The time of equipoise on use of biologic DMARDs in inflammatory arthritis during pregnancy is finally over: a reappraisal of evidence to optimise pregnancy management

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Abstract

Active inflammatory arthritis (IA) in pregnancy is associated with an increased risk of adverse pregnancy outcomes. Treatment of active inflammation and maintenance of low disease activity with medication reduces these risks. Therapeutic decisions on disease modifying anti-rheumatic drugs (DMARD) in pregnancy are complicated by safety concerns, which have led to inappropriate withdrawal of treatment and consequential harm to mother and fetus. Studies of IA in pregnancy have consistently shown: minimal safety concerns with biologic (b)DMARD usage and an increased risk of flare with bDMARD discontinuation. During pregnancy, it is our opinion that the benefits of disease control with bDMARDs, when required in addition to conventional DMARDs,

outweigh the risks. This review highlights the reasons for re-consideration of equipoise and an agenda for future research to optimise the use of bDMARDs in IA pregnancy.

Background and rationale

Rheumatoid arthritis (RA) is a chronic inflammatory arthritis with global prevalence estimated at 0.46% (1) and is more common in women (2). Other forms of inflammatory arthritis (IA), including axial spondylarthritis (AxSpA), psoriatic arthritis (PsA) and juvenile idiopathic arthritis (JIA), can all affect women of childbearing age with estimates for global prevalence of these conditions of: 0.13% for PsA ; 0.01 to 1.61% for AxSpA (3); and 0.1% for JIA (4). These diseases require early initiation of treatment to prevent irreversible damage to joints and escalation of treatment, often with bDMARDs, to induce remission (5). The bDMARDs are categorised by their ability to inhibit tumour necrosis factor alpha (TNF), thus TNF inhibitors (TNFi) or non-TNFi that target other cytokines and immune targets. Around 20-29% of people with IA may require bDMARDs in addition to conventional DMARDs to achieve disease control (6).

Active disease before and during pregnancy is associated with an estimated 2-4-fold increase in the risk of adverse pregnancy outcomes (APO) (7, 8). To reduce these risks, multiple international guidelines recommend using pregnancy-compatible medications to maintain low / no disease activity. These guidelines may not be followed when medications are withdrawn from a pregnant woman over unfounded concerns about the risk for fetal harm (9). We argue that drug withdrawal is not in the best interest of women with IA, nor the baby, particularly because discontinuation of treatment before or during early pregnancy substantially increases the risk of disease activity (10).

This review presents evidence, selected criteria shown in Box 1, relating to the impact of bDMARD usage on disease control, pregnancy and infant outcomes from IA pregnancies to highlight the substantial benefits on these outcomes. It will highlight unmet needs, risk/benefit considerations and propose a re-consideration of equipoise and an agenda for future research to optimise the safe and effective use of bDMARDs in IA pregnancy.

Structural properties of biologic DMARDs affect placental transfer

Biologic drugs are recombinant proteins; most commonly monoclonal immunoglobulin (Ig) G1 class antibodies directed against specific targets or fusion proteins containing the fragment crystallisable (Fc) portion of IgG1 joined to receptor-blocking proteins. These drugs share similar structure with maternal IgG (~150 kDa) that are unable to cross the placenta via simple diffusion. Active trans-placental transfer of maternal IgG occurs via neonatal fragment of crystallisable component/Fc receptors (FcRn), present on syncytiotrophoblast and increases exponentially from 16 weeks of pregnancy to term (11). Of the IgG (1 to 4) subclasses, placental transfer of IgG1 and IgG4 is most efficient from mother to fetus compared with IgG2 and IgG3 subclasses (12).

The presence of the Fc region of IgG1 in most bDMARDs and IgG4 in Ixekizumab (13) mediates active placental transfer (14-21) to maximal in-utero exposure at term. Certain biologic drugs are fusion proteins containing part or none of the IgG structure, principally certolizumab pegol (CZP) (22), etanercept (ETA) (14, 23, 24), anakinra and abatacept (ABA), with varying degrees of placental transfer, determined by their structure and presence/absence of Fc region, Table 1.

