions studied; §: indicates whether case-specific DMARD exposure(s) and congenital malformation outcome(s) was conducted; [D1]: indicates primary drug of interest studied; [D2]: indicates that drug is concomitant to a primary drug studied; [DM]: indicates multiple drugs studied or reported in single paper including particular drug; [DD]: indicates primary disease(s) studied with reporting of exposure to particular drug.
SLE: systemic lupus erythematosus; RA: rheumatoid arthritis; SLEn: lupus nephritis; JIA: juvenile idiopathic arthritis; ASOD: adult-onset Still's disease; PAN: polyarteritis nodosa; R: registry data; T: teratology information service (TIS) data; A: administrative data.

disease (18). In two pregnancies, exposure to cyclosporine was in combination with an additional DMARD, including hydroxychloroquine, cyclophosphamide (18), and azathioprine (29). We recorded 1 premature infant who was born with multiple abnormalities resulting in neonatal death (58).

*Cyclophosphamide*

We identified 14 studies reporting pregnancy exposure to cyclophosphamide including 5 case reports (64-68), 2 case series (28, 55), 5 cross-sectional studies (32, 35, 69-71), 1 case control (42), and 1 cohort study (59). We extracted information on 21 pregnancies exposed to cyclophosphamide, 5 of which were exposed in combination with hydroxychloroquine (28, 67) and 3 with azathioprine (28, 55). Among these there were 11 live births and 3 reports of 3 infants with multiple severe anomalies (64-65, 68). In 4 studies aggregately reporting pregnancy outcomes in women with SLE, we could not extract case-specific cyclophosphamide exposure (with or without other DMARDs) (32, 35, 42, 70).

*Methotrexate*

Fifteen studies reported outcomes following methotrexate exposure during pregnancy including 5 case reports (72-76), 3 case series (23-24, 77), 3 cross-sectional studies (58, 78-79), 2 surveys (to rheumatologist; to TIS) (50, 80), and 2 cohorts studies (48, 81). We extracted case-specific information from 13 studies, representing 108 pregnancies. Of these, 19 exposures occurred in combination with another DMARD including hydroxychloroquine (23-24), sulfasalazine (50), leflunomide (81), and anti-TNFs (78), and 89 occurred in the absence of other DMARDs. Sixty-four of these 108 exposed pregnancies resulted in live births and we extracted the following information on malformations: 3 infants with multiple severe abnormalities (73, 75-76), 3 with un-described congenital abnormalities (80), 1 with bilateral metatarsus varus and eye lid hemangioma (50), and 1 with functional abnormality (seizures and developmental delay) (74). Although Chakravarty *et al*.'s 2011 study primarily described 153 pregnancies exposed to rituximab (79), it warrants mention here as some patients (including RA and SLE), had concomitant exposures to methotrexate, although the number (and the timing of exposure) was not provided. In the previously described cohort study by Verstappen *et al*. (Table III), which primarily investigated anti-TNFs, 13 pregnancies were also exposed to methotrexate (48). However, as previously described, it was impossible to link these exposures to underlying rheumatic disease or extract outcomes of these patients (48).

*Leflunomide*

Eight studies reported pregnancies exposed to leflunomide, including 1 case report (82), 1 case series (83), 2 cross-sectional studies (58, 78), 1 survey (to rheumatologists) (80), and 3 cohort studies (48, 81, 84). From 7 studies (58, 78, 80-84), we extracted information on 99 pregnancies exposed to leflunomide, of which 94 occurred in the absence of other DMARDs, 2 occurred in combination with an anti-TNF (78), and 3 occurred in combination with methotrexate (81). Among 78 live births, congenital abnormalities were reported in 7 infants: 1 set of twins, each with a patent ductus arteriosus in association with atrioseptal and ventricular septal defect, and coccygeal vertebrae dysplasia, respectively (82); 1 infant

