A Systematic Review of the safety of non-TNF inhibitor biologic and targeted synthetic drugs in rheumatic disease in pregnancy

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ABSTRACT

Introduction: Despite increasing evidence to support safe use of tumour necrosis factor inhibitors (TNFi) and other biologic disease modifying anti-rheumatic drugs (bDMARDs) during pre-conception/pregnancy, there remains a paucity of evidence regarding the safety and compatibility of other non-TNFi and novel targeted synthetic (ts)DMARDs during pre-conception/pregnancy. Therefore, we conducted a systematic review to determine the compatibility of these drugs in pre-conception, during pregnancy and post-partum period.

Method: Databases including; EMBASE, Pubmed (MEDLINE), and Cochrane were searched up to 23rd October 2020 to find relevant peer-reviewed papers, using keywords including; rheumatic disease, pregnancy, conception/pre-conception, lactation/breastfeeding, childhood and vaccination/infection, and commonly prescribed non-TNFi drugs and tsDMARDs.

Results: Our search yielded 1483 papers that were screened independently by two authors, and 109 full-text papers were eligible for final analysis. These studies reported 1291 maternal pregnancies exposed to non-TNFi bDMARDs and tsDMARDs with known outcomes, including 721 live births, 219 spontaneous miscarriages and 27 congenital abnormalities. Paternal exposures in 174 pregnancies had reassuring outcomes. A total of 48 breast-fed infants were exposed to non-TNFi bDMARDs and no adverse events reported upon long-term follow-up. Fifteen infants exposed to bDMARDs received normal vaccination regimes, including live vaccines, and had normal developmental outcomes, without any complications or infections.

Conclusion: Overall, the findings are reassuring and do not suggest a cause for any major concerns or an increased risk of adverse pregnancy outcomes for maternal or paternal exposures to non-TNFi bDMARDs or tsDMARDs. There were no major concerns for breastfeeding exposures to non-TNFi bDMARDs.

Key Words: Rheumatic disease, pregnancy, biologic, targeted synthetic drugs, disease modifying anti-rheumatic drugs, breast feeding.

1. Introduction

Women with an inflammatory rheumatic disease (IRD) such as rheumatoid arthritis (RA) and systemic lupus erythematosus (SLE) have an increased risk of experiencing adverse pregnancy outcomes (APO) [1–4]. This risk is increased if conception occurs during poorly controlled disease activity. These risks are well established in SLE and RA and include miscarriages, premature delivery, hypertensive disorders (13-23%) or intrauterine growth restriction (5%) [1–3,5].

Consequently, women of reproductive age with an IRD who attain disease control with a biologic disease modifying anti-rheumatic drug (bDMARD) may become pregnant on these drugs. Commonly utilised bDMARDs may be distinguished by their ability to inhibit tumour necrosis factor alpha (TNF) and are thus known as TNF inhibitors (TNFi) or non-TNFi. In addition, a new class of targeted synthetic (ts)DMARDs are now part of standard management regimes for many IRD.

The question of safety of these drugs in women with IRD during pregnancy is important to address because maintenance of disease control during pregnancy is required to increase the chance of successful pregnancy outcomes. Evidence-based guidance documents from the British Society of Rheumatology (BSR) [6,7], European League Against Rheumatism (EULAR) [8] and American College of Rheumatology (ACR) [9] discuss the utility of a variety of anti-rheumatic drugs, including bDMARDs and tsDMARDs in pregnancy.

Overall, these documents describe TNFi as being compatible with pregnancy with recognition that if certain TNFi with high rates of placental transfer are given in the third trimester the infant should not then receive live vaccines until six months of age. Recommendations however, on use of non-TNFi bDMARDs and tsDMARDs in pregnancy are less robust given their more limited evidence base.

This limited information leads to uncertainty around their use in pregnancy, thus consequent withdrawal of treatment from pregnant women unnecessarily [10]. Discontinuation of treatment in preparation for/during early pregnancy can increase the risk of disease activity, and flares during pregnancy are reported following discontinuation of biologics in patients with IRD [11]. Breastfeeding mothers may also be concerned about the effects of the transfer of medications through breastmilk.

Questions also arise regarding prescription of drugs, including bDMARDs and tsDMARDs to breastfeeding mothers, and in men. There may be concerns about the effect on male fertility, medication associated teratogenicity, or seminal fluid transfer to the mother during unprotected sexual intercourse in pregnancy. There is little evidence relating to the safety of DMARDs in men with IRD wishing to conceive. Data available are based mainly on animal or in vitro experimental data, as relevant human evidence is often lacking. Paternal exposure to DMARDs have rarely been reported to result in infertility [12,13]. In contrast, animal studies have established that thalidomide has an adverse impact on male fertility, via transfer into seminal fluid at low concentrations penetration into sperm cells [14,15]. Similarly, cyclophosphamide has a direct adverse impact on spermatogenesis and can cause infertility [13,16–18].

Additionally, unplanned pregnancies are not uncommon (an estimated 44% of pregnancies are accidental worldwide) [19]. Male and female patients with rheumatic disease may present to healthcare professionals following either accidental exposure, or accidental conception whilst taking a medication. In this situation, any data relating to pregnancy outcomes could help to inform patients and their healthcare professionals when making difficult decisions about future pregnancy care.

Therefore, we have conducted this systematic review to ask whether non-TNFi biologics and tsDMARDs may be safely given in pregnancy, breastfeeding, during post-partum vaccinations and in men wishing to conceive.

2. Methods

A systematic literature search of databases including; EMBASE, PubMed/MEDLINE, and Cochrane from inception to 23rd October 2020 was conducted using guidelines of preferred reporting items for systematic reviews (PRISMA) [20]. Our keyword search terms related to individual non-TNFi bDMARDs and tsDMARDs, pregnancy, paternal and childhood exposures plus vaccination. Search terms are shown in Box 1.

2.1 Protocol and Registration

This systematic review was registered in the International Prospective Register of Systematic Reviews (PROSPERO) database (record ID: CRD42020219710). It is available online at https://www.crd.york.ac.uk/prospero.

2.2 Inclusion criteria

Relevant papers and published registry data reporting maternal and paternal exposures to non-TNFi bDMARDs and tsDMARDs and pregnancy outcomes, maternal and/or fetal long-term health outcomes during post-partum follow-up, and/or neonatal vaccination outcomes were included.

2.3 Exclusion criteria

Non-peer reviewed abstracts, reviews, animal or *in-vitro* studies, and non-English language papers were excluded. Letters not including unpublished original data were excluded. Published studies describing pre-/during pregnancy exposure of patients to cancer chemotherapy and/or transplantation were excluded due to different dosing regimens and underlying disease processes.

2.4 Study selection

Titles and abstracts were independently reviewed by two authors, and relevant papers were selected for full-text review. Any disagreement was resolved by discussion. Reference lists of relevant reviews and included papers were checked for additional original papers.

A data extraction sheet was designed and piloted using three papers. The final version included study design and methodology, number and description of women (or paternal exposure), time-points of drug exposure in pregnancy, number and description of any control group, pregnancy outcomes, maternal/infant health post-partum/during breastfeeding period. Study limitations were also documented. Limitations were considered and results summarised. The quality of evidence available per drug was assessed using the GRADE methodology [21].