Evidence on the use of biosimilars in patients with IA in pregnancy is limited (25), with only one study of placental transfer demonstrating transplacental passage of infliximab biosimilar (26). Given their similarity to originator compounds in terms of structure and target, patients are counselled regarding biosimilar use in pregnancy based on existing evidence for each originator compound, Table 1.

Improved disease control reduces adverse pregnancy outcomes

A systematic review and meta-analysis of prospective studies using objective measures of disease activity in RA pregnancy found that 60% of women with active RA improved during pregnancy, although not all reached remission, and ~50% had a disease flare by six months postpartum (27). Treatment data were lacking and no studies included data on bDMARD use in pregnancy. A recent report of a treat-to-target (T2T) protocol for minimal disease activity in RA pregnancy, including TNFi-bDMARD use in 47.3% of women at any time during pregnancy, described 90.4% remission/low RA disease activity (28). Studies of other IA report disease flare/activity in 25-78% of PsA, AxSpA and JIA pregnancies (29-31).

A systematic review and metanalysis for RA (32) found a significantly increased risk of adverse pregnancy outcomes (APO). Compared to healthy women, women with RA had rates of caesarean section, preeclampsia, gestational hypertension, stillbirth, small for gestational age, and low birth weight each with statistically significant OR 1.35-1.50-fold higher; preterm birth was elevated with an OR of 1.58 (CI 1.44-1.74). This analysis, however, did not provide absolute numbers for outcomes or control for disease activity and may be confounded by concomitant medication usage, such as methotrexate in unplanned pregnancies or corticosteroids in active disease. Increased risks of APO have been confirmed in other IA pregnancies (7, 29, 30). Overall, these risks are less than observed with active systemic lupus erythematosus (SLE) in pregnancy (33).

There are clear links between increased disease activity and a several-fold increase in APO, Table 2. Active disease when compared with population control pregnancies, is associated with an increased risk of: pre-term delivery in RA and AxSpA pregnancies (7); pre-term birth and small for gestational age in RA-pregnancies (9); and pre-eclampsia in RA pregnancies (34). Active RA at enrolment and any time during pregnancy was associated with pre-term delivery (35). Increased patient-reported and physician-reported RA activity is also associated with increased preterm birth (36). Elective caesarean section has also been found to occur more frequently in AxSpA pregnancies with active disease and both elective and emergency caesarean sections were more frequent in PsA pregnancies with active disease (37), Table 2.

Withdrawal of bDMARDs in early pregnancy is associated with disease flare in RA and AxSpA (31) and with disease flare and pre-term delivery in RA (38). A prospective study of 188 pregnant women with RA who were treated to a T2T protocol including TNFi use during pregnancy was associated with increased birth weight of offspring of people with well-controlled RA (39). Failure to adopt T2T strategies for prolonged periods, such as before/during/after single or multiple pregnancies is likely to increase the risk of irreversible joint damage. Increased disease activity during RA pregnancy is also associated with rapid postnatal catch-up growth in infants, a risk factor for adverse cardiovascular and metabolic profiles in adults (40).

The impact of poor disease control in people with IA extends beyond pregnancy. Delayed time to pregnancy has been shown in RA compared with population controls (OR 1.6; 95% CI 1.0-2.4) (41)

and is associated with high disease activity, increasing age, use of NSAIDs and prednisolone ≥10mg/day (42). Reduced family size in people with RA has been linked with patient choice and reduced fertility (43). The causes underlying reduced family size in IA include impaired sexual function, decreased gonadal function, pregnancy loss, therapy and personal choices that are all impacted by active disease (44).