**Table II.** Included studies for biologic DMARDs according to design.

| ID | Study | Design (data) | Rheumatic disease* | Case-specific data extracted§ |
|---|---|---|---|---|
| | | **Infliximab (IFX)** | | |
| (42) | Rosner 2007 (56) | Case series [D1] | RA, JIA | Y |
| 73 | Katz 2004 (90) | Cross-sectional study (R) [D1] | RA, JIA | N |
| (64) | Hyrich 2006 (78) | Cross-sectional study (R) [D1] | RA | Y |
| (44) | Ostensen 2008 (58) | Cross-sectional study [DM] | SLE, RA | Y |
| (66) | Chakravarty 2003 (80) | Survey (rheumatologist) [DD] | RA | Y |
| 74 | Berthelot 2009 (91) | Survey (rheumatologist) [D1] | SpA, RA | Y |
| (34) | Verstappen 2011 (48) | Cohort study (R) [D1] | RA, JIA | N |
| | | **Etanercept (ETA)** | | |
| 75 | Carter 2006 (87) | Case report [D1] | PSA | Y |
| (13) | Almarzouqi 2007 (27) | Case series [D2] | RA | Y |
| 76 | Roux 2007 (88) | Case series [D1] | RA | Y |
| (42) | Rosner 2007 (56) | Case series [D1] | RA, JIA | Y |
| 77 | Scioscia 2011 (89) | Case series [D1] | RA | Y |
| (64) | Hyrich 2006 (78) | Cross-sectional study (R) [D1] | RA | Y |
| (44) | Ostensen 2008 (58) | Cross-sectional study [DM] | SLE, RA | Y |
| (66) | Chakravarty 2003 (80) | Survey (rheumatologist) [DD] | RA | Y |
| (74) | Berthelot 2009 (91) | Survey (rheumatologist) [D1] | SpA, RA | Y |
| (34) | Verstappen 2011 (48) | Cohort study (R) [D1] | RA, JIA | N |
| | | **Adalimumab (ADA)** | | |
| (76) | Roux 2007 (88) | Case series [D1] | RA | Y |
| (64) | Hyrich 2006 (78) | Cross-sectional study (R) [D1] | RA | Y |
| (74) | Berthelot 2009 (91) | Survey (rheumatologist) [D1] | SpA, RA | Y |
| (34) | Verstappen 2011 (48) | Cohort study (R) [D1] | RA, JIA | N |
| | | **Rituximab (RTX)** | | |
| 78 | Sangle 2013 (92) | Case series [DD] | SLEn | Y |
| (44) | Ostensen 2008 (58) | Cross-sectional study [DM] | SLE, RA | Y |
| (65) | Chakravarty 2011 (79) | Cross-sectional study (R) [D1] | RA, SLE | N |
| | | **Ustekinumab (UST)** | | |
| 79 | Andrulonis 2012 (93) | Case report [D1] | PsA | Y |

* indicates underlying rheumatic disease of women with pregnancy exposures to DMARD under study. In studies involving women with other conditions (*e.g*. inflammatory bowel disease), we listed the two most representative rheumatic conditions studied.

§ indicates whether case-specific DMARD exposure(s) and congenital malformation outcome(s) was conducted; [D1] indicates primary drug of interest studied; [D2] indicates that drug is concomitant to a primary drug studied; [DM] indicates multiple drugs studied or reported in single paper including particular drug; [DD] indicates primary disease(s) studied with reporting of exposure to particular drug. SLE: systemic lupus erythematosus; RA: rheumatoid arthritis; SLEn: lupus nephritis; JIA: juvenile idiopathic arthritis; ASOD: adult-onset Still's disease; PAN: polyarteritis nodosa; R: registry data; T: teratology information service (TIS) data; A: administrative data.