3. Results

From the initial search of 1483 papers, a total of 109 mostly very low GRADE evidence quality articles were selected for final analysis (Figure 1). Eligible studies included 1291 maternal pregnancies and 174 paternal exposures to non-TNFi bDMARDs or tsDMARDs. None of the selected studies included control pregnancies. From known outcomes of 721 live births there were 219 spontaneous miscarriages and

27 congenital abnormalities. A total of 48 breast-fed infants exposed to these drugs were identified, and no adverse events were reported on long-term follow-up. Fifteen infant cases exposed to non-TNFi bDMARDs received normal vaccination regimes, including live vaccines, with no complications or infections reported on follow-up. Drugs are grouped according to size and structure as follows: monoclonal antibodies (immunoglobulins directed against specific targets containing Fc chain, thus capable of active placental transfer via neonatal fragment of crystallisable component/Fc receptors (FcR) present on syncytiotrophoblast in second/third trimester placental transfer); recombinant fusion proteins (that may/may not contain Fc chain); and targeted synthetic DMARDs (small molecule inhibitors of much lower molecular weight that could theoretically cross the placenta).

3.1 Maternal exposures to non-TNFi bDMARDs and tsDMARDs

Results for monoclonal antibodies are shown in Table 1. These monoclonal immunoglobulins all contain the Fc region.

3.1.1 Rituximab pregnancy outcomes

Table 1 shows 51 studies reporting pregnancy cases exposed to rituximab at various time points before/during pregnancy; 32 case reports [22–48], 10 case series [49–58] and 9 cohort studies [59–66]. A total of 269 pregnancies were exposed to rituximab: within 6-12 months pre-conception only (n=127); at preconception and during pregnancy (n=114); and from 6 weeks up to 12 months post-partum (n=28). Disease indications included RA, SLE, anti-phospholipid syndrome (APS), vasculitis, lymphoma, immune thrombocytopenic purpura, MS, pemphigus vulgaris (PV), myasthenia gravis (MG), neuromyelitis optica (NMO) and atopic dermatitis.

Of 262 known pregnancy outcomes reported, there were 188 live births (two sets of twins), 37 early spontaneous miscarriages, 2 late term miscarriages (2^{nd}/3^{rd} trimester), 3 still births (one preterm twin), 32 elective terminations and 2 infant cases with congenital abnormalities (one clubfoot in a twin and cardiac malformation in a singleton birth). 39/188 live births were <37 weeks and/or had low birth weight (one preterm twin), and 1 full term infant had a perinatal stroke (Table 1). Concomitant medication in patients with miscarriage included: 5 methotrexate within 6 months of conception; 1 mycophenolate mofetil and prednisolone (time-points unreported); 2 leflunomide stopped in the first trimester and received cholestyramine [59]. One infant had a perinatal stroke at full-term delivery from a mother with MS treated with rituximab 9.5 months pre-pregnancy [62]. In 5 neonates haematological abnormalities included transient neonatal lymphopenia and B cell depletion up to 6 months post-partum without infectious complications [34,39,41,47,67]. Perinatal infections occurred in 4 neonates [61]. Two maternal deaths occurred; 1 mother with lupus nephritis had an unplanned pregnancy complicated by hypertensive crisis and hemorrhagic stroke [50] and 1 mother died from pre-existing auto-immune thrombocytopenia [61].

Two cohort studies including control groups described 4 pregnancy outcomes of mothers with MS and pre-conception exposure to rituximab and 698 MS non-RTX exposed pregnancies [63,64]. They reported 3 (n=1 <37 weeks) live births and 1 unknown outcome from RTX exposed compared with 371 (n=104 <37 weeks) live births, 1 ectopic pregnancy, 42 spontaneous miscarriages, 2 congenital malformations, 37 induced abortion and 113 unknown outcomes from control pregnancies [63,64].

3.1.2 Belimumab pregnancy outcomes

Seven studies including 5 case reports [68–72] and 2 double blinded, open-label randomised clinical trials (RCT) [73,74] of belimumab in SLE were identified, Table 1. A total of 63 pregnancies were exposed to belimumab: within 12 months preconception only (n=1); to first trimester (n=2); to second trimester (n=2); throughout pregnancy and breastfeeding (n=3); breastfeeding only (n=1); and unknown timepoints (n=54). Pregnancy outcomes included 27 live births (one twin), 13 spontaneous miscarriages, 1 stillbirth, 10 elective terminations, and 4 major congenital abnormalities, detailed in Table 1 [69,71,73]. Overall, 11 patients with 4 live births and 7 fetal losses were anti-cardiolipin (aCL) positive [73]. Reporting of concomitant medications was not always specific to pregnancy and included corticosteroids, antimalarials, immunosuppressives, non-steroidal anti-inflammatory drugs, and angiotensin pathway anti-hypertensives. There were limited comparisons with non-belimumab exposed pregnancies.

3.1.3 Tocilizumab pregnancy outcomes

A total of 11 studies including; 4 case reports [75–78], 3 case series [79–81] and 4 cohort studies [82–85] reported on 385 pregnancies (Table 1). Exposure to tocilizumab occurred: between 3 weeks to 15 months preconception (n=100); preconception and during first trimester (n=22); during first trimester (n=200); during second and third trimesters (n=21); from preconception and throughout pregnancy and breastfeeding (n=5); during breastfeeding only (n=4); and at unknown time-points (n=33). Disease indications included RA, juvenile idiopathic arthritis (JIA); adult onset stills disease (AOSD); systemic sclerosis; Takayasu's arteritis and PsA. Known outcomes from 377 pregnancies were: 230 live births (n=3 sets of twins); 82 spontaneous miscarriages; 2 second trimester fetal deaths; 2 still births (n=1 at 25 weeks in a mother on concomitant methotrexate concomitantly and n=1 neonatal asphyxia); and 61 elective terminations (Table 1).

The largest study of 288 pregnancies from a global safety database found live births before 37 weeks gestation in 35/110 (31.8%) pregnancies reporting gestational age at birth (prospective and retrospective data). Additionally, they reported spontaneous abortion in 31.7% of patients with prospective data collection, although 21% of patients were on concomitant methotrexate in this prospective cohort [83]. The authors concluded that there was no increased risk of congenital malformations but could not exclude an increased risk of preterm and low birth weight infant outcomes and speculate whether discontinuation of tocilizumab in the first trimester may lead to high disease activity later in pregnancy and thus an adverse impact on pregnancy outcomes.

A multicentre prospective registry study investigating the safety of corticosteroids and/or bDMARDs in juvenile patients, included outcomes from 9 JIA pregnancies exposed to non-TNFi biologics [85]. Of these 7 were exposed to tocilizumab three months pre-conception and 4 in the first trimester. Collectively reported outcomes for pregnancies exposed to non-TNFi biologics were: 2 elective terminations; 1 minor congenital anomaly; 6 live births; and no major congenital anomalies/miscarriages [85].