Growing evidence of biologic DMARDs safety in pregnancy

Studies of IA in pregnancy have consistently shown: no safety concerns with bDMARD usage; an increased risk of flare with bDMARD discontinuation; and increased risk of adverse pregnancy outcomes with high IA disease activity. Taken together these findings suggest it is time to revise our approach to bDMARD use in pregnancy that has evolved over time, Figure 1. Randomised controlled trials on biologic medications in pregnancy are lacking and most data are from case series, cohort and population studies. Several articles have systematically reviewed maternal and neonatal outcomes from pregnancy exposure to mostly TNFi bDMARDs in inflammatory diseases, principally IA and inflammatory bowel disease (IBD). These studies, including an analysis of 11,172 pregnancies have not identified any increased risk of adverse outcomes in TNFi-bDMARD exposed pregnancies compared to disease matched non-bDMARD treated controls (45). This wealth of reassuring data on TNFi-bDMARD exposures in pregnancy means they are now far more extensively studied than sulfasalazine (46) that is considered compatible with pregnancy. The data supporting the likely safety of non-TNF-bDMARDs continue to grow, led by data from patients with IBD.

Barriers remain to routine use of bDMARDs to treat arthritis in pregnancy

Despite the large body of evidence supporting TNFi-bDMARDs and growing evidence supporting non-TNFi-bDMARDs, barriers remain to their routine use in pregnancy, Table 3, and evidenced by reduced bDMARD use in pregnancy compared to before and after pregnancy (47, 48).

There is marked variation in prescribing of bDMARDs in pregnancy

Our own experience from providing specialist services and producing international guidelines on prescribing anti-rheumatic drugs in pregnancy is that confidence in prescribing bDMARDs in pregnancy is proportional to the amount of specialist rheumatology and obstetric medicine input available. Large centres with specialist maternal medicine clinics are more likely to continue TNFi-bDMARDs throughout pregnancy and consider continuing non-TNFi-bDMARDs depending on perceived risk of loss of disease control with drug cessation. Centres lacking specialist input are more inclined to follow international guidelines that recommend stopping of TNFi at varying gestations to allow normal infant vaccination schedule and remain cautious regarding non-TNFi bDMARDs in pregnancy. The approach of ceasing bDMARDs at specific gestations, does not consider the adverse impact of stopping bDMARDs on disease control or pregnancy outcomes.

Balancing the risk of IA activity in pregnancy

Biologic DMARDs are frequently continued through pregnancy in women with IBD. The severe consequences of loss of disease control to the mother (bowel perforation, sepsis, and death) and baby (high frequency of early prematurity) mandates aggressive treatment and led to the early and frequent use of TNFi-bDMARDs and recently non-TNFi-bDMARDs in pregnancy (49). In contrast, the medical risks of active IA in pregnancy tend to be less catastrophic, but still can result in pain, disability, and long-term joint damage, as well as real, through more modest, increases in adverse pregnancy outcomes (10). The difference in the risks posed by uncontrolled IBD and IA impact on shared decision making.

Differences in outcomes between IBD and IA pregnancies may influence the perception of risk for both patient and healthcare provider, thereby affecting shared decision making. Many women with chronic disease do not perceive their pregnancy as high risk (50). Their pregnancy-related behaviour and engagement with healthcare services are influenced by this perception of pregnancy risk, which often differs from that of their healthcare professional (51). This altered perception of risk in pregnancy may mean that long term outcomes of poorly controlled IA such as long-term irreversible damage to joints, may not be perceived as negatively as those associated with poorly controlled IBD in pregnancy that risk death.

Patients may choose to avoid bDMARDs in pregnancy due to lack of trust in the available data
Studies across long-term conditions, including RA, show that the decision to take medication (ie adherence to treatment) reduces over time (52). Nonadherence is often related to patients' beliefs regarding their medication, doubts about continued need, and safety concerns, even when doing well on treatment. A survey of 34 patients with RA or SpA regarding the compatibility of bDMARDs during pregnancy found only 3% considered them safe, 39% thought they were not safe and 58% did not know (53). A meta-analysis of over 25,000 patients across 24 long-term conditions, including RA, showed that nonadherence was related to doubts about medication necessity and concerns about potential adverse effects (54). A study of 460 patients with RA on stable dose sub-cutaneous TNFi-bDMARDs found that beliefs about medicines strongly correlated with medication adherence (55).

