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Review

Biologic therapies and pregnancy: the story so far

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Abstract

Biologic therapies have revolutionized treatment outcomes for patients with inflammatory arthritis. However, there remains a concern regarding their safety during conception, pregnancy and breastfeeding. Data on the safety of these treatments are largely limited to uncontrolled case reports. Collective evidence from many hundreds of pregnancies in inflammatory arthritis and IBD have suggested that exposure to anti-TNF therapies at the time of conception or during the first trimester does not result in an increased risk of adverse pregnancy and fetal outcomes. Monoclonal antibodies, and to a lesser extent recombinant fusion proteins, do cross the placenta during the second and third trimester and are functional in the fetus, as evidence by lymphopaenia reported at birth in children exposed to rituximab *in utero*. In addition, live vaccines should be avoided in children with *in utero* exposure to biologics for at least the first 6 months of life. The longer-term effects of *in utero* exposure remain unknown. Studies suggest that many of these drugs do enter breast milk in small amounts, but the extent to which they are absorbed by the infant is less clear. Limited reports have not suggested adverse pregnancy outcomes in women whose partners were exposed to anti-TNF therapies or rituximab at the time of conception. Data on other biologic therapies, including anakinra, abatacept and tocilizumab, in both men and women remain extremely limited.

Key words: biologic therapies, anti-TNF therapies, rituximab, tocilizumab, abatacept, anakinra, inflammatory arthritis, pregnancy outcomes, breastfeeding.

REVIEW

Introduction

The introduction of biologic therapies has significantly improved outcomes for patients with inflammatory rheumatic diseases. Between 1999 and 2012, nine biologic agents were approved for RA. These include anti-TNF inhibitors (etanercept, infliximab, adalimumab, golimumab and certolizumab pegol), an IL-6 inhibitor (tocilizumab), an anti-CD-20 antibody (rituximab), an IL-1 receptor antagonist (anakinra) and a T cell co-stimulation modulator (abatacept). Many of these, primarily the TNF inhibitors, are also approved for the treatment of other inflammatory arthritides, including PsA, AS and JIA, as well as psoriasis and IBD. Rituximab is also a long-standing treatment for B cell non-Hodgkin's lymphoma (NHL). The efficacy and safety of these agents have been studied in both clinical trials and, increasingly, in longer-term observational studies such as drug registries. However, the safety of these therapies during pregnancy remains a concern among both patients and health care professionals, especially as most of the inflammatory arthritides can affect both men and women during their child-rearing years and the conditions may flare if previously effective medication is discontinued prior to a planned conception. In addition, many traditional DMARDs such as MTX are contraindicated during pregnancy due to the risk of spontaneous abortion and congenital malformations.

Current manufacturers' guidelines in the UK [1] recommend that all of the currently licensed biologic therapies be discontinued prior to conception for variable periods of time (Table 1), primarily due to the lack of controlled studies of these treatments in pregnant women. Studying the safety of new medications in pregnancy and lactation is challenging. Pregnant women are usually excluded from clinical trials and strict contraception is advised throughout participation and treatment, therefore information regarding the safety of these therapies during pregnancy and breastfeeding remains extremely limited, often limited to animal studies. Most post-marketing experience is obtained through studying uncontrolled reports of inadvertent exposure. Case reports are not without limitations.

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TABLE 1 Biologic drug structure and current UK summary of product recommendations on use during pregnancy