Three case series [79–81], reported on 22 mothers with RA following preconception/first-trimester exposure to tocilizumab, and pregnancy outcomes included 16 live births (n=2 <37 weeks). Additional pregnancy outcomes reported were: 1 mother who was diagnosed with a partial molar pregnancy and had a miscarriage at 11 weeks [79]; 4 spontaneous abortions; and 1 elective termination for personal reasons [81].

There was incomplete reporting of concomitant medication, such as other biologics, corticosteroids, non-steroidal anti-inflammatory drugs [80], and other DMARDs including methotrexate [81,82]. One study reported 8/16 RA mothers (50%) had one/more of the following concomitant diseases:

hypertension, fibromyalgia, depression, eating disorder, polycystic ovarian syndrome, hypothyroidism, Hashimoto-thyroiditis, cholelithiasis, nephrolithiasis, and thrombophilia due to a heterozygote prothrombin mutation [81]. Of these 16 pregnancies there were: 11 live-births; 4 spontaneous miscarriages; and 1 elective termination.

Other small case-series [79] of 4 RA pregnancies (with n=3 live births all >37 weeks and n=1 miscarriage) and case reports [75–78] of 4 pregnancies, all resulted in full-term live births without complications, thus were reassuring.

3.1.4 Secukinumab pregnancy outcomes

Four studies including 3 case reports [86–88] and 1 cohort study [89] reported on 241 pregnancies from mostly (n=155) preconception period and first trimester exposure to secukinumab. Disease indications included psoriasis, psoriatic arthritis (PsA) and ankylosing spondylitis (Table 1). From the cohort study, 50% of pregnancy outcomes [89] were unknown as they were either lost to follow-up (39.5%) or ongoing in pregnancy (10.5%). No distinctive differences were observed in pregnancy outcomes between different inflammatory conditions. Outcomes from 238 pregnancies with preconception/first trimester exposure included a total of 53 live (n=46 full-term healthy infants) births, 26 spontaneous abortions (up to 20 weeks), 36 elective terminations, 3 ectopic pregnancies and 2 congenital malformations. Outcomes from 18 mothers with second/third trimester exposure were 1 healthy live birth, 4 elective terminations, 3 spontaneous abortions, 1 ongoing pregnancy and 9 cases lost to follow-up/unknown outcomes [89]. The authors concluded that there were no major safety concerns and the rate of APO were similar to the general population.

Two case reports were both confounded by severe maternal disease: 1 first trimester miscarriage in the sixth pregnancy of 40 year old mother on concomitant medication including methotrexate [86] and an intrauterine death at 38 weeks in a pregnancy complicated by intrauterine growth restriction (IUGR) and second trimester exposure to secukinumab [88].

3.1.5 Ustekinumab pregnancy outcomes

A total of 20 studies including 10 case reports [90–98] and 9 case series [99–107] reported on 41 pregnancies exposed to ustekinumab (Table 1). This drug exposure occurred: up to 8 months preconception (n=3); to first trimester (n=24); to second trimester (n=3); to third trimester (n=2); throughout pregnancy and breastfeeding (n=3); and during breastfeeding (n=6, of which 2/6 were stopped preconception and restarted during breastfeeding, and 1/6 was stopped in second trimester and restarted during breastfeeding). Disease indications included psoriasis, PsA, RA, JIA, MS, vasculitis and inflammatory bowel disease. Of 40 known outcomes there were 36 live births (1 set of twins and n=3 ≤ 37 weeks), 2 first trimester miscarriages; 1 spontaneous miscarriage (unknown gestation), and 1 elective termination. Of 19 cases where birthweight was reported, there were 2 cases with low birth weight.

A case series study [101] described 10 pregnancies in 7 mothers with chronic plaque psoriasis exposed to ustekinumab in first (n=9) and second (n=1) trimester, with no other concomitant medications in pregnancy. Overall pregnancy outcomes were favourable, with 8 healthy infants (all full-term aside from one delivery at 36 weeks) and 2 miscarriages [101]. Case reports of adverse outcomes such as first trimester miscarriage [90] and premature delivery [92] were complicated by severe maternal disease.

3.1.6 Canakinumab pregnancy outcomes

Two studies, 1 case report [108] and 1 cohort study [109], reported 9 pregnancy outcomes from pre-conception and/or mostly first trimester pregnancy exposure to canakinumab in patients with various auto-inflammatory diseases (Table 1). Of 9 pregnancy exposures there were 8 live births and 1 spontaneous miscarriage, with no congenital anomalies/premature/low birthweight babies reported. One infant had a genetic mutation consistent with maternal diagnosis of Muckle-Wells syndrome. Two mothers with cryopyrin associated periodic fever syndrome (CAPS) received concomitant anakinra until 8 and 36 weeks of pregnancy and then continued on anakinra alone, one of whom had gestational diabetes at an unknown time-point [108,109].

3.2 Recombinant fusion proteins

Results for these drugs are shown in Table 2. Anakinra is a recombinant form of human IL-1 receptor antagonist that does not contain any Ig structure, hence lacks the Fc region, and Abatacept contains the Fc region of IgG1 fused to the extracellular domain of CTLA-4.

3.2.1 Abatacept pregnancy outcomes

A total of 6 studies including; 1 case report [110], 1 case series [51] and 4 cohort studies [60,85,111,112] reported on 165 pregnancies after first trimester (n=163) and up to third trimester (n=2) exposure. Disease indications included RA, PsA, JIA, spondyloarthropathies, dermatomyositis, Behçet's disease, and psoriasis (Table 2). Of 156 known outcomes, there were: 94 live births; 39 early spontaneous miscarriages; 1 late spontaneous miscarriage at 21 weeks; 22 elective terminations; and 7 major congenital anomalies. Data regarding the 7 infants with congenital anomalies were retrieved from the Bristol-Myers Squibb safety database, and although clinical information on maternal disease was lacking, 20 mothers were also exposed to methotrexate and no specific pattern of congenital anomalies was identified following maternal exposure to abatacept [111]. Case reports of exposure in RA pregnancy with concomitant DMARDs and corticosteroids, were reassuring with healthy full-term deliveries reported [51][110].

3.2.2 Anakinra pregnancy exposures

A total of 8 studies including 4 case reports [113–116], 4 case series [117–120] and 3 cohort studies [60,85,109] reported on 59 pregnancies exposed to anakinra. Pregnancy exposures occurred during preconception (n=1); to first trimester (n=5); to second trimester (n=2); to third trimester (n=4); preconception to post-partum/breastfeeding (n=20); started during pregnancy (n=13); and with unknown time-points (n=14). Disease indications included AOSD, RA, JIA, PsA, familial mediterranean fever (FMF), CAPS, TNF receptor-associated periodic fever syndrome, spondyloarthropathies (TRAPS), dermatomyositis, and Behçet's disease. Of these 59 pregnancies, there were 54 live births (1 set of twins and n=6 ≤ 37 weeks); 1 spontaneous miscarriage; 3 elective terminations; 1 fetal death at 30 weeks gestation (renal agenesis in a twin pregnancy). There was 1 major congenital malformation (Table 2).