People with the lived experience of IA in pregnancy may make different benefit/risk calculations from healthcare professionals, therefore shared decision making is vital. For example, the desire to protect an unborn baby can be felt very strongly and a wish to stop/avoid medication might be an instinctive reaction, even in those with knowledge of medication safety and benefits of disease control. One possible perspective is that information on bDMARDs in pregnancy remains limited to less than 25 years, whilst people with IA have been getting pregnant and having children for centuries without these drugs, so they may still feel anxious about using them in pregnancy, despite risks relating to poor disease control in pregnancy. Others may be more worried about the impact of their arthritis than their medications on pregnancy, so may be more inclined to continue medications. A desire to continue bDMARDs in pregnancy however may still be outweighed by feelings of guilt concerning subsequent immunosuppression and a need to avoid live vaccines in infants in the first six months of life. These feelings of guilt may lead people who were inclined to continue bDMARDs instead to stop them in pregnancy or to believe that IA will improve naturally in the third trimester allowing medication to be stopped, so their children can be fully vaccinated and protected in their first year of life. These contrasting viewpoints show why shared decision making is so important when considering biologic use in pregnancy to maintain disease control.

The long-term impact of IA and bDMARDs of offspring is not entirely known
Concerns relate to potential immunosuppression in infants, particularly those exposed to bDMARD in-utero near term, leading to increased infection risk. Studies of long-term follow-up of children exposed to bDMARDs in-utero have mainly focussed on TNFi (46). One study of 196 children with intrauterine exposure of TNFi during the third trimester for maternal IBD followed for 5 years, found no association with long-term adverse health outcomes when compared to TNFi-unexposed controls (56). Similarly, other studies (of n=229-388) children exposed to TNFi in utero for maternal RA or IBD did not find an increased incidence of severe infections compared with TNFi-unexposed children of disease controls after 1-5 years of follow-up (57, 58). Immunological analysis of eight infants

exposed to TNFi in-utero compared with eight healthy controls up to 18 months post-partum revealed a reduction in white blood cells, immature B cell phenotype and reduced numbers of regulatory T cells, without increased infection risk (59). Larger and longer studies are required to further evaluate these findings.

Few studies have examined long-term outcomes of children born to mothers with IA and none have considered the potential impact of in-utero exposure to bDMARDs. Observational studies suggest a possible increased risk of autism spectrum disorders in children born to people with RA compared to those born to people without RA (60). Evaluation of cognitive impairment in 1000 children found reduced school performance in RA exposed children compared with peers (61). A study of 18 school age children born to 16 people with IA found children at a high risk of behavioural problems were born to people with a longer history of arthritis (62). It is uncertain however, whether the relationship between IA and neurodevelopmental outcome is causal, or related to treatment of IA, or indeed eliminated by treatment of inflammation during pregnancy. More detailed consideration of the impact of IA on outcomes of children born to people with rheumatic disease can be found in the accompanying article in this series (JOURNAL TO ADD LINK).

Differences exist in guidance issued by various organisations on bDMARD used in pregnancy
Guidance differs across specialities and countries, Table 4. Gastroenterology guidance relating to IBD, uniformly states the importance of disease control and mostly advises continuation of all bDMARDs throughout pregnancy (49, 63, 64), with some noting lack of evidence for certain non-TNFi-bDMARDs (65). They mostly consider bDMARDs to be low risk in breastfeeding (49, 63, 64), or lacking evidence for certain non-TNFi (65).

Rheumatology guidance uniformly highlights the importance of counselling to advise benefits of control against risks of untreated disease and advise continuation of TNFi bDMARDs throughout pregnancy (46, 65-68). British and European (46, 66) guidance recommends continuation of non-TNFi-bDMARDs to manage severe maternal disease, whilst Austrian, Australian and American guidance recommends discontinuation of most non-TNFi apart from Anakinra (65) and RTX (65, 67, 68) that may be considered in severe disease. With regards breastfeeding, all rheumatology guidance considers TNFi-bDMARDs to be compatible (46, 65-68), British and American guidance also recommend non-TNFi, (46, 67, 68) whilst European and Austrian guidance (65, 66) does not recommend them.