**Table III.** Summary of studies that included a comparator group.

| ID | Study | Design | Rheumatic disease* | DMARD | Congenital exposure(s) | Outcome(s) malformation is primary outcome? | Reported congenital malformation outcomes? | | Reported risk estimates (OR/RR)? |
|---|---|---|---|---|---|---|---|---|---|
| | | | | | | | Exposed (/# pregnancies) | Unexposed (/# pregnancies) | |
| 28 | Andrade 2008 (42) | Case control | SLE | HCQ<br>CTX<br>CSP<br>AZA | N | 1. combined adverse outcome | N | N | N |
| 45 | Ramsey 1993 (59) | Cohort | SLE | AZA<br>CTX<br>MTX | N | 1. miscarriage<br>2. stillbirth<br>3. SGA<br>4. CM | 0 (/23) | 0 (/113) | N |
| 29 | Buchanan 1996 (43) | Cohort | SLE | HCQ | N | 1. miscarriage<br>2. prematurity<br>3. CM | 1 (/36) | 1 (/53) | N |
| 30 | Costedoat 2003 (44) | Cohort | SLE | HCQ | N | 1. miscarriage<br>2. prematurity<br>3. CM | 3 (/133) | 4 (/70) | N |
| 31 | Clowse 2006 (45) | Cohort | SLE | HCQ | N | 1. miscarriage<br>2. prematurity<br>3. CM | 1 (/79) | 1 (/163) | N |
| 46 | Goldstein 2007 (60) | Cohort (TIS data) | SLEn | AZA | Y | 1. prematurity<br>2. birth weight | 6 (/189)§ | 6 (/230)§ | OR 1.17§<br>(95%CI 0.37–3.69) |
| 47 | Langagergaard 2007 (61) | Cohort (administrative data) | SLE, PAN | AZA | N | 1. miscarriage<br>2. prematurity<br>3. CM | 6 (/64)§ | 49 (/1,243)§ | OR 2.3§<br>(95%CI 1.0–5.2) |
| 48 | Cleary 2009 (62) | Cohort (administrative data) | SLE | AZA | N | 1. miscarriage<br>2. prematurity<br>3. CM | All<br>30 (/476)§<br>Cardiac<br>7 (/476)§ | 55,548 (1,181,450) §<br><br>0 | OR 1.41§<br>(95%CI 0.98–2.04)<br>OR 2.82§<br>(95%CI 1.13–5.82) |
| 70 | Chambers 2010 (84) | Cohort (TIS data) | RA, JIA | LEF | N | 1. miscarriage<br>2. prematurity<br>3. CM | 3 (/56) | 4 (/95) | N |
| 34 | Verstappen 2011 (48) | Cohort (registry data) | RA, JIA | Gold<br>LEF<br>SZS<br>AZA<br>MTX<br>LEF<br>IFX<br>ETA<br>ADA | N | 1. miscarriage<br>2. prematurity<br>3. CM | 4 (/109) | 0 (/10) | N |
| 67 | Cassina 2012 (81) | Cohort (TIS data) | RA, JIA | MTX<br>LEF | N | 1. miscarriage<br>2. prematurity<br>3. CM | 2 (/16) | 0 (/27) | N |
| 32 | Levy 2001 (46) | Controlled trial | SLE | HCQ | N | Baby:<br>1. gestational age<br>2. Apgar score<br>Mother:<br>3. flares<br>4. skin changes<br>5. toxemia | 0 (/10) | 0 (/10) | N |

* indicates underlying rheumatic disease of women with pregnancy exposures to DMARD under study. In studies involving women with other conditions (*e.g.* inflammatory bowel disease), we listed the two most representative rheumatic conditions studied; § estimate obtained for entire cohort, which includes women without rheumatic disease.
HCQ: hydroxychloroquine; CTX: cyclophosphamide; CSP: cyclosporine; AZA: azathioprine; MTX: methotrexate; LEF: leflunomide; SZS: sulphasalazine; IFX: infliximab; ETA: etanercept; ADA: adalimumab; SGA: small-for-gestational-age; CM: congenital malformation.

with aplasia cutis congenita (81); 1 infant each with Pierre-Robin sequence, spina bifida occulta, patent ductus arteriosus, chondrodysplasia punctate with congenital heart block (81); 1 infant with occult spinal dysraphism (84); 1 infant with unilateral ureteropelvic junction obstruction and multicystic kidney disease (84), and 1 infant with microcephaly (84). Three infants had functional abnormalities including one infant each with sensorineural hearing loss (81), vesico-uteroreflux (84), and grade 2 hydronephrosis (84).