Drug	Structure/function	Current UK summary of product recommendations for use during pregnancy[a]
Etanercept	Soluble p75 TNF-receptor and IgG1 Fc portion fusion protein	Discontinue at least 3 weeks prior to conception
Infliximab	Chimeric human-murine IgG1 monoclonal antibody against TNF	Discontinue at least 6 months prior to conception
Adalimumab	Fully human monoclonal IgG1 antibody against TNF	Discontinue at least 5 months prior to conception
Golimumab	Fully human monoclonal IgG1 antibody against TNF	Discontinue at least 6 months prior to conception
Certolizumab pegol	Pegylated humanized antibody Fab′ fragment against TNF	Discontinue at least 5 months prior to conception
Rituximab	Chimeric human-murine IgG1 monoclonal antibody against CD-20 (on B cells)	Discontinue at least 12 months prior to conception
Anakinra	Recombinant human IL-1 receptor antagonist	Not recommended during pregnancy—no details on cessation advice
Abatacept	Extracellular CTLA-4 domain and IgG1 Fc portion fusion protein	Discontinue at least 14 weeks prior to conception
Tocilizumab	Humanized monoclonal IgG1 antibody against IL-6 receptor	Discontinue at least 3 months prior to conception

[a]Source: www.medicines.org.uk [1].

They cannot capture the full denominator of treated women and include a significant amount of both underreporting and selective reporting. Also, for drugs that have been on the market for a longer time, case reports of pregnancy become less novel and therefore the rates of reporting decrease over time. Therefore we can be certain that these cases do not capture the full experience of anti-TNF use during pregnancy. These limitations aside, it is important to study this collective experience to help gain an understanding of the potential risk of exposures to help counsel patients who are considering pregnancy or who become pregnant while receiving these therapies and also direct future research in the area. This review aims to summarize the current information available regarding the use of biologic therapies during conception, pregnancy and breastfeeding. It is largely directed at use in patients with inflammatory arthritis, although, where necessary, data from use in other conditions, primarily IBD, are used for discussion.

Potential risks of biologic therapies to the pregnant patient

TNF is known to play a crucial role in the body's defence against bacterial and viral infections. The use of anti-TNF therapies is associated with an increased risk of serious and opportunistic infection [2]. This risk is felt to be higher earlier on in the course of treatment and may decrease as disease activity comes under control [3]. Pregnancy is a state of relative immunosuppression and therefore there is a theoretical risk that the use of anti-TNF therapies during pregnancy could increase this risk of infection further. Of particular interest in pregnancy is the increased risk of intracellular infections, such as *Listeria monocytogenes*, associated with the use of anti-TNF therapies [4, 5]. Women are provided with guidance on safe food consumption during pregnancy to avoid this infection, as it is known to be associated with pregnancy loss and neonatal morbidity and mortality [6], and this information should be specifically reiterated in women who have been exposed to anti-TNF drugs just prior to or during pregnancy.

Potential risks of biologic therapies to the pregnancy/fetus

Transplacental transfer of biologic therapies

It is well recognized that maternal IgG antibodies cross the placenta into the fetal circulation [7, 8]. At term, the majority of antibodies in a newborn are of maternal origin. This knowledge is often exploited to ensure protection of the newborn against certain infectious diseases by immunizing pregnant women in the later stages of pregnancy [9].

Antibodies are large proteins (>100 kDa) and therefore simple diffusion of monoclonal antibodies across the placenta is unlikely to occur. Instead, they rely on active transport across the placenta via Fc receptors on trophoblasts. These receptors begin to develop around the beginning of the second semester of pregnancy (~week 14), with active transport beginning during the second trimester and rapidly increasing over the third trimester. At term, fetal levels of IgG often exceed maternal levels. Based on this knowledge, it is felt that exposure to maternal antibodies at the time of conception and during organogenesis is extremely limited.

All of the currently licensed biologic drugs for use in inflammatory arthritis have an antibody structure. The

majority are monoclonal antibodies, and animal studies suggest they are handled in the same fashion as naturally occurring maternal antibodies. There are now a small number of human studies that have assessed this in a more direct manner (Table 2) with direct measures of drug levels in newborns and breast milk in women exposed to anti-TNF therapies during pregnancy. Studies with infliximab have largely been limited to women receiving the drug for IBD. Unlike RA, improvement of IBD during pregnancy is less common, with many women requiring treatment throughout pregnancy [10]. In the majority of cases, infliximab and adalimumab levels in the child at birth and in the first few weeks of life were at least equivalent to those in the mother. However, in all cases these levels declined in the baby, even despite breastfeeding and repeated infusions in the mother. Studies of etanercept have also found drug levels in the newborn, although these were at a significantly reduced fraction of the levels in the mother's circulation, suggesting a lesser degree of active transport of this antibody structure, and again, the levels continued to decline even in cases with continued breastfeeding.