The immunosuppression in the infant after In-utero exposure to bDMARDs leads to concerns about live vaccine administration
Childhood national vaccination schedules and coverage differ globally (https://immunizationdata.who.int/listing.html?topic=&location=) and require alteration of live vaccines in the first year of life of infants following in-utero exposure to bDMARDs. These live vaccines include those against rotavirus (at 2 and 3 months), BCG (within first month) and MMR (from 11 months). There is concern that infection can be caused by attenuated virus in infants who may be immunocompromised following in-utero exposure to bDMARDs, since it is generally recommended to avoid these vaccines in paediatric patients treated with immunosuppressive drugs (69). There are no data about the safety of the first MMR dose in children treated with biologics. If there is a high risk of infection to an infant with in-utero exposure to bDMARDS, MMR vaccination should be considered before 12 months of age given that no adverse reactions have been reported following MMR vaccination of infants exposed to bDMARDs in utero (70).

Although rotavirus vaccine is not included in National vaccination schedules in all countries its use has led to reduced numbers of hospital visits and hospitalisations in the US due to rotavirus infection (https://www.cdc.gov/vaccines/pubs/pinkbook/rota.html#epi). A systematic review of live vaccine outcomes in infants exposed to bDMARDs in utero found 7 mild reactions to rotavirus vaccination among 46 infants that were vaccinated against rotavirus infection (70). A prospective study of live rotavirus vaccination after antenatal exposure to (mostly TNFi) bDMARDS found no clinically significant abnormalities in infant immunologic function after in-utero bDMARD exposure and no serious adverse effects after rotavirus vaccine administration (71). American College of Rheumatology guidelines recommend Rotavirus vaccination for infants following in-utero exposure to any bDMARDs except Rituximab (72).

BCG vaccination is routinely recommended in countries (Eastern Europe, Asia, sub-Saharan Africa) with a high prevalence of tuberculosis (TB), whilst in other countries (Western Europe, USA, Australia) with low prevalence of TB it is only offered to infants ≤12 months of age who live in an area with high rates of TB or their parents or grandparents came from a country with high rates of TB. A study performed in infants born to mothers treated with TNFi-bDMARDs for IBD showed that BCG vaccination after 6 months of age is of low risk with no serious adverse events (73).

Medicines and Healthcare products Regulatory Agency and European Medicines Agency guidance (74) is that infants exposed to Infliximab in utero should not receive live vaccinations until 12 months of age and that live vaccinations should be avoided in infants exposed to Infliximab through breast milk. These recommendations were based on findings that clearance of infliximab in the infant's blood stream takes a mean of 7 and up to 12 months postpartum (15) and detection of small amounts of Infliximab in breast milk (75). No clinically harmful effects have been reported in breastfed infants and have only been found following administration of BCG vaccine to infants ≤3 months old exposed in-utero to TNFi with high transplacental transfer rates, primarily Infliximab (70). Experts have cautioned against a one-size fits all approach and highlight that the risk of infants developing TB post BCG vaccination associated with breast milk infliximab exposure is extremely low and propose evidence based advice on effects of maternal bDMARDs on suitability of childhood vaccinations (76).

Gastroenterology guidelines recommend delays of live vaccination in infants exposed to bDMARDs in-utero varying from 6 (49) to 12 months (64, 65) or an unspecified time period (63). British rheumatology guidance advises no alteration in vaccine schedule for certolizumab and delay of 6 months for all other bDMARDs if they are used throughout pregnancy (46). European rheumatology guidance recommends delay of six months for live vaccines in first six months of infants exposed to bDMARDs later in pregnancy with caveat that measurement of child serum levels of the bDMARD in question could guide decision making (66). Separate European vaccine guidance recommends that live-attenuated vaccines should be avoided during the first 6 months of life in newborns of mothers exposed to anti-TNF biologics during the second half of pregnancy (77). American vaccine (72) and Australian rheumatology guidance (68) recommends that rotavirus vaccination can be given to infants in first six months of life after second & third trimester exposure to any high/low placental transfer TNFi, with delay until after six months of age recommended following in-utero exposure to RTX.