*Mycophenolate mofetil*

There were 8 studies reporting outcomes following exposure to MMF including 3 case reports (20, 53, 85), 1 case series (56), and 4 cross-sectional studies (38-39, 58, 79). From 7 studies, we extracted information on at least 44

pregnancies in women with rheumatic disease exposed to MMF (20, 38-39, 53, 56, 58, 85). At least 5 exposures occurred in combination with another DMARD such as hydroxychloroquine (20), azathioprine (53), or etanercept (56). There were 6 cases of congenital abnormalities including 3 infants with multiple severe abnormalities (39), 1 with bilateral moderate-to-severe microtia, external auditory canal atresia, bilateral conductive hearing loss, and mild microcephaly (20), 1 with severe facial clefts, preaxial limb anomalies, cardiovascular, gastrointestinal and urogenital malformations (53), 1 with tracheoesophageal atresia (39), and 1 non-communicating esophageal duplication (85). Of note, the mother of the infant described in the case report by Anderka *et al*. was also exposed to an ACE inhibitor (20) and the mother of the infant described by Somalanka *et al*. had concomitant exposure to an angiotensin receptor blocker (85). Finally, the cross-sectional study by Chakravarty *et al*. described co-exposure to MMF and Rituximab and, although two abnormalities were reported (see Rituximab section), the outcomes were not linked to either treatment indication (rheumatic disease versus other) or exposure to MMF (79).

*D-Penicillamine*

Three studies reported on pregnancy exposures to D-Penicillamine, including 1 case report (86), 1 case series (17), and 1 cross-sectional study (29). We extracted information on 3 pregnancies exposed to D-Penicillamine, resulting in 3 live births. Two exposures occurred in the absence of other DMARDs (17, 29). In a case report by Solomon *et al*., D-Penicillamine exposure in combination with chloroquine, and an infant with multiple congenital abnormalities resulting in neonatal death was reported (86).

**Biologic DMARDs**

*Anti-tumour necrosis factor (TNF) biologics*

Eleven studies reported outcomes of pregnancies exposed to anti-TNFs including 1 case report (87), 4 case series (27, 56, 88-89), 3 cross-sectional studies (58, 78, 90), 2 surveys (80, 91), and 1 cohort study (48). From 9 of the studies, we extracted information on 143 pregnancies exposed to anti-TNFs including 24 to infliximab, 99 to etanercept, and 20 to adalimumab. Thirty-six exposures occurred in combination with another DMARD, including methotrexate in 22 cases, leflunomide in 5 cases, azathioprine in 4 cases, sulfasalazine in 4 cases, hydroxychloroquine in 4 cases, and gold and MMF in one case each. There were 91 live births among which there were 3 congenital abnormalities including pyloric stenosis (48), congenital dysplasia of the hip (48), and VATER association (87). Katz *et al*.'s study, reported on 96 pregnancies exposed to anti-TNFs prescribed primarily for inflammatory bowel disease, and a small subset for RA. Of 68 live births, 2 children had congenital abnormalities, including tetralogy of fallot and intestinal rotation, and 1 child had developmental delay (90). The indication for the anti-TNF in the infant with intestinal malrotation was RA; however, the biologic was given in combination with leflunomide. The indication for therapy was not provided for the other two infants. Finally, while warranting mention in prior sections as patients had concomitant exposures, Verstappen *et al*.'s cohort study using data from the BSRBR primarily investigated anti-TNF pregnancy exposures among women with rheumatic disease, mostly RA (48). They reported 88 live births from 130 exposures to anti-TNF before or during pregnancy, noting 4 infants with congenital malformations – 2 among women exposed to anti-TNF alone during pregnancy and 2 among women exposed to anti-TNF alone prior to conception (Table III) (48). No risk estimates were provided and authors commented that no firm conclusions can be drawn on the safety of anti-TNFs based on their study.