The experience with certolizumab pegol may be different. The drug is a pegylated humanized antibody Fab′ fragment against TNF, and as such lacks an Fc receptor. Thus active placental transport is not thought to occur, as evidenced by studies with a surrogate pegylated antibody in rats [11]. Data in women largely confirm this finding, although there have been reports of trace levels of the drug in newborns [10]. The mechanism of this presumably passive transfer is not currently understood. There are no published human studies of rituximab, abatacept, anakinra or tocilizumab drug levels in newborns.

Collected safety experience of anti-TNF agents in pregnancy

There is now a growing body of evidence surrounding the use of anti-TNF therapies prior to or during pregnancy. As discussed, the majority of these reports are cases reports or case series and a number of recent systematic reviews have brought these cases together [12–16]. The majority of cases are in women exposed to infliximab, adalimumab or etanercept, reflecting the time since the licensing of these treatments. A review of cases through 2011 with clear documentation of exposure and outcome included 472 cases across indications [14]. The most recent review, although limited to patients receiving the drug for IBD, included 462 reported pregnancies in the literature to January 2013 in women exposed to adalimumab, infliximab or certolizumab pegol either in the months preceding pregnancy or during the pregnancy itself [15].

The vast majority of women with inflammatory arthritis discontinued the therapy during the first trimester, although there are reports of women continuing the therapies through pregnancy. In most cases it was not known whether discontinuation was a decision of the patient or a recommendation from their physician. Much of the evidence surrounding later trimester exposure to anti-TNF therapies comes from women receiving the treatments for IBD. These summaries of published observations have found that overall, exposure either pre-conception or during pregnancy, including the second and third trimesters, was not associated with an increase in the risk of adverse pregnancy outcomes or congenital malformations compared with general population statistics. Of importance, where major congenital malformations had been reported, they were found to occur at rates less than the estimated population background rate (~3%) [17] and with no consistent patterns. One case report of VACTERL association in an infant exposed to etanercept *in utero*, a syndrome with congenital abnormalities including three or more of vertebral defects, anal atresia, cardiac defects, trachea-oesophageal fistula, renal anomalies and limb abnormalities, with a follow-up review of the US Food and Drug Administration (FDA) database received much attention, although the full review of the FDA safety database did not confirm any additional reported cases of this syndrome [18–21].

The collected experience of 139 pregnancies in women exposed to certolizumab before or during pregnancy (Crohn's disease, 109; RA, 17; healthy, 2; unknown, 1) from the manufacturer's database was presented in 2012 in abstract form [22]. Seventy-four per cent of pregnancies ended in live births, 15% ended in miscarriage and 11% ended in termination and two infants were born with congenital abnormalities, in keeping with results for other anti-TNF therapies and in line with the general population.

Although the collected evidence, based largely on case reports, is reassuring about exposure to anti-TNF therapies during conception and pregnancy, there are limitations to these data. Interestingly, data presented from a large national prospective observational study of anti-TNF therapies, which actively followed women receiving these drugs from a point prior to conception, found a slight trend towards higher rates of early spontaneous miscarriage among women inadvertently exposed to anti-TNF therapies [12] at the time of conception. However, these results were also confounded by the added exposure to MTX in many of these women at the time of conception. Reassuringly, in keeping with other reports, there were no increases in congenital abnormalities.