A case series of 5 mothers (n=3 AOSD and n=2 systemic JIA) reported successful pregnancy outcomes following antenatal exposure to anakinra in the first/second (n=4) and third (n=5) trimester [117]. Pregnancy outcomes included 5 full-term live births with 1 low birth weight infant delivered by caesarean-section (medically indicated for pregnancy-induced hypertension and low fluid levels) and no major congenital anomalies.

Two case reports of mothers exposed to anakinra in second/third trimesters were confounded by severe maternal disease with haemophagocytic lymphohistiocytosis (HLH). Outcomes included 2 live births, 1 preterm (31 weeks and 5 days), both delivered via emergency caesarean-section due to slowed fetal growth, and one neonate presented with severe marrow suppression that required red cell transfusion. Both mothers received concomitant corticosteroids and one had intravenous immunoglobulin treatment [115,116].

3.3 Targeted synthetic DMARDs

Results for these drugs are shown in Table 2, that are small molecule inhibitors of much lower molecular weight that could theoretically cross the placenta.

3.3.1 Tofacitinib and Baricitinib pregnancy outcomes

Two studies, 1 cohort [121] and 1 RCT [122] have reported 58 pregnancies exposed to tofacitinib: to first trimester (n=45); to second trimester (n=1); or throughout pregnancy to third trimester (n=12) with no post-partum/breastfeeding exposures reported. Disease indications included ulcerative colitis, RA, psoriasis, PsA, Table 2. Of these 58 pregnancies, there were 48 known pregnancy outcomes: 29 live births including 1 infant with major congenital anomaly; 9 spontaneous miscarriages (n=4 mothers treated with tofacitinib only and n=3 mothers received tofacitinib and methotrexate 20mg/week); 10 elective terminations (n=1 decision based on potential risks of tofacitinib and n=9 unknown); and no fetal deaths/neonatal deaths [121,122]. There was only one case report [123] of an RA pregnancy exposed to baricitinib from pre-conception up to 17 weeks gestation with a healthy infant delivered at 38 weeks gestation by caesarean section.

3.4 Paternal exposures to non-TNFi bDMARDs and tsDMARDs and pregnancy outcomes

Compared with maternal drug exposure findings, there is even less evidence on the impact of peri-conception drug exposure in men on their offspring. We identified 8 studies reporting a total of 174 paternal exposures including; 2 case series [81,121], 5 cohort studies [61,83,89,109,111] and 1 RCT [124] to rituximab (n=22), tocilizumab (n=24), secukinumab (n=54), abatacept (n=6) anakinra (n=10) and tofacitinib (n=58) respectively, as shown in Table 3.

From these exposures there were 116 known pregnancy outcomes: 93 full-term live births; 1 preterm live birth, exposed to secukinumab; 19 spontaneous miscarriages (including n=10 first trimester) and 3 elective terminations. There was one major congenital abnormality following paternal exposure to secukinumab, where the father was not exposed to any other concomitant treatments [89]. For the paternal cases exposed to all other drugs, no other adverse outcomes were reported.

3.5 Post-partum follow-up, breastfeeding and vaccination outcomes

Table 4 shows post-partum follow-up data reported in a total of 93 infants exposed to rituximab (n=34), belimumab (n=4), tocilizumab (n≥6), ustekinumab (n=6), canakinumab (n=7), abatacept (n=18), anakinra (n≥17) and baricitinib (n=1), for periods ranging from 6 weeks to 4.5 years [51,111].

Minimal complications were reported for all drugs. Two infants exposed to rituximab experienced mild asthma [31] and multiple infections [59] respectively, whilst the remaining 32/34 infants followed-up had no complications reported [23,24,27,32,35,37–41,43,46,51,58,59,125]. One infant exposed to anakinra had a low platelet count at birth, which was treated by three infusions of intravenous immunoglobulin and normalised at 2 months post-partum follow-up [119]. Overall, the long-term outcomes for all infants where follow-up details were available concluded that infants had normal developmental outcomes, with no adverse events reported.

Breastfeeding was reported in 48 infants exposed to: rituximab (n=28) [23,35,37,41,62]; ustekinumab (n=3) [96,98]; canakinumab (n=4) [109] and anakinra (n=13) [109,114,117] without any complications. Of 28 infants breastfed by mothers receiving rituximab; 24 infants were breastfed within 12 months of mothers resuming rituximab post-partum, and no developmental problems were reported [62]; 1 infant was born with mild rhinitis and conjunctivitis at one month follow-up, and the infant developed normally with no neurological/other abnormalities occurring at 24 months follow-up [35]; 1 infant was reported to have normal development up to 1.5 years follow-up [23]; 1 infant from a mother resuming rituximab at 4 and 6 weeks post-partum had demonstrated normal growth milestones and there were no infectious concerns up to 9 months of follow-up [37]; and 1 infant had a normal development, no infections and normal B-cell counts reported at 6 month follow-up [41]. One infant out of 3 breastfed by mothers receiving ustekinumab had normal physical and mental development at 12 months follow-up [98] and 2 infants had normal growth curve reported (follow-up period unknown) [96]. Four infants breastfed by mothers receiving canakinumab had no reported serious infections/developmental abnormalities at a mean follow-up period of 2.2 years (range 5 months to 4 years) [109]. Out of 13 infants breastfed by mothers taking anakinra for up to 10 months; 10 infants had no infections/developmental abnormalities reported [109]; 1 infant had a steady growth and inconspicuous psychomotor development during follow-up [114]; and 2 breastfed infants had no follow-up information available [117].

Fourteen studies reported on 15 infants that received routine (including live) vaccinations after birth without any significant adverse events: rituximab (n=5) [32,39,41,46,125], belimumab (n=2) [68,126], tocilizumab (n=4) [76,78,80], ustekinumab (n=2) [94,103], abatacept (n=1) [110] and baricitinib (n=1) [123]. Only 1/15 infant exposed to rituximab had vaccinations delayed until 3 months of age when infant's CD19+ B cell count was 19.8% [125]. Infants received the following vaccinations: rotavirus (at 6 weeks), diphtheria–tetanus–pertussis, haemophilus influenzae type b and pneumoccocus (at 3 and 5 months), inactivated polio vaccine, Bacillus Calmette–Guérin (BCG), and hepatitis B.

4. Discussion

In our systematic review we found generally reassuring pregnancy outcome data following maternal and paternal exposures to non-TNFi bDMARDs and novel tsDMARDs for rheumatic disease. Maternal exposures did not appear to display increased rates of APO with any specific drug compared to the general population rates, such as congenital anomalies 2.7 % (27/1000 live births) [127] and miscarriages 8.3% (83/1000 live births) [128]. Similarly, evidence relating to paternal exposure, breastfeeding, use of live vaccines and long-term follow-up in children born to exposed mothers was reassuring but data remains limited.

Existing guidelines and recommendations for prescribing drugs in pregnancy and breastfeeding [6–9] have all produced statements on use of various medications in pregnancy based upon systematic evidence reviews. Given the work involved in finalising each of these documents, the associated systematic reviews are inevitably 2-3 years outdated by the time of publication. The 2020 ACR guidelines for the management of reproductive health in rheumatic and musculoskeletal diseases contain recommendations based on a systematic review in May 2017 and a paucity of data for many medications [9]. Therefore, continued surveillance of published data is required to update healthcare professionals on cumulative pregnancy exposures and risk to mother/baby with individual drugs.