*Rituximab*

Three studies reported pregnancy exposure to rituximab including 1 case series (92) and 2 cross-sectional studies (58, 79). Sangle *et al*. reported on 5 women who conceived 8 months or more after rituximab treatment was stopped and, therefore, do not represent a true exposure (92). Ostensen *et al*. reported on 3 SLE pregnancies exposed to rituximab resulting in two live births with no congenital anomalies (58). Finally, Chakravarty *et al*. reported on 153 pregnancies exposed to rituximab using manufacturer registry data; however, the indication and concomitant medications were not linked with the outcomes of 90 live births (79). Among infants, there were two with abnormalities including 1 with ventral septal defect, patent foramen ovale, and patent ductus arteriosus, and 1 twin with a clubfoot (79).

*Other biologics*

A case report of a PsA patient exposed to Ustekinumab during pregnancy reported delivery of an infant with no abnormalities (93).

**Discussion**

To our knowledge, there are no clinical practice guidelines on the management of rheumatic diseases and use of DMARDs in pregnancy. Clinicians' decisions are often based on the US Food and Drug Administration (FDA) classification system (94). Sulfasalazine is the only traditional DMARD assigned to category B and considered generally safe to use through pregnancy. Hydroxychloroquine, chloroquine, gold, and cyclosporine are assigned to category C, meaning the risk through pregnancy cannot be ruled out and must be weighed with the risk of withdrawing therapy. In the context of SLE where the risk of flare in pregnancy may be increased or withdrawal of hydroxychloroquine may lead to increased and sometimes serious flare (95), continuing therapy may be more beneficial than withdrawing therapy. However, in RA, which tends to remit in pregnancy (7), continuing these DMARDs may not be justified and the decision must be individualised to the patient. Azathioprine, MMF, and cyclophosphamide are assigned category D, meaning there is evidence of risk but azathioprine is sometimes continued in particular clinical conditions. Methotrexate and leflunomide are assigned category X and contraindicated in pregnancy. Patients

considering pregnancy must discontinue these medications according to their half-lives. However, there are cases of healthy pregnancies following exposure to these medications and therefore, in unplanned pregnancies, patients should be provided with a balanced overview of the risks. In terms of biologics, all anti-TNFs are under category B and Rituximab is assigned to category C. Of note, this system is largely based on animal studies and is limited in that once assigned, drug categories are generally unchanged despite addition of new data. As such, clinical decisions regarding the management of DMARDs during pregnancy should involve careful discussion with the patient, taking into account disease severity and, risk and implications to both the patient and her unborn child, while considering the available information and its quality.

With 79 articles, this is the largest systematic review to specifically address the use of DMARDs during pregnancy among women with rheumatic disease and the risk of congenital malformations. An important consideration was the extent of published information for each particular DMARD. We rigorously extracted data on pregnancy exposures to obtain a count of the number of studies, accounting for the fact that a particular study may describe more than one DMARD (singly or in combination). This led to a key finding that the number of included studies was less than ten for most drugs, except hydroxychloroquine (n=31), azathioprine (n=27), methotrexate (n=15), cyclophosphamide (n=14), and etanercept (n=10). However, given how drug exposures were reported in the papers, it was often not possible to assign a single study to a single drug exposure. As such, a paper that may have been assigned as primarily studying a particular drug, such as Almarzouqi *et al*.'s case series (27) reporting on gold exposures and assigned "D1" for gold, may have also been assigned as one reporting a concomitant exposure to another drug, for example, hydroxychloroquine "D2" (Table I). Of note, the five aforementioned drugs also represent the most primarily studied drugs or having "D1" assignment (hydroxychloroquine 10, azathioprine 6, methotrexate 9, cyclophosphamide 8, etanercept 7).