Risks of in utero exposure to anti-TNF therapies to the developing child

Due to the nature of placental transport of monoclonal antibodies in particular, it is also important to consider the neonatal period and development of the child exposed to anti-TNF therapy *in utero* and at birth. Despite an increasing collection of case reports of children born to mothers exposed to anti-TNF, there is limited information about their ongoing immune development. A study of macaque monkeys treated with golimumab during pregnancy and lactation did not identify any differences in the development or maturation of the immune system compared with standard saline injections [23]. Routine childhood vaccinations, such as DPT, appear to be safe and effective based on very limited published experience at this

Table 2 Reports of drug levels in breast milk and infants of women exposed to anti-TNF therapies during pregnancy and lactation

Reference	Drug	Diagnosis	Details of exposure	Drug levels in breast milk	Drug levels in infant	Reported outcome in child/ children
Fritzsche *et al.* [41]	ADA	IBD	Treatment during pregnancy and breastfeeding	At week 21, fetal levels <1/1000 the corresponding maternal levels	At birth: fetal levels twice that of maternal; not repeated at week 21	Child remains healthy at 14.5 months of age
Fritzsche *et al*. [41]	ADA	IBD	Treatment during pregnancy and breastfeeding	8 weeks post-partum <0.1% of maternal levels	8 weeks post-partum: undetectable	Child remains healthy at 15 months of age
Mahadevan *et al.* [10]	ADA	IBD	10 patients treated during pregnancy, including T3 and post-partum; 6/10 were breastfed	NR	At birth, infant levels higher than maternal levels in all children; levels detectable for at least 11 weeks post-partum	No birth defects or infections in newborns; one child had brief pulmonary oedema at birth
Ben-Horin *et al.* [42]	ADA	IBD	ADA discontinued at week 30 of gestation	<1/100 of the corresponding maternal serum levels	NR	NR
Mahadevan *et al.* [10]	CZP	IBD	10 patients treated during pregnancy, including T3 and post-partum (12 babies—two sets of twins); 9/12 babies were breastfed	CZP undetectable in breast milk (one patient tested)	Minimal levels of CZP detectable in newborns	No birth defects or infections in newborns
Ostensen and Eigenmann [43]	ETN	RA	ETN started 30 days post-partum; mother lactating but not breastfeeding	Trace levels at week 12	NR	NR
Murashima *et al.* [44]	ETN	RA	Continued ETN throughout pregnancy and breastfeeding	Trace levels at week 12	Cord blood level 3.6% that of maternal levels at birth; not detected at week 12	Healthy term delivery
Berthelsen *et al.* [45]	ETN	AS	ETN continued throughout pregnancy at 25 mg s.c./week and continued during breastfeeding	0.25% of maternal levels at day 43	Cord blood levels ~7% of maternal levels and <0.2% at day 43	Uncomplicated pregnancy and baby was healthy
Keeling and Wolbink [46]	ETN	RA	ETN restarted at 3 months post-partum with continued breastfeeding	Pre-injection levels <1.5 ng/ml; 72 h post 50 mg injection 7.5 ng/ml	NR	Child remains healthy at 3 years of age
Vasiliauskas *et al.* [25]	INF	IBD	INF throughout pregnancy up to 2 weeks pre-delivery, then again at 10 weeks postpartum; child breastfed	Not detected	Equivalent to maternal levels at week 6 but undetectable at week 26	Normal response to routine vaccinations and child remains healthy at 1 year of age
Stengel and Arnold [47]	INF	IBD	Treatment during pregnancy and breastfeeding	Undetectable (daily samples for 30 days following infusion)	NR	Child remains healthy at 27 months of age
Kane *et al.* [48]	INF	IBD	Three patients with INF exposure at regular intervals up until weeks 25–32 and resumed INF within 3–14 days after birth Samples collected between 5 and 43 days after INF infusion post-partum	Undetectable (<0.1 μg/ml)	Undetectable (<0.1 ug/ml)	Normal response to routine vaccinations and child remains healthy at ~1 year of age
Zelinkova *et al.* [24]	INF	IBD	Four patients with INF during pregnancy until weeks 21–30	NR	Therapeutic levels of INF found in cord blood in all mothers with detectable INF at delivery and higher than levels in mothers	Normal response to routine vaccinations and the children remain healthy during the first 4–11 months of life
Ben-Horin *et al.* [49]	INF	IBD	Treatment started while lactating but after breastfeeding discontinued	<1/200 of maternal serum levels	NR	NR

(continued)

TABLE 2 Continued

Reference	Drug	Diagnosis	Details of exposure	Drug levels in breast milk	Drug levels in infant	Reported outcome in child/children
Fritzsche *et al.* [41]	INF	IBD	Treatment during breastfeeding	Week 34 post-partum 1/20 of maternal levels	Week 34, undetectable	Child remains healthy at 22 months of age
Fritzsche *et al.* [41]	INF	IBD	Treatment during breastfeeding	5 days after INF infusion (~4 months post-partum), 2% of maternal level	NR	Child remains healthy at 18 months of age
Steenholdt *et al.* [50]	INF	IBD	Regular infusions until week 31; continued infusions post-partum; child breastfed until week 14	NR	INF detectable at week 16 but not detectable at week 28	Child remains healthy at 13 months of age
Mahadevan *et al.* [10]	INF	IBD	11 patients treated during pregnancy, including T3 and post-partum; 9/11 breastfed	NR	At birth, infant levels higher than maternal levels in all children; levels undetectable after 2–7 months	No birth defects; three children with minor infections between 2 weeks and 9 months

ADA: adalimumab; CZP: certolizumab pegol; INF: infliximab; ETN: etanercept; T: trimester; NR: not reported.

point in time [24, 25]. However, caution with live vaccines should be exercised following the death of an otherwise healthy 4.5-month-old baby from disseminated Bacillus Calmette-Guérin (BCG) following BCG vaccination at 3 months of age. The mother had received infliximab for Crohn's disease throughout pregnancy [26]. A suggestion is to wait at least 6 or more months before administering live vaccines. If more urgent immunizations are required for travel, the advice of an immunologist should be sought.

Collected safety experience of rituximab in pregnancy

The number of reports of pregnancies in women exposed to rituximab either prior to or during pregnancy is increasing. Chakravarty *et al.* [27] reported on pregnancy outcomes from the rituximab global drug safety database. In total they reported 153 pregnancies with a known outcome, including 90 live births, 33 miscarriages, 28 terminations, 1 stillbirth and 1 maternal death. The indications for rituximab varied, with the majority of women receiving the drug for non-rheumatic conditions, including serious hematologic conditions or NHL. Details of concomitant medications were not always available. Seventy pregnancies occurred during or after rituximab treatment as part of a clinical trial. In these cases there was improved reporting of concomitant medications and exposure to potentially teratogenic medications, including MTX, was reported in >50% of these pregnancies. There are now at least 26 cases included in the literature as case reports (Table 3) with exposures ranging from 22 months prior to conception in a patient with SLE [28] to third trimester exposure for idiopathic thrombocytopenic purpura [29]. Again, the majority of reports of exposure during pregnancy are in women with non-rheumatologic conditions. Prematurity was common, although the role of the underlying disease or concomitant medications cannot be discounted. Three congenital malformations have been reported (one clubfoot, one oesophageal atresia and one cardiac abnormality). All live births were reported as healthy at the latest follow-up, ranging from a few weeks to a few years.

Of importance with rituximab is the clinical significance of anti-CD20 monoclonal antibody exposure *in utero* to the developing fetus, with particular respect to B cell depletion and immune development. Across the case series, B cell status was reported in 11 children at birth and was found to be low in 6. Five of six children with preconception or first trimester exposure were found to have normal B cell levels at birth, with low levels reported in one child. However, all children with exposure during the second or third trimester who had B cells measured at birth ($n = 5$) were found to have low or absent levels. All recovered within a few months and response to routine childhood vaccinations, where reported, appeared to be normal. Rituximab has a long half-life (up to 35.9 days) [1]. As the long-term effects of B cell depletion *in utero* and in early infancy remain unknown, it is recommended that

Table 3 Case reports of rituximab exposure either prior to or during pregnancy

Citation	Time of exposure	Diagnosis	Reported neonatal condition	B cell count at birth	B cell count at follow-up (months)	Ig levels at birth	Routine childhood vaccination response
Ostensen *et al.* [51]	Pre (12, 6 and 4 m)	SLE	One termination, two healthy (one premature)	—	—	—	—
Pellkofer *et al.* [52]	Pre (1 w)	Neuromyelitis optica	Healthy term	Normal	—	Normal	Normal
Ng *et al.* [53]	Pre (6 m)	Infertility, positive autoantibodies	Healthy term	—	—	—	—
Ton *et al.* [54]	Pre (6 w)	RA	Twins (one clubfoot)	Normal	Normal (8 m)	Normal	—
Ojeda-Uribe *et al.* [32]	Pre (9 w)	TTP	Healthy term	Normal	—	Normal	
Sangle *et al.* [28]	Pre (10 m)	GPA	Healthy term	—	—	—	—
	Pre (10 m)	SLE	Healthy term	—	—	—	—
	Pre (12 m)	SLE	Premature, oesophageal atresia	—	—	—	—
	Pre (18 m)	SLE	Premature, low birth weight	—	—	—	—
	Pre (22 m)	SLE	Healthy term	—	—	—	—
	Pre (8 m)	SLE	Healthy term	—	—	—	—
Kimby *et al.* [55]	Pre and T1	NHL	Healthy term	Low	Normal (2 w)	Normal	Normal
Ojeda-Uribe *et al.* [56]	T1	AIHA	Healthy term	Normal	Normal (8 w)	Normal	—
Ponte and Lopes [57]	T1	Atopic dermatitis	Healthy term	Normal	—	—	—
Ojeda-Uribe *et al.* [32]	T1 (w 2 and w 4)	RA	Healthy term	—	—	—	—
Rey *et al.* [58]	T2	NHL	Premature	—	—	—	—
Gall *et al.* [59]	T2 (w 26)	ITP	Healthy term	Low	Normal (4 m)	—	
Martinez-Martinez *et al.* [60]	T2	ITP	Premature	Absent	—	—	—
Alkaabi *et al.* [61]	T2	SLE/thrombocytopenia	Premature	—	—	—	—
Daver *et al.* [62]	T2	Hairy cell leukaemia	Healthy term	—	—	—	—
Herold *et al.* [63]	T2/T3	NHL	Healthy, w 35	—	Normal (8 w)	—	—
Friedrichs *et al.* [64]	T2/T3	NHL	Healthy term	Absent	Normal (4 m)	—	Normal
Decker *et al.* [65]	T2/T3	NHL	Healthy, w 33	Low	Normal (12 w)	Normal	Normal
Perez *et al.* [66]	T2/3	NHL	Premature	—	—	—	—
Klink *et al.* [29]	T3	ITP	Healthy term	Absent	Normal (6 m)	Normal	Normal

Pre: pre-conception; w: week; m: month; T: trimester; TTP: thrombotic thrombocytopenic purpura; GPA: granulomatosis with polyangiitis; AIHA: autoimmune haemolytic anaemia.

women should not electively receive rituximab during pregnancy unless the risks of the underlying disease to the mother warrant its use. Women should be advised that pregnancy is not indicated for 12 months following an infusion of rituximab and effective contraception should be used. The exact length of time they should be advised to wait is not known, although current guidelines suggest 12 months. The small number of cases with reported exposure to rituximab in the 12 months prior to conception, the majority with no untoward effects on the pregnancy or neonate, is reassuring, but these cases do not provide enough information to allow a change in the current guideline of 12 months.

Collected safety experience of anakinra, abatacept and tocilizumab in pregnancy

Published pregnancy experience with anakinra, tocilizumab and abatacept is extremely limited. Anakinra was administered throughout pregnancy to three patients with adult-onset Stills disease who all delivered healthy babies [30, 31]. First trimester exposure to abatacept in combination with MTX was reported in a 33-year-old woman with RA. She delivered a healthy term infant who remained well at age 3.5 years [32]. Experience with tocilizumab has largely been limited to conference abstracts. The outcomes of 31 pregnancies were reported at the ACR Annual Meeting in 2010. Outcomes included 13 elective termination, 7 spontaneous abortions (5 also receiving MTX) and 11 delivered full-term newborns (9 also receiving MTX). Of these, 10 were healthy and 1 died 3 days postpartum from complications following placenta previa [33].

Biologic therapies and breastfeeding

Information on biologic therapy use while breastfeeding is largely limited to anti-TNF therapies. The predominant antibody in breast milk is IgA, although smaller quantities of IgG and IgM are also seen [34, 35]. Where studied, the levels of anti-TNF therapies detectable in breast milk have been found to be significantly lower than those in the maternal circulation (Table 2). Drug levels in the newborn continue to drop or are undetectable despite continued breastfeeding. One challenge of breastfeeding is it is not known what quantity of milk each child consumes over the course of a day. It is also not known how much proteolytic digestion of these proteins in the infant's digestive tract affects the degree of absorption of any drug that is present. To date, in the few case reports of women receiving anti-TNF therapies (primarily etanercept and infliximab) who continued to breastfeed, no untoward effects have been noted in the infants.

Biologic therapies in fathers

There is limited published experience in men exposed to anti-TNF therapies at the time of conception. However, the issues around safety are equally important for men given the limitations on the use of standard DMARDs, including MTX and SSZ, prior to conception. Two early case series suggested semen abnormalities in men exposed to infliximab. A series reported asthenozoospermia in two of four men with AS receiving infliximab [36]. A second study of 10 men with Crohn's disease reported a significant increase in semen volume with a trend towards decreased sperm motility and normal forms post-infusion [37]. However, a further study of 25 men with SpA, including 15 patients receiving anti-TNF therapies (infliximab, adalimumab or etanercept), found no differences in sperm quality between anti-TNF-treated patients and healthy controls. Interestingly, patients with SpA who were not receiving anti-TNF were more likely to have poor motility compared with those on treatment [38].

Overall, exposure to anti-TNF therapies in men at the time of conception does not appear to be associated with any adverse pregnancy outcomes in their partners or newborns. Published clinical experience remains limited, with a total of 25 pregnancies reported from 20 men resulting in 23 healthy babies, 1 miscarriage and 1 therapeutic first trimester termination following the development of hydrocephaly in the fetus (it should be noted that the father was also receiving MTX for PsA at the time of conception) [39, 40]. Data in abstract form also report 13 pregnancies from fathers exposed to certolizumab, including 10 live births, 2 miscarriages and 1 termination [22]. There are no reports of male-related infertility in relation to these therapies.

Data on paternal exposure to other biologic therapies are limited. The rituximab global drug safety database reported eight cases of men exposed to rituximab at the time of conception. Outcomes included seven healthy term infants and one spontaneous miscarriage [27].

Summary

Overall, the collected experience does not suggest an adverse effect of exposure to anti-TNF therapies at the time of conception. Exposure to anti-TNF therapies in later pregnancy, particularly to monoclonal antibodies, is associated with high drug levels in the newborn. Live vaccines should be avoided for at least the first 6 months of life in children with *in utero* exposure to biologics. The longer-term effects of this exposure remain unknown. Although it may seem tempting to draw conclusions from the growing, generally positive, experience with anti-TNF therapies, blockade of alternative cytokines and immune pathways may have different implications for conception, implantation, early fetal development and neonatal safety and therefore the use of other classes of biologic therapies in pregnancy cannot be recommended at this time.

Rheumatology key messages

- Growing evidence suggests that maternal exposure to anti-TNF agents at conception is not associated with adverse outcomes.
- Monoclonal antibodies cross the placenta and the long-term effects on the child remain unknown.
- Pregnancy data for non-anti-TNF biologics are lacking and routine use in pregnancy cannot be recommended.

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