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Rheumatoid arthritis and pregnancy: evolution of disease activity and pathophysiological considerations for drug use

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Abstract

It has long been known that pregnancy and childbirth have a profound effect on the disease activity of rheumatic diseases. For clinicians, the management of patients with RA wishing to become pregnant involves the challenge of keeping disease activity under control and adequately adapting drug therapy during pregnancy and post-partum. This article aims to summarize the current evidence on the evolution of RA disease activity during and after pregnancy and the use of anti-rheumatic drugs around this period. Of recent interest is the potential use of anti-TNF compounds in the preconception period and during pregnancy. Accumulating experience with anti-TNF therapy in other immune-mediated inflammatory diseases, such as Crohn's disease, provides useful insights for the use of TNF blockade in pregnant women with RA, or RA patients wishing to become pregnant.

Key words: Pregnancy, Rheumatoid arthritis, Disease activity, Pregnancy outcome, Drug treatment, Anti-TNF, Review.

Introduction

The first observation that the symptoms of RA often ameliorate during pregnancy dates back to the landmark publication of Hench in 1938 [1] and has been confirmed many times since then. The mechanisms responsible for decreased disease activity during pregnancy and post-partum flare of RA, however, have remained elusive, although the potential role of a number of immunological and hormonal factors has been described. In AS, disease activity does not seem to be influenced by pregnancy, whereas in SLE an increased risk of disease flares has been described both during pregnancy and the post-partum period, especially in patients with active disease at conception.

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For rheumatologists, the management of RA patients wishing to become pregnant involves adaptation of the therapeutic regimen, thereby balancing the need to withdraw teratogenic drugs, such as MTX and LEF, while keeping disease activity under control. In the rheumatological setting, little data are available on the use of anti-TNF therapy in the preconception period or during pregnancy in RA women.

This article reviews the effect of pregnancy on disease activity in RA, discusses the effects of disease activity on pregnancy outcome and gives an overview of drug use before and during pregnancy and lactation. In particular, literature data on the use of anti-TNF therapy during pregnancy in immune-mediated diseases are summarized in order to provide guidance on whether anti-TNF therapy is safe and useful to treat pregnant RA patients or RA patients wishing to become pregnant.

Effect of pregnancy on disease activity

Since the publication by Hench [1], several studies have confirmed the spontaneous improvement of RA during pregnancy and an increased risk of flare after delivery [2–7] (Table 1). Hench [1] reported improvement in 33 of 34 pregnancies recalled by 20 patients, while Oka observed symptomatic improvement, mostly starting in

Table 1 Overview of studies describing improvement of RA symptoms during pregnancy and relapse after delivery

Reference	Study type	Number of patients (pregnancies)	Study period	Disease activity evaluation	Patients with improvement during pregnancy, %	Patients with post-partum exacerbation, %	Disease activity during pregnancy	Disease activity after delivery
Hench [1]	Retrospective	20 (34)	–	Patient reporting	90	90	–	–
Oka [4]	Retrospective	93 (114)	Until 7 months post-partum	Patient files and interviews clinical examination	77	81	–	–
Hargreaves [3]	Retrospective	10 (11)	Until 2–3 months post-partum	Patient history clinical examination	91	91	–	–
Ostensen *et al.* [7]	Prospective	31 (49)	12 months before conception to 12 months after delivery	Clinical examination	75	62	–	–
Klipple and Cecere [5]	Retrospective	93 (114)	4 months post-partum	Clinical examination	77	82	–	–
Nelson *et al.* [6]	Mixed (prospective: $n=18$, retrospective: $n=39$)	41 (57)	3 months before conception to 3 months after delivery	Patient reporting Clinical examination ESR	60	–	–	–
Barrett *et al.* [10]	Prospective	140	last trimester to 6 months post-partum	VAS, Likert-scale, HAQ	66	75	–	–
Ostensen *et al.* [11]	Prospective	10	Preconception to 6 months post-partum	Clinical examination, RADAI, 44-joint count, HAQ	70	60	–	–
Forger *et al.* [8]	Prospective controlled	10 (vs. 40 Non-pregnant RA, 29 pregnant controls)	First trimester to 6 months post-partum	Clinical examination, RADAI, SF-36	–	–	↓ (pain, physical functioning)	↑ (pain)
de Man *et al.* [9]	Prospective controlled			DAS-28, ESR, CRP, HAQ	–	–	Remission in 0–23% of patients depending on type of DAS-28 caluclation ↑ HAQ first to third trimester	DAS-28 +0.22 *vs* third trimester = HAQ
de Man *et al.* [12]	Prospective	84	Preconception/first trimester to 6 months post-partum	DAS-28	39	38	↓ DAS-28	↑ DAS-28
de Man *et al.* [24]	Prospective	118 (118)	Preconception/first trimester to 6 months post-partum	EULAR response criteria DAS-28	43–75	33–42		