Along with the extent of the published information, we also considered the quality of publications, according to study design. Since pregnant women are excluded from clinical trials, research on pregnancy exposures and outcomes is largely based on observational studies. The majority of studies were descriptive in nature and lacked comparator groups, precluding the ability to evaluate associations between DMARD pregnancy exposure and congenital malformation outcomes. Nonetheless, case reports and case series allowed the extraction of case-specific data, as well as detailed data on dosage and timing of exposure in pregnancy, and thus will remain important since outcomes such as congenital malformations may be clinically significant although previously undescribed. While cross-sectional studies provided descriptions over a larger number of women (and pregnancies), they were more limited given our inability to extract case-specific data – for example, actual DMARD(s) used, timing of exposure, and specific outcomes. We identified a much smaller number of analytic observational studies (n=12) (Table III). Of these, only 1 cohort study by Goldstein *et al*. evaluated a specific DMARD exposure (azathioprine) and primary congenital malformation outcomes (60). Eight studies did not report risk estimates (odds ratios or relative risks) for congenital malformations and the 3 studies (60-62) that did were based on cohorts that included women with rheumatic disease as well as other indications, primarily inflammatory bowel disease (IBD), with no reported disease-specific estimates. As in cross-sectional studies, we also found a limitation in that we could not extract case-specific exposures and outcomes from included analytic observational studies.

Taking together considerations on the extent and quality of published evidence, there are key conclusions that can be drawn from our systematic review. First, for drugs that represent the majority of included studies, findings are in line with recommendations or current attitudes towards safety of particular medications. For example, we synthesised 10 congenital malformations out of 294 live births that we could ascertain exposure to hydroxychloroquine, which approximately corresponds to a malformation rate of 3.4% (compared to rate in the general population of approximately 3%). Methotrexate represents another well-studied drug in our review and we synthesised 6 congenital abnormalities out of 64 live births, which correspond to a malformation rate of 9.4%. Indeed, as controlled trials in this patient population are unlikely, observational studies will continue to be important in this area; however, there is need for improved future studies. Specifically, from our data extraction and synthesis, we put forward recommendations for future studies to include detailed information on timing of exposure during pregnancy, which we found to be an important limitation with many studies we included. Also an important consideration for future research is the type of data, particularly consideration of emerging data resources. While the majority of included studies were based on medical chart or record data, a few were based on registry data such as the BSRBR (48) and administrative data (61-62). Despite limitations of these data, which may include lack of information on comorbidities or disease activity, advantages such as information on medication use (of potentially both exposed and non-exposed women) and outcomes (of potentially both mother and infant) allow for evaluation of associations.

Our synthesis expands on the small number of systematic reviews on the impacts of DMARDs during pregnancy in rheumatic diseases, which to our knowledge are limited to methotrexate (96), hydroxychloroquine (97), and biologics (8). As with these works, we solely focused on women with rheumatic diseases for reasons including the fact that in contrast to IBD (98), there is consistent evidence on the impact of rheumatic diseases on congenital malformations (99, 100). Furthermore, by focusing on rheumatic diseases, this systematic review addresses an important clinical question in rheumatology. Nonetheless, experiences in other patient populations may be drawn from, particularly for less-studied DMARDs

in rheumatology such as sulfasalazine, which has received greater study in IBD (101-103). However, despite providing a comprehensive synthesis of the published information on DMARDs and congenital malformations, no clear recommendations can be drawn from our systematic review. Another limitation that arose was assigning exposures in instances where more than one drug was reported. While this reflects actual clinical practice, we attempted to ameliorate this challenge by indicating whether a study was reporting a primary drug of interest, reporting on a concomitant drug to a primary drug studied, reporting on multiple drugs or studying a disease primarily but with reporting of exposure to a particular drug. Finally, we specifically focused on congenital malformations, although we extracted information on other outcomes such as stillbirths and prematurity whenever possible.

## Conclusion

Overall our systematic review describes the extent and quality of published data on use of traditional and biologic DMARDs during pregnancy among women with rheumatic diseases and congenital malformation outcomes and highlights the need for future, well-designed, observational studies that report detailed medication exposure data.

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