Overall, an individualised assessment regarding use of live vaccines in infants after in-utero exposure to bDMARDs must evaluate timing of exposure, bioavailability and persistence of the drug, mechanism of action of the drug, and infection risk to ensure that infants are not denied vaccines

inappropriately.

Unmet needs of people with arthritis

Patient and public engagement in the UK has highlighted the importance of increased knowledge around disease activity and medication usage in rheumatic disease in pregnancy. Patient engagement in 2016, with the Versus Arthritis patient network identified three key concerns: how will pregnancy affect my arthritis; how will arthritis affect my pregnancy; and what drugs are safe in pregnancy and breastfeeding? Further meetings with patient partner networks in the UK, including individuals with IA and experience of bDMARD use in pregnancy, confirmed the importance of questions relating to medication use in pregnancy and their direct relevance to people with IA considering/during pregnancy (78). Discussions highlighted how much thought and planning is given to future pregnancy, particularly the question of whether stopping bDMARDs may have an adverse impact on disease activity, pregnancy or infant outcomes. The fear of stopping medications may lead some people to choose not to become pregnant at all. All discussants recognised the positive impact that better knowledge of the risks/benefits of bDMARD continuation would have on risk management of IA pregnancy.

Experts By Experience and Versus Arthritis involvement team coproduced an online questionnaire in 2022 to address safety concerns and timing of stopping/starting biologic drugs in pregnancy. There were 178 respondents with IA and lived experience (actively considering or had been pregnant) in the past five years. Based on responses of concern on a Likert scale of 1-10 (where 10 = very concerned) there were more concerns about the impact of IA than medication on pregnancy; 82.5% (8-10 Likert) were worried about the effect of IA on pregnancy, 50.6% (Likert 8-10) were worried how treatment will affect their pregnancy and 36.5% (8-10 Likert) were worried about using bDMARDs in pregnancy, although 68.0% (8-10) also reported wanting to reduce or stop treatment in pregnancy. Overall, 74% reported they would participate in a clinical trial that includes randomisation for stopping biologic drugs in pregnancy, Supplementary Table 1.

These engagement activities all revealed a powerful desire for improved information and resources in relation to treatment and rheumatic disease control in pregnancy and revealed more concerns in most respondents around how arthritis affects a pregnancy than medication. Whilst attitudes of healthcare professionals towards prescribing in pregnancy seem to be changing with increasing awareness of the importance of disease control, it is still an area of concern and uncertainty for people with arthritis.

Limited therapeutic alternatives exist to bDMARDs in pregnancy

If a person does not want to take a bDMARD in pregnancy, it should be replaced with an alternative conventional (non-biologic) DMARD, such as HCQ, SSZ to maintain adequate control of IA activity. If these conventional drugs however, have previously been tried or are started and fail that exposes the individual to a risk of significant flare, with limited treatment options to regain remission rapidly beyond oral or intra-articular corticosteroids. Furthermore, pregnancy compatible conventional (non-biologic) DMARDs can take 3-6 months to gain full clinical benefit so changes must be planned appropriately in advance of pregnancy. Whilst corticosteroids have a rapid onset of action, their prolonged use in pregnancy has been associated with an increased infection risk, preterm premature rupture of membranes, gestational hypertension and gestational diabetes mellitus that are all associated with an increased risk of adverse pregnancy outcomes, independently of disease activity (46). Therefore, the dose and duration of steroid use in pregnancy should be adjusted as required to control IA activity and thus reduce associated risks of adverse pregnancy outcomes.

Furthermore, alternative medications such as non-steroidal anti-inflammatory drugs are advised to be used sparingly beyond 20 and weaned to stop by 30 weeks of pregnancy (67), a time when bDMARDs may be stopped.