SF-36: short-form 36 health survey; VAS: visual analogue scale.

the first trimester, in 77% of patients, and post-partum flare within 4 months after delivery in 81% [4]. In a study by Ostensen *et al*. [7], pregnancy-associated remission of RA was reported in 75% of patients, with post-partum exacerbation in 62%. Klipple and Cecere [5] reported ~70% of patients improving during pregnancy, with >90% of them experiencing a disease relapse in the first year post-partum. A study of 57 pregnancies in 41 women by Nelson *et al*. [6] found remission in 22 (39%) and improvement of the disease in 12 (21%) pregnancies.

These high remission or improvement rates need to be interpreted with caution, as the data mostly come from small retrospective analyses that use various definitions of disease activity and clinical amelioration, often rely on patients' recall of symptoms, and sometimes fail to use validated clinical measurements of disease activity. Pregnancy itself has been shown to influence the measurement of disease activity [8, 9]. In a comparison of different disease activity scoring tools in pregnant women with RA *vs* healthy controls, 28-joint DAS (DAS-28)-CRP without assessment of global health was the preferred tool for measuring RA disease activity in pregnant patients [8, 9].

In the UK, a nationwide prospective study of 140 pregnant women with RA, recruited during pregnancy and followed until 6 months post-partum, reported improvement in joint swelling and pain in about two-thirds of patients, although the extent of improvement was limited, with only 16% of women reaching remission during pregnancy [10]. More recent prospective studies using validated clinical tools to measure RA disease activity confirmed the improvement of RA during pregnancy and increased risk of flares post-partum, but the extent of improvement was smaller than in earlier studies. Ostensen *et al.* [11] reported a decrease in disease activity during pregnancy, measured with several validated clinical tools [swollen joint count, RA disease activity index (RADAI) score and HAQ] in a small group of 10 RA patients. The Dutch Pregnancy-induced Amelioration of Rheumatoid Arthritis (PARA) study [12] prospectively evaluated disease activity using DAS-28-CRP-3 in RA patients fulfilling the ACR criteria for RA and recruited between 2002 and 2006. Mean disease activity scores significantly decreased during pregnancy and increased post-partum. Overall, 39% of patients improved during pregnancy, mirrored by flares observed in 38% of patients from 12 to 26 weeks post-partum. The highest impact on disease activity was observed in patients with moderate or high disease activity in the first trimester. Improvement of RA was observed despite the concomitant reduction of drug therapy: MTX, LEF and biologicals were not used at all during pregnancy in this study.

Apart from the use of more objective disease activity measurements and elimination of recall bias, the fact that treatment options for RA have substantially improved over the past decade offers an additional explanation why recent prospective studies yield lower improvement rates than older retrospective studies. Better disease control before conception obviously leaves less room for pregnancy-associated amelioration.

Pregnancy not only mitigates disease activity in RA patients, but also decreases the risk for RA onset [13–15]. According to Lansink *et al*. [13], this protective effect lasts until the first 3 months post-partum, whereas other studies observed a higher risk to develop RA in the first 6 months [4] or the first year post-partum [14]. A Norwegian registry study found a peak RA incidence in the first 2 years after delivery [16]. Women who have ever been pregnant have an almost 2-fold lower risk of getting RA [14, 17–19], and a better outcome if they do get RA [20]. Additionally, multiple pregnancies may have a slightly beneficial effect on the long-term disease outcome of RA, with slightly fewer erosions and better functional level [21].