Two recent articles have systematically reviewed maternal and neonatal outcomes from pregnancy exposure to biologic drugs. Tsao et al [129] conducted a meta-analysis of 24 studies comparing

pregnancy outcomes in biologic and non-biologic exposed pregnancies and did not find any association between biologic exposure and congenital malformation, pre-term birth or low birth weight. Ghalandari et al. [130] systematically reviewed 143 studies, primarily considered data on miscarriages and congenital malformations from biologic pregnancy exposures, and did not report any major safety issues. There are important methodological differences between these studies and our own, such that each yields distinct and useful information upon biologic use in pregnancy. The meta-analysis of Tsao et al. [129] calculated potential risks of all biologics as a whole and the majority (19 of 24) of articles analysed only considered TNFi biologic outcomes. The broader range of articles systematically reviewed by Ghalandari et al. [130] described outcomes from pregnancy exposures to TNFi and non-TNFi biologics separately and also additional secondary outcomes such as vaccination response and detectable drug levels during different stages of conception and pregnancy. In contrast, we have focussed solely on pregnancy outcomes from exposures to non-TNFi biologics as well as tsDMARDs and considered paternal and breastfeeding exposures, as well as long-term outcomes in children potentially exposed in utero.

Overall, our findings agree with these other recent systematic reviews [129,130] and have not identified any evidence of an increased risk of APO compared to the general population, when considering either non-TNFI and tsDMARDs as a whole, by mode of inhibition or as individual drugs. The increasing body of evidence from ours and other recent systematic reviews should be viewed as useful adjuncts to existing guidelines/recommendations [6–9], particularly where either conditional or no recommendations could be made due to lack of evidence.

Consideration of drugs according to size and structure is also important. Biologic drugs containing Fc region (all monoclonal antibodies and certain recombinant fusion proteins) undergo active placental transfer. There is minimal data on actual degrees of placental transfer and fetal/neonatal drug levels for non-TNFi DMARDs and advice on potential discontinuation of these drugs in current guidance [7–9] is based upon theoretical knowledge of limited placental transfer of IgG in first trimester and lack of harm with a small number of reported pregnancy exposures.

The BSR guidelines [7] found insufficient evidence to recommend non-TNFi (rituximab, belimumab, tocilizumab, anakinra and abatacept) in pregnancy, whilst the equivalent EULAR recommendations [8] (covering the same non-TNFi with the addition of ustekinumab) were that these drugs should only be used during pregnancy when no other pregnancy-compatible drug can effectively control maternal disease. The more recent ACR guidance [9] has provided conditional recommendations for maternal use of RTX, stating it can be used pre-conception, but then should only be continued if there is severe maternal life/organ threatening disease. For other non-TNFi (belimumab, tocilizumab, secukinumab, ustekinumab abatacept and anakinra) however, the ACR guidance conditionally recommends against their use in pregnancy unless maternal disease cannot be controlled with other pregnancy compatible medications. In this case, possible risks from these medications versus the risks of uncontrolled disease during pregnancy should be discussed. The increasing evidence base reporting safety of these drugs provided by this and other recent systematic reviews will inform these risk-benefit conversations between healthcare professionals and patients, either during pregnancy planning conversations and/or following accidental exposure to these drugs at conception.

Other non-TNFi bDMARD (canukinumab) have not been covered in any of the published guidelines to date, and we found limited evidence. Reassuringly, 8 of 9 pregnancy exposures to canukinumab [108,109] reported healthy live births, and normal development in all 7 infants for whom follow-up data were available [109]. Therefore, although it is not yet possible to make recommendations for use of this drug in pregnancy, this limited evidence may inform a risk/benefit discussion in the case of accidental exposure, or absence of other pregnancy compatible medications.

Only ACR guidelines have attempted to review available evidence for tsDMARDs (tofacitinib and baricitinib) use in pregnancy, and they were unable to offer any recommendations for the use/safety of these drugs during pregnancy due to lack of evidence, although they highlighted that these drugs are likely to cross the placenta and into breastmilk [9]. Most of our findings of maternal exposures to tsDMARDs occurred in the first trimester only. Therefore. there remains a lack of evidence regarding the safety of these drugs in pregnancy.

Tthe large size of biologic drugs means that minimal amounts are likely to be transferred into breastmilk and we did not identify any studies that measured non-TNFi DMARD drug levels in breast milk. There was limited but reassuring evidence on non-TNFi DMARDs in breastfeeding. BSR guidelines [7] found insufficient evidence to recommend use of non-TNFi (rituximab, belimumab, tocilizumab, anakinra and abatacept) in breastfeeding. EULAR recommendations [8] (regarding same non-TNFi with addition of ustekinumab) were also to avoid these drugs during lactation if another therapy is available to control the disease. However, they included a comment that, based on pharmacological properties of bDMARDs, lactation should not be discouraged when using these agents if no other options are available. In the more recent ACR guidance [9] rituximab is highly recommended as compatible with breastfeeding, and despite a lack of data other non-TNFi (belimumab, tocilizumab, secukinumab, ustekinumab abatacept and anakinra) were advised as being compatible to restart during post-partum/breastfeeding period, as theoretically there is minimal chance of drug transfer via breast milk due to these drugs having a large molecular size. Reassuringly, our systematic review has shown increasing evidence of compatibility of the use of these non-TNFi biologics in breastfeeding. A total of 48 breastfed infants were identified form our analysis and no adverse events were reported for these infants upon long-term follow-up. We did not, however, find any additional evidence on use of tsDMARDs in breastfeeding and note ACR guidance stating that since tsDMARDs are small molecule inhibitors of low molecular weight they could theoretically cross the placenta and into breastmilk [9].

There remains a paucity of studies reporting on paternal exposure to these drugs. The BSR and ACR guidelines reviewed paternal exposure to various drugs and both recommend use of rituximab, whilst only the ACR made a conditional recommendation for use of anakinra. Neither considered there to be sufficient evidence to make recommendations on paternal use of other non-TNFi (belimumab, tocilizumab, secukinumab, ustekinumab, abatacept) or tsDMARDs. We found data from 8 studies on 6 drugs (rituximab, tocilizumab, secukinumab, abatacept, anakinra and tofacitinib) with a total of 174 paternal exposures. Data were largely reassuring with only one adverse outcome reported with paternal exposure to secukinumab, but overall no increased risk of adverse outcomes compared to the general population was reported. These findings agree with other reviews of paternal DMARD usage published in 2018 [13,131]. Therefore, evidence is building towards safety of paternal exposure to a larger group of non-TNFi biologics.

From our systematic review of available data regarding the longer-term outcomes for infants exposed to various non-TNFi bDMARDs and one tsDMARD (rituximab, belimumab, tocilizumab, ustekinumab, canakinumab, abatacept, anakinra and baricitinib) in utero, we have found reassuring results including; normal development and no reports of complications/adverse events/developmental abnormalities in infants followed up post-partum (follow-up range 6 weeks to 4.5 years). However, it should be noted that data remains very limited.

We also found reassuring outcomes from the longer-term follow-up of children exposed to a variety of non-TNFi and tsDMARDs through breastfeeding, and after vaccinations. The BSR and EULAR [7,8] guidance discusses stopping certain TNFi (infliximab, etanercept and adalimumab) at various stages of pregnancy depending upon drug half-life and bioavailability to ensure low/no levels of drug in cord blood at delivery and thus allow a normal vaccination schedule. If however, these drugs are continued

later in pregnancy to treat active disease, then live vaccines should be avoided in the infant until 6-7 months of age. We found studies that reported a small number of infants that have mounted a normal immune response to vaccinations, and there were no increased rates of complications, developmental problems/adverse events observed.

Limitations of the studies obtained for final analysis in this systematic review include small numbers of pregnancy cases, a lack of control groups/data to enable comparisons of pregnancy outcomes, very few randomised controlled trials. Additionally, most studies published data obtained from registries or pharmaceutical databases and, no large prospective cohort studies were available for analysis. Some studies also included patients on combination drug regimes. Thus, determining whether a reported APO was directly due to the drug of interest or a concomitant medication proved challenging.

None of the selected studies were able to control for the impact of inflammatory systemic disease upon pregnancy. Interestingly, Tsao et al., [129] confirmed and expanded findings of a previous systematic review published by Komaki et al., [132] of 11 studies and found that the presence of an underlying inflammatory systemic disease is associated with APOs, and not the use of biologics drugs. Although our study was not designed to examine the effect of disease per-se upon pregnancy the majority of studies we analysed included a number of different inflammatory systemic diseases, i.e., RA, SLE, JIA, PsA, psoriasis, Crohn's disease, AOSD, APS, ITP, TTP, MS, FMF, HLH, CAPS, TRAPS, PV, MG, dermatomyositis, systemic sclerosis, vasculitis, lymphoma, atopic dermatitis and Behçet's disease and NMO, thus any confounding effects of disease are likely to be present across all studies that we have included.

There remains a strong need for larger comprehensive studies including control groups, larger sample sizes with specific rheumatic/autoimmune diseases, paternal cases and longer-term follow-up data for infants exposed to non-TNFi and tsDMARDs.

5. Conclusions

Overall, available data suggests that women and men who take non-TNFi/tsDMARDs at pre-conception and during pregnancy have good/favourable pregnancy outcomes. Our findings do not suggest any major concerns/increased risk of APOs for pregnancies exposed to non-TNFi and tsDMARDs. There were no major concerns for breastfeeding exposures to non-TNFi bDMARDs. Given that there is limited pregnancy exposure/outcome data available, these medications should only be considered in pregnancy if the benefit of maintaining disease control justifies any potential risks to the fetus. Despite these limitations, our findings will be useful for healthcare professionals when counselling women and men about the potential risks/benefits of using these types of drugs during conception, pregnancy and breastfeeding. In addition, in the not uncommon case of unplanned pregnancy/accidental exposure, our findings could provide vital information and reassurance to potential parents, and their healthcare professionals, in deciding on future pregnancy care.

6. Contributions

IG, HN and JF came up with the concept. IG, HN and JF designed the protocol. HN, JF, KA and WL undertook the searches, synthesis and extraction, and along with IG interpreted the findings. All authors provided input into the findings and draft article and approved the final text before submission.

7. Declaration of Competing Interest

IG provides consulting advice to and has received an unrestricted educational grant from UCB Pharma. The other authors declare no competing interests.

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Table 1 – Pregnancy outcomes for maternal cases exposed to monoclonal antibody therapies

Drug	Number of studies & study design	Number of pregnancies exposed to drug	Live births/total known PO	Pregnancy losses	Congenital abnormalities (proportion of live births)	Other PO	Overall impression of evidence	GRADE of evidence
RTX	n=32 cr [22–48] n=10 cs [49–58] n=9 ct [59–66]	269 (includes two sets of twins)	188/262	Of 262 PO: n=37 early spontaneous miscarriages n=2 late term miscarriages (2^{nd}/3^{rd} trimester) n=3 still births (includes one preterm twin) n=32 elective terminations	2/188 (n=1 clubfoot case in a twin & cardiac malformation in a singleton birth)	39/188 live births were either delivered < 37 weeks/had LBW (includes one preterm twin) 1 perinatal stroke (full-term)	No safety signals reported by small number of studies. No major cause for concerns. Low evidence of harm.	Low
BEL	n=5 cr [68–72] n=2 RCT [73,74] (integrated data from n=5 clinical trials)	63 (includes one set of twins)	27/51	Of 51 PO: n=13 spontaneous miscarriages n=10 elective terminations n=1 stillbirth	4/27 (included n=1 Ebstein anomaly, n=1 extra-renal pelvis, n=1 Dandy walker syndrome, n=1 inherited chromosomal translocation)	2/27 premature live births (twins) delivered by c-section at 32 weeks/LBW. At 3 & 6 months post-partum, umbilical hernias were detected in both infants	No safety signals reported by small number of studies. No major cause for concerns. Lack of control & infant follow-up data available. Very low evidence of harm.	Very low

TOC	n=4 cr [75–78] n=3 cs [79–81] n=4 ct [82–85]	385 (includes 1 ectopic pregnancy)	230/377 (included 3 sets of twins)	Of 377 known PO: n=82 early spontaneous miscarriages n=2 late spontaneous miscarriages (2nd trimester) n=2 stillbirths (n=1 postnatal asphyxia & death, n=1 at 25 weeks) n=61 elective terminations	10/230	Largest study demonstrated increased rate of pre-term birth & LBW. Other studies reported 12 premature/LBW babies/52 reported exposures.	Small number of studies reported a potential increased rate of preterm and LBW live births. Findings do not suggest a substantial increased risk congenital malformation/ anomalies. No safety signals and no cause for major concerns. Low evidence of harm	Low
SEC	n=3 cr [86–88] n=1 ct [89]	241	54/127	Of 127 known PO: n=29 spontaneous miscarriages (n=26 </=20 weeks) n=40 elective terminations n=3 terminations (due to ectopic pregnancy) n=1 intrauterine death (at 38 weeks)	2/47 (included n=1 ventricular septal defect with minor left–right shunt, n=1 case of Angelman syndrome)	Out of 18 pregnancies: 6 preterm births, 1 ongoing pregnancy, 9 cases lost to follow-up/unknown PO, where SEC was continued throughout pregnancy or discontinued at 3rd trimester.	Very small number of studies available reporting no safety signals. No cause for major concerns. Very low evidence of harm.	Very low

UST	n=10 cr [90–98,133] n=9 cs [99–101,103–107]	41	36/40 (included 1 set of twins)	Of 40 known PO: n=2 spontaneous early miscarriages (at 8 & 12 weeks) n=1 spontaneous abortion (gestation unknown) n= 1 elective abortion	No congenital malformations reported	3/36 premature infants (at 35, 36 & 37 weeks gestation) & 2 LBW/19 cases with BW/gestational age reported.	Small number of studies reported no safety signals/increased risk of APOs. No major cause for concern. Very low evidence of harm	Very low
CAN	n=1 cr [108] n= 1 ct [109]	9	8/9	Of 9 known PO: n=1 early spontaneous miscarriage (at 6 weeks)	None reported	1 infant had NLRP3 gene mutation that matched with mother's MWS genetic condition. No premature births/LBW.	Very small number of available studies reporting no safety signals. No major cause for concerns. Very low evidence of harm	Very low

Abbreviations: *RTX: Rituximab; BEL: Belimumab; TOC: Tocilizumab; SEC: Secukinumab; UST: Ustekinumab; CAN: Canakinumab; cr: case report; cs: case-series; ct: cohort; RCT: randomised controlled trial; PO: pregnancy outcomes; GA: gestational age; BW: birth weight; LBW: low birth weight; APO: adverse pregnancy outcomes; MWS: Muckle-Wells syndrome; C-section: Caesarean section.*

Table 2 - Pregnancy outcomes from maternal cases exposed to recombinant fusion proteins and tsDMARDs.

Drug	Number of Studies & study design	Number of pregnancies exposed to drug	Live births/total known PO	Pregnancy losses	Congenital abnormalities (portion of live births)	Other PO	Overall impression of evidence	GRADE of evidence
Recombinant fusion proteins								
ABA	n=1 cr [110] n=1 cs [51] n=4 ct [60,85,111,112]	165 (includes 1 ectopic pregnancy)	94/156	Of 156 known PO: n=39 early spontaneous miscarriages (1st trimester/unknown) n=1 late spontaneous miscarriage (2nd trimester - 21 weeks) n=22 elective terminations	7/94 congenital anomalies (no pattern observed)	1/94 preterm birth	Very small number of available studies reporting little evidence of harm.	Very low
ANA	n=4 cr [113–116] n=4 cs [117–120] n=3 ct [60,85,109]	59	54/59 (includes one twin pregnancy)	Of 59 known PO: n=1 spontaneous miscarriage n=3 elective terminations n=1 fetal death at 30 weeks (renal agenesis in twin pregnancy)	1/54 (ectopic neurohypophysis with growth hormone deficiency & renal agenesis) [109]	6/54 preterm births/had a LBW.	Very limited number of studies reported no safety signals. No major cause for concern. Very low evidence of harm.	Very low
Targeted synthetic drugs								
TOF	n=1 ct [121] n=1 RCT [122]	58	29/48	Of 48 known PO: n=9 spontaneous miscarriages n=10 elective terminations	1/29 (pulmonary valve stenosis)	Of 6 healthy babies born to mothers on TOF monotherapy: 1 LBW & 1 preterm	Very limited evidence and studies reported no safety signals/cause for major concerns. Very low evidence of harm.	Very low

BAR	n=1 cr [123]	1	1/1	NA	NA	NA	Lack of evidence available. No safety signal/major concerns reported. Very low evidence of harm.	Very low

Abbreviations: *ABA: Abatacept; ANA: Anakinra; TOF: Tofacitinib; BAR: Baricitinib; cr: case-report; cs: case-series; ct: cohort; RCT: randomised controlled trial; PO: pregnancy outcomes; APO: adverse pregnancy outcomes; GA: gestational age; BW: birth weight; LBW: low birth weight; NA: not applicable.*

Table 3. Pregnancies outcomes for paternal cases exposed to non-TNFi and tsDMARDs during pre-conception until first trimester.

Drug	Number of studies & study design	Number of pregnancies exposed to drug	Pregnancy outcomes	Number of APO cases relating to paternal exposure	Overall impression of evidence	GRADE of evidence
Mono-clonal antibodies						
RTX	n=1 ct [61]	22	n=8 healthy live births/14 known PO (includes one set of twins) n=6 spontaneous miscarriages (early/1st trimester)	No congenital malformations/APO reported.	Lack of evidence available. No safety signal reported & no major cause for concerns. Very low evidence of harm.	Very low
TOC	n=1 cs [81] n=1 ct [83]	24	n=9 healthy live-births/14 known PO (includes one set of twins) n=4 spontaneous miscarriages n=1 elective termination	No congenital malformations/APO reported.	Limited evidence available. No safety signal reported & no major cause for concerns. Very low evidence of harm.	Very low
SEC	n=1 ct [89]	54	n=27 healthy live births (full term)/33 known PO n=1 premature live birth n=1 elective termination n=4 spontaneous miscarriages (up to 20 weeks)	1 congenital malformation (club foot, right hand underdeveloped & short finger)	Lack of evidence available. No safety signal reported & no major cause for concerns. Very low evidence of harm.	Very low
Recombinant fusion proteins						
ABA	n= 1 ct [111]	10	n=9 healthy live births/10 known PO n=1 elective abortion.	No congenital malformations /APO reported.	Lack of evidence available. No safety signal reported & no major cause for concerns. Very low evidence of harm.	Very low
ANA	n=1 ct [109]	6	n=6 healthy live births/6 known PO (includes one set of twins)	No congenital malformations/APO reported	Lack of evidence available. No safety signal reported & no major cause for concerns. Very low evidence of harm.	Very low

Targeted synthetic DMARDs						
TOF	n=1 cs [121] n=1 RCT [122]	58	n=34 healthy live births/39 known PO n=5 spontaneous miscarriages	No congenital malformations/APO reported.	Lack of evidence available. No safety signal reported and no major cause for concerns. Very low evidence of harm.	Very low

Abbreviations: *RTX: Rituximab; TOC: Tocilizumab; SEC: Secukinumab; ABA: Abatacept; ANA: Anakinra; TOF: Tofacitinib; cs: case-series; ct: cohort; RCT: randomised controlled trial; PO: pregnancy outcomes; APO: adverse pregnancy outcomes.*

Table 4 – Post-partum follow-up, breastfeeding and vaccination outcomes

Drug	Total number of infants	Long-term childhood follow-up outcomes	Overall impression of evidence	GRADE of evidence
Monoclonal antibodies				
RTX	34	No complications in 32/34 infants where follow-up was reported [23,24,27,32,35,37–41,43,46,51,58,59,125]; 1 mild asthma [31]; 1 multiple infections [59]. Follow-up period range: 3 months to 4.5 years. Overall, infants demonstrated good normal developmental outcomes & no serious infections.	Limited evidence available. No safety signals/major cause for concern. Very low evidence of harm	Very low
BEL	4	Good normal development and no infections reported in in 4 infants; 1 at 3 months [70], 2 at 12 months [68,69] & 1 at 15 [126] months follow-up.	Lack of evidence available. No safety signals/major cause for concern. Very low evidence of harm	Very low
TOC	≥6	Good normal development in 6 breastfed infants. No adverse events/serious infections reported [76,78,80,84]	Lack of evidence available. No safety signals/major cause for concern. Very low evidence of harm	Very low
UST	6	Good normal developmental outcomes reported in 6 infants followed up at; 12/14/25 months [93,94,96,98,133]	Lack of evidence available. No safety signals/major cause for concern. Very low evidence of harm	Very low
CAN	7	Good normal development in 7 infants and 4/7 breastfed infants had no serious infections & no developmental abnormalities reported at a mean follow-up of 2.2 years (range 5 months to 4 years) [109].	Lack of evidence available. No safety signals/major cause for concern. Very low evidence of harm	Very low
Recombinant fusion proteins				
ABA	18	No complications/apparent abnormalities reported in 18 infants followed up from 6 weeks to 42 weeks [51,110,111]	Very little evidence available. No safety signals/major cause for concern. Very low evidence of harm.	Very low

ANA	≥17	At least 10/17 infants were breastfed up to 10 months and no infections/developmental abnormalities reported [109,114,117]. One infant received IVIG treatment for low platelet count at birth & at 2 months follow-up platelet counts resolved [119]	Very little evidence available. No safety signals/major cause for concern. Very low evidence of harm.	Very low
Targeted synthetic drugs				
BAR	1	1 infant exposed to drug up to 17 weeks gestation had normal growth & psycho-motor development at 9 months. Infant received vaccinations – no significant AE reported [123].	Lack of evidence available. No evidence of harm.	Very low

Abbreviations: *RTX: Rituximab; BEL: Belimumab; TOC: Tocilizumab; UST: Ustekinumab; CAN: Canakinumab; ABA: Abatacept; ANA: Anakinra; BAR: Baricitinib; IVIG: intravenous immunoglobulin; NA: Not applicable; AE: adverse events.*

Figure 1. Flow diagram for study selection

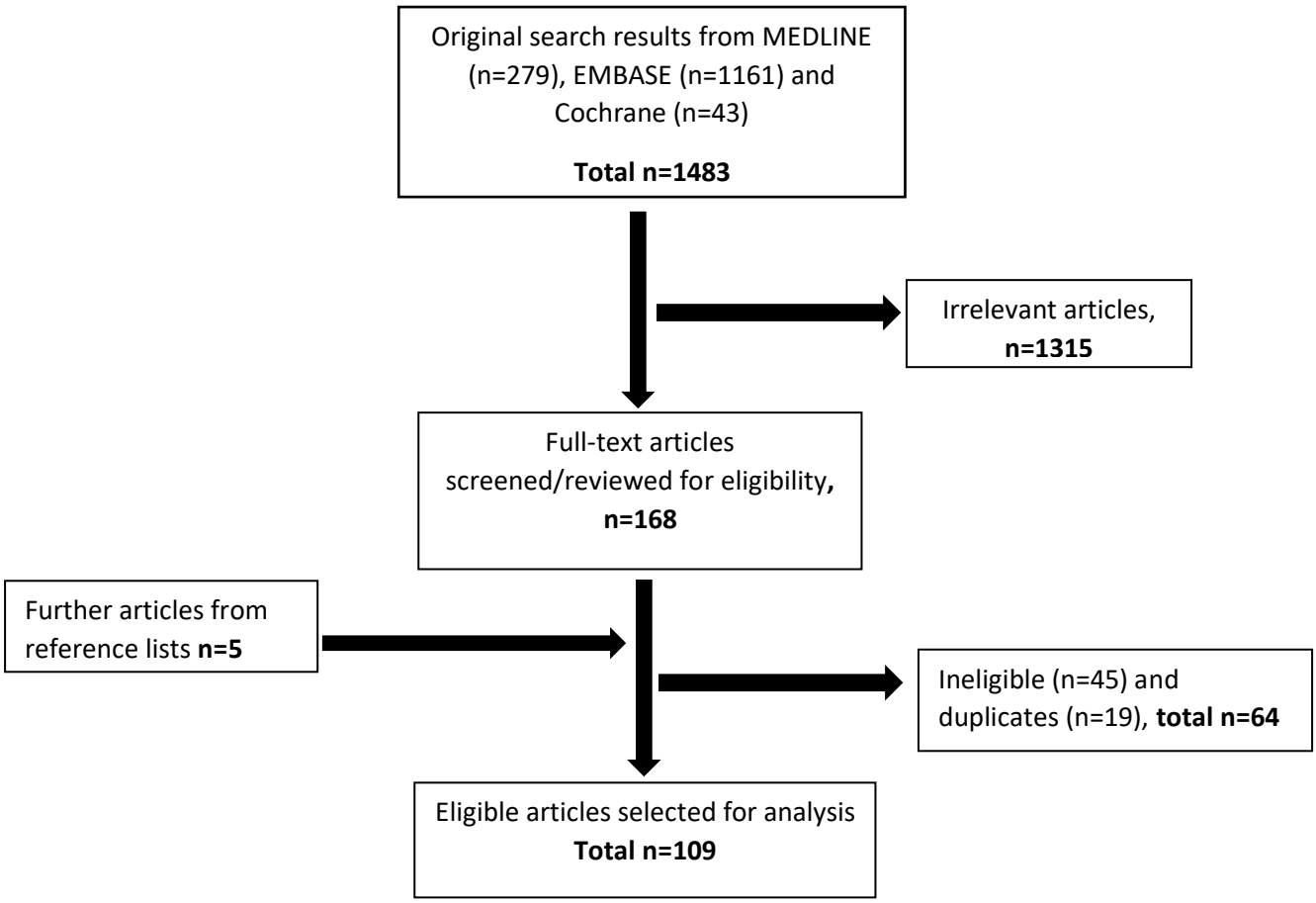

Fig 2. BOX 1. Literature review search terms

(A) Individual non-TNFi drugs and tsDMARDs drug names:

Abatacept OR Orencia
OR Rituximab OR Rituxan OR MabThera OR Zytux OR Truxima
OR Tocilizumab OR Actemra OR RoActemra
OR interleukin 6 inhibitor OR IL-6 inhibitor OR IL6 inhibitor
OR Anakinra OR Kineret
OR Interleukin 1 inhibitor OR IL-1 inhibitor OR IL1 inhibitor
OR Belimumab OR Benlysta
OR Tofacitinib OR Xeljanz OR Jakvinus
OR Baricitinib OR Olumian
OR JAK inhibitor OR Janus tyrosine kinase inhibitor OR janus kinase inhibitor
OR Canakinumab OR Ilaris
OR Ustekinumab OR Stelara
OR Secukinumab OR Cosentyx
OR Ixekizumab OR Taltz
OR Sarilumab OR Kevzara
OR Interleukin inhibitor OR IL17 inhibitor OR IL-17 inhibitor OR IL23 inhibitor OR IL-23 inhibitor OR Il-12 inhibitor OR IL12 inhibitor
OR Apremilast OR Otezla

(B) Conception
OR 'conceive'
OR pre-conception
OR pre-conceive
OR pregnancy OR pregnant OR pregnan*
OR lactation OR breastfeeding

(C) Childhood OR paediatric OR neonate OR newborn OR baby

AND

Vaccination OR immmunisation OR infection

Our suggestion for running searches:
Search 1 – combine search terms (A) AND (B) for birth outcomes
Search 2 – combine search terms (A) AND (C) for longer term infection/vaccination outcomes