Personal view of optimal use of bDMARDs in pregnancy

Our personal view is that all TNFi-bDMARDs should be continued during conception and most of pregnancy to maintain disease control. In people we consider to have low risk of disease flare on withdrawal of bDMARD we discuss stopping the IgG-based bDMARD at 20-32 weeks of pregnancy (depending on expected placental transfer and bDMARD half-life) to allow the infant to have a more normal immune system at delivery and receive live vaccines, then restart medication post-partum even if breast feeding. However, if there is a concern that stopping the bDMARD will lead to increased disease activity that will adversely affect maternal or fetal outcomes, then we advise continuation throughout pregnancy and breastfeeding with modification of the infant's vaccination schedule according to guidance, Figure 2.

More nuanced discussion and shared decision making is required for the non-TNFi-bDMARDs for which there are fewer data, however we typically follow similar practices. Many women who enter pregnancy on a non-TNFi-bDMARD have already failed treatment with a TNFi-bDMARD, and have more severe IA that can be harder to control. For patients at high risk for significant flare without a non-TNFi-bDMARD, we continue it through pregnancy, omitting one or two doses near delivery, but only if doing so will not negatively impact the woman or pregnancy and then advise avoidance of live vaccines in infants until they are six months of age.

Future research agenda

Gaps in current knowledge require an increased research agenda, Box 2. A specific RCT is required to enhance knowledge on how TNFi and non-TNFi biologic drugs can be used to maintain disease control in patients with different levels of disease activity. If the study demonstrates that stopping all or certain biologic drugs in pregnancy leads to loss of disease control, worse pregnancy and/or infant outcomes, patients and healthcare professionals will be better informed when making decisions about using these medications in pregnancy. Consequently, this information will influence global health policy and practice as well as future national and international guidance on use of bDMARDs in pregnancy. Research is also required to study the long-term impact of in utero exposure to bDMARDs as well as corticosteroids and conventional DMARDs on long term outcomes of children born to mothers with IA. Such trials in pregnant women and children post-partum are challenging to conduct and recruit to target, hence a multi-centre approach is essential.

Conclusions

Therapeutic decisions in pregnancy are challenging as they need to balance the risks of medications on the developing fetus with the risks of uncontrolled disease for both mother and baby. Currently, unsubstantiated concerns of fetal harm by maternal bDMARDs have led to withdrawal of treatment from pregnant women. Discontinuation of treatment in anticipation of and during early pregnancy increases the risk of disease flare. Given the association between increased IA activity to preterm birth and small for gestational age, it is likely that stopping effective bDMARD treatment, elevates the long-term health risks to offspring. We propose a re-consideration of equipoise and an agenda for future research to optimise the safe and effective use of bDMARDs for IA in and around pregnancy, Box 3.

List of Tables, Figures and Boxes

Contributors

IG and IT conceptualised the study. IG, IT and NS wrote the original draft. All other authors reviewed and edited the draft. All authors had full access to all the data in the study and had final responsibility for the decision to submit for publication**.**

Declaration of interest

IG has grants from UCB; received honoraria as co-author on an educational review article in 2020 (MGP); speaker fees from UCB; and participated in advisory boards for UCB. IT has received speaker fees from UCB. CNP has received speaker fees from UCB and participated in advisory boards for UCB. CT has received honoraria to provide an online lecture in a related area in 2022, and to be co-author on an educational review article in 2020 (MGP); and acted as an expert witness for obstetric cases in the UK. SD has received speaker and consulting fees from UCB. NF has received consulting fees from ALK, Sanofi Aventis, Gideon Richter, Abbot, Galderma, Astra Zeneca, Ipsen, Vertex, Thea, Novo Nordisk, Aimmune; speaker fees from Abbott Singapore; and participated in advisory boards for Orion. RJEMD has grants from Dutch Arthritis Association, ZonMw, UCB, Galapagos paid to his department; consulting fees from Galapagos & UCB; participated in advisory board for Galapagos and UCB; and speaker fees from UCB, Roche, Abbvie, Genzyme, Novartis, Astra Zeneca and Eli LilY. MC has grants from GSK and UCB; consulting fees from GSK and UCB; and participated in advisory boards for MotherToBaby. All other authors declare no competing interests.

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