Except for a slight decrease in fecundity [6] and a modest risk of prematurity and low birthweight in patients with highly active disease, the course and outcome of pregnancy in RA patients are generally favourable [22, 23]. In the Dutch PARA study, lower birthweight of babies born to RA patients was independently associated with active disease in the third trimester of pregnancy, and indirectly with prednisone use, which was associated with shorter gestational age [22].

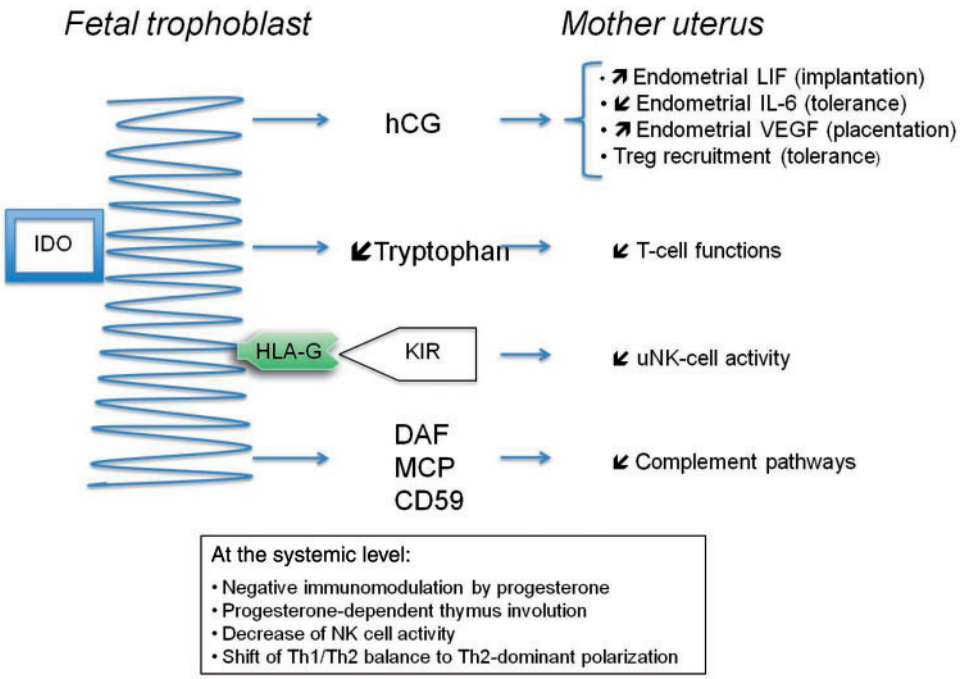
Potential mechanisms mediating the effect of pregnancy on disease activity

Despite intensive research, the main factors responsible for the favourable influence of pregnancy on RA remain largely unknown. Decreased RA disease activity during pregnancy may well be the net result of complex pregnancy-related hormonal and immunological alterations (reviewed in [23]). Clinical improvement of RA is not reflected by parallel changes in anti-CCP or RF levels, although patients negative for anti-CCP and RF were more likely to improve during pregnancy [24].

A number of hormonal and immunological factors that undergo extensive changes during pregnancy have been investigated with respect to their contribution to the pregnancy-associated RA amelioration. So far, serum levels of cortisol, sex hormones and alpha-2 pregnancy-associated globulin (PAG) have been studied, but did not provide a satisfactory explanation for the improvement of RA during pregnancy and its relapse after delivery.

Although the discovery of CSs as therapy for RA by Hench [1] was linked to his initial observation of clinical improvement in pregnant RA patients, increased serum cortisol levels during pregnancy cannot account for the pregnancy-associated decrease in disease activity [25]. The concurrence of rises in alpha-2 PAG and amelioration of disease symptoms during pregnancy was not consistent across different studies [26–28] and the value of PAG as a parameter of disease activity in RA is limited [29]. The higher prevalence of rheumatic and autoimmune diseases in women [30] prompted investigation into the role of sex

Fig. 1 Mechanisms of feto-maternal tolerance. Pregnancy is a situation of induced immunological tolerance in the mother against the semi-allogeneic fetus. The immunological mechanisms responsible for this state of tolerance consist of local components, triggered by trophoblast-induced changes in uterine cytokine profile, decreased T- and NK-cell function and complement activation. In addition, systemic changes in immune function during pregnancy include progesterone-induced thymus involution, decreased NK-cell activity and a shift towards a more Th2-dominated immune-response pattern. KIR: killer cell immunoglobulin-like receptor; uNK: uterine natural killer cell.



hormone levels in pregnancy-associated remission. Increases in oestrogen and progesterone levels may play an indirect role by their effect on the immune response [14, 17, 30–33]. The combined effect of increased levels of cortisol, oestrogen and vitamin D has been implicated in lowering the pro-inflammatory cytokines, IL-12 and TNF-α, during pregnancy [34].

Disease flares post-partum have been linked to a rise in prolactin levels in breastfeeding mothers, as increased RA disease activity at 6 months post-partum was observed in first-time breastfeeding mothers [35]. Prolactin has been described as an immunomodulatory molecule with certain inflammatory effects and a potential role in autoimmunity [36, 37], but whether breastfeeding influences the risk of developing RA remains controversial, since other studies observed a protective effect of breastfeeding on future RA risk [38, 39].

Increased galactosylation of serum IgG correlated with disease remission in a small study with 23 pregnant RA patients [40]. These findings were later confirmed in a larger cohort study [41]. In view of the important function of oligosaccharide modifications of immunoglobulins [42], IgG galactosylation is thought to diminish the antigenicity and pro-inflammatory properties of Ig autoantibodies such as RF. Arguments for this hypothesis are mainly derived from animal models where arthritis could only be induced by infusion of agalactosyl IgG and not by galactosylated IgG [43, 44]. Whether changes in IgG galactosylation are a mere epiphenomenon or a causative factor in pregnancy-related reduction in disease activity remains a matter of debate [42].

Pregnancy is a situation of induced immunological tolerance in the mother against the semi-allogeneic fetus. Immunological changes in pregnancy necessary for this so-called feto-maternal tolerance are summarized in Fig. 1 and include thymic involution [45], decreased NK-cell function [46], and a decrease in Th1 immune response shifting towards a more Th2-dominated immune response pattern [17, 31, 47], whereas T- and B-cell numbers, antibody production and response to vaccines do not change during pregnancy.

Although from the second trimester of pregnancy on, shed trophoblast cells bring fetal antigens into contact with the maternal immune system, pregnancy is not a state of general immunosuppression, as the main mechanisms inducing tolerance towards the fetus are only active at the feto-maternal interface. Syncytiotrophoblast cells express the complement inhibitors, decay-accelerating factor (DAF), membrane cofactor protein (MCP) and cluster of differentiation 59 (CD59), thereby protecting fetal cells from complement-mediated lysis [48]. T-cell activation at the feto-maternal interface is inhibited by the local expression of indoleamine-2,3-dioxygenase (IDO). IDO degrades the amino acid tryptophan, which in T cells is an essential amino acid required for T-cell activation, thereby inducing a strictly local,

TABLE 2 US Food and Drug Administration categories for drug safety during pregnancy [56]

FDA category	Description
A	Adequate and well-controlled studies have failed to demonstrate a risk to the fetus during the first trimester of pregnancy (and there is no evidence of risk in later trimesters).
B	Animal reproduction studies have not demonstrated a fetal risk, but there are no adequate and well-controlled studies in pregnant women. Or Animal reproduction studies have shown an adverse effect, but adequate and well-controlled studies in pregnant women have failed to demonstrate a risk to the fetus during the first trimester of pregnancy (and there is no evidence of a risk in later trimesters).
C	Animal reproduction studies have shown an adverse effect on the fetus, there are no adequate and well-controlled studies in humans, and the benefits from the use of the drug in pregnant women may be acceptable despite its potential risks. Or There are no animal reproduction studies and no adequate and well-controlled studies in humans.
D	There is positive evidence of human fetal risk based on adverse reaction data from investigational or marketing experience or studies in humans, but the potential benefits from the use of the drug in pregnant women may be acceptable despite its potential risks.
X	Studies in animals or humans have demonstrated fetal abnormalities or there is positive evidence of fetal risk based on adverse reaction reports from investigational or marketing experience, or both, and the risk of the use of the drug in a pregnant woman clearly outweighs any possible benefit.

reversible T-cell anergy [49]. Trophoblast cells have a special HLA expression pattern. They do not express HLA-A, HLA-B or Class II molecules, but instead express only HLA-C molecules in addition to the non-classical HLA-E and HLA-G molecules, all of which interact with inhibitory receptors on NK cells. The most specific embryonic signal, human chorionic gonadotrophin (hCG), plays an active role in implantation of the embryo, placental angiogenesis and tolerance of the fetal allograft through stimulation of endometrial leukaemia inhibitory factor (LIF) and VEGF, as well as inhibition of endometrial IL-6, respectively [50]. Finally, Tregs have been shown to accumulate at the feto-maternal interface [31], in response to fetal hCG secretion [51]. Tregs at the feto-maternal interface protect the fetus by inhibiting activation of effector T cells by expressing the inhibitory cytokines IL-10 and TGF-β, by lysing effector T cells or by inhibiting the maturation and function of dendritic cells [17]. Treg dysfunction or deficiency has also been implicated in the pathogenesis of RA. The number of Tregs in pregnant women with RA was found to correlate inversely with RA disease activity in the third trimester of pregnancy and post-partum [17]. The immunological effects of exposure to fetal antigens during pregnancy may contribute to both reducing RA risk as well as mitigation of disease activity during pregnancy, as several studies have shown these effects to be correlated with the degree of materno-fetal HLA class II disparity [39, 52, 53].

Drug treatment of RA during preconception, pregnancy and lactation

Counselling RA patients wishing to become pregnant and treating RA during pregnancy and post-partum can be quite a challenge to the clinician, since several RA medications are contraindicated during pregnancy and lactation, leaving only a limited number of therapeutic options. Ethical constraints prevent the evaluation of the safety of drugs for use in pregnancy during pre-marketing clinical trials, and post-marketing assessment of teratogenicity poses a number of methodological difficulties [54, 55]. Therefore, drug safety information for use in pregnant patients heavily relies on safety classification systems such as the Food and Drug Administration (FDA) categories for drug use in pregnancy (Table 2). This latter classification system places a lot of potentially harmless drugs in Category C due to a lack of sufficient data from controlled studies in humans.

Additional drug safety data often come from voluntary reports of adverse events during post-marketing surveillance or from uncontrolled observational studies or clinical experience. These data are obviously poor sources for evidence-based clinical decision making, since they are mostly retrospective, are subject to recall and publication bias, do not include accurate exposure data, are limited with respect to follow-up of patients or do not include a comparator population. So the clinical management of pregnant RA patients suffers from the wide gap between formal safety data and the need to make therapeutic decisions for adequate disease control in daily clinical practice [54, 56].

Since RA disease activity is likely to improve during pregnancy in a majority of patients, with a subset of patients even achieving remission, the most critical period is the preconception period in the case of planned pregnancy. In this period, conventional DMARDs with teratogenic properties must be stopped, while low disease activity needs to be preserved. Table 3 gives an overview of the FDA categories of drugs commonly used in RA treatment and summarizes the current recommendations

Table 3 Anti-rheumatic drugs and risk during pregnancy

Drug class	FDA category	Clinical recommendations
Symptom-modifying drugs		
NSAIDs	B	First part of pregnancy
	C	After 30 weeks of gestation. Increased risk of premature closure of the ductus arteriosus
CSs	C	Use during the first trimester is associated with increased risk of oral cleft in the newborn
		Increased risk of adrenal insufficiency
DMARDs		
SSZ	B	No increased risk of congenital malformations
		Combine with folate supplements
AZA	D	Can be continued to maintain remission during pregnancy
MTX	X	Contraindicated in pregnancy
		Discontinue 3–6 months before conception
LEF	X	Contraindicated in pregnancy
		Discontinue 2 years before pregnancy or use cholestyramine washout procedure until plasma levels are $<0.02\,\mu g/ml$ on two measurements spaced at least 2 weeks apart
Anti-malarials	C	HCQ is compatible with pregnancy
		Risk for retinal toxicity and ototoxicity higher for chloroquine than for HCQ
Biologicals		
Anti-TNF	B	Anti-TNF antibodies are not transferred to the embryo/fetus in first trimester of pregnancy
Abatacept	C	No human pregnancy data available
		Discontinue 10 weeks before planned pregnancy
Rituximab	C	Reversible B-cell depletion or lymphopenia in the neonate
		Long half-life. Discontinue 1 year before planned pregnancy
Tocilizumab	C	No human pregnancy data available.
		Discontinue 10 weeks before planned pregnancy

for their use in pregnant patients or patients wishing to become pregnant.

NSAIDs

NSAIDs generally fall into FDA Category B and most of them can be used safely in the first part of pregnancy, although increased risk [odds ratio (OR) = 1.8, 95% CI 1.0, 3.2] of first trimester miscarriage under NSAID treatment has been reported [57]. The risk associated with NSAID use increases with pregnancy duration, since NSAIDs used late in pregnancy can cause premature closure of the ductus arteriosus and increase the risk of neonatal bleeding [58]. Moreover, NSAID use in pregnancy has been associated with reversible impairment of fetal renal function and the development of oligohydramnios, in which case immediate discontinuation of NSAID administration is required [58]. Most NSAIDs therefore receive an FDA Category C labelling beyond 30 weeks of gestation.

Data on the use of selective cyclo-oxygenase-2 (COX-2) inhibitors during pregnancy are scarce, hence these drugs are not recommended for treating RA inflammatory symptoms during pregnancy [58, 59]. Moreover, the use of COX-2 inhibitors for prevention of premature labour in at-risk pregnancies was associated with a reversible negative effect on fetal renal function and an increased incidence of delivery before 37 weeks of gestation [60].

Most NSAIDs are considered safe during lactation, although they are excreted in milk in low quantities. Aspirin should not be used in doses exceeding 100 mg/day. Feeding immediately before administration of the drug can help to limit drug exposure in infants [59, 61, 62].

CSs

CSs at doses up to 15 mg/day (prednisolone equivalent) are believed to be safe throughout pregnancy [58]. Higher doses increase the risk of infection and premature delivery [59]. Systemic treatment with CSs during the first trimester of pregnancy is believed to slightly augment the risk of oral clefts, from 1 per 1000 live births to 1.3–3.3 per 1000 live births [63]. In the PARA study, the use of CSs during pregnancy in RA patients was associated with lower gestational age at delivery and increased incidence of premature delivery, even at doses <7.5 mg/day. Women taking prednisone delivered on average 1 week earlier [22].

Pregnant women are preferably treated with prednisone or prednisolone, as these CSs are largely converted to inactive metabolites by placental 11β-hydroxy steroid dehydrogenase, the mechanism in place to protect the fetus from raised levels of maternal cortisol during pregnancy. When the fetus is the target of corticoid therapy, dexamethasone or betamethasone are the compounds of

choice, as they cross the placental barrier more efficiently [64, 65].

Corticotherapy is also considered safe during lactation [62]. Prednisolone is secreted in milk at doses estimated at <0.1% of the maternal dose, which is thought to correspond to <10% of the infants endogenous cortisol level [66].

MTX

MTX is a known teratogen and as such is contraindicated during pregnancy (FDA Category X; Table 2). MTX causes embryotoxicity and teratogenicity in mice, rats and rabbits. In humans, the aminopterin syndrome, consisting of growth deficiency and major CNS, bone and cardiac abnormalities, has been described in children born after exposure to MTX in the first trimester of pregnancy [67]. In view of the long tissue retention time of the active metabolites of MTX, its administration must be stopped 3–6 months before conception [68]. MTX is a folic acid antagonist. Therefore, folic acid supplementation after MTX discontinuation is very important. Past exposure to MTX has no negative effects on pregnancy outcomes [69]. A recent systematic review found that the risk of minor birth defects after conception while using low-dose MTX (5–15 mg/week) is ~5%, with no indication of the serious aminopterin syndrome, and questions whether elective abortion is required for pregnancies conceived during low-dose MTX therapy [68]. MTX is excreted into breast milk in low concentrations [66], but can accumulate in the infant's tissues, and is therefore contraindicated during lactation.

LEF

LEF blocks *de novo* pyrimidine synthesis by inhibiting dihydroorotate-dehydrogenase, and additionally inhibits protein tyrosine kinase activity. Animal reproduction studies indicate that LEF is both embryotoxic and teratogenic, mainly leading to craniofacial, skeletal and cardiovascular malformations [70], which caused the FDA to classify this drug in pregnancy Category X. Due to the long half-life of its metabolites, LEF should be discontinued for 2 years before pregnancy. Alternatively, a washout procedure with cholestyramine should be used until plasma levels are <0.02 μg/ml on two separate measurements at least 2 weeks apart [71].

A recent prospective study compared pregnancy outcomes in 64 RA patients exposed to LEF during pregnancy (61 of which underwent a cholestyramine washout procedure), 108 RA patients not exposed to LEF and 78 healthy controls. In this study, the overall rate of major structural defects between the studied groups was not significantly different, nor did prenatal LEF exposure give rise to a specific pattern of major or minor anomalies [72]. LEF is secreted into breast milk and therefore continues to be contraindicated during breastfeeding [59, 73].

SSZ

It is generally regarded as safe to keep using SSZ during pregnancy (FDA Category B drug), despite some reports noting a higher incidence of neural tube defects, oral clefts and cardiovascular defects. The outcome of pregnancies exposed to SSZ has mainly been studied in women with IBD. A number of studies have concluded that SSZ use during pregnancy does not give rise to increased rates of birth defects in women with IBD when compared with untreated IBD patients or the general population [74, 75]. In a recent meta-analysis treatment of IBD patients with 5-ASA, these drugs did not significantly increase the risk of congenital abnormalities (OR = 1.16, 95% CI 0.76, 1.77, $P = 0.57$), stillbirth (OR = 2.38, 95% CI 0.65, 8.72, $P = 0.32$), spontaneous abortion (OR = 1.14, 95% CI 0.65, 2.01, $P = 0.74$), preterm delivery (OR = 1.35, 95% CI 0.85, 2.13, $P = 0.26$) or low birthweight (OR = 0.93, 95% CI 0.46, 1.85, $P = 0.96$) [76].

SSZ therapy should be accompanied by extra folate supplementation, as this medication halts folate synthesis by inhibiting dihydrofolate reductase. Folic acid supplementation was shown to decrease the augmented risk of oral clefts and cardiovascular anomalies associated with folate antagonist treatment during pregnancy [77]. The SSZ metabolite sulphapyridine is secreted into breast milk. SSZ is generally considered safe during lactation, although a case of bloody diarrhoea in an infant has been reported [62, 78].

Anti-malarial agents

Use of HCQ during pregnancy at the low doses used for malaria prophylaxis does not increase the risk of congenital abnormalities or pregnancy loss [79]. When used as a DMARD at much higher doses, the continuation of this drug during pregnancy has long been controversial and the FDA classifies HCQ in Category C. This controversy was mainly due to reports on retinal toxicity and ototoxicity observed after treatment with chloroquine [80].

HCQ use during pregnancy has been reported in more than 250 pregnancies in SLE patients, with no indications for increased congenital malformations or hearing or vision impairment. A more limited number of children exposed to HCQ have been assessed for retinal toxicity or cardiac conductivity disturbances, again with no indications of adverse effects of the drug. HCQ is secreted into milk at low concentrations, but in view of the transplacental crossing of the drug and the relatively long tissue half-life, it is not deemed necessary to advise against lactation of children exposed to the drug during pregnancy [80].

AZA

AZA and 6-mercaptopurine (6-MP) are designated as FDA Category D drugs (Table 2), indicating that increased risk for the fetus exists, but the risk must be weighed against the possible benefits of the drug. Although AZA is teratogenic in animals, inducing skeletal and visceral malformations in rabbits and mice at doses equivalent to the human dose, multiple case series and cohort studies in human pregnancy, mostly in transplant recipients and IBD patients, have not revealed increased incidence of

congenital anomalies or recurrent patterns of malformations [74, 81–85].

A recent cohort study in Denmark, including birth outcomes of 76 exposed pregnancies, showed an increased risk of preterm delivery and low birthweight in women exposed to AZA or 6-MP during pregnancy, but no significant increase in congenital malformations. However, the data suggest that adverse birth outcomes are caused by the underlying disease rather than by use of AZA or MP [86].

Thiopurines undergo a complex metabolization process and the placenta forms a partial barrier to their metabolites. Indeed, the active metabolites 6-thioguanine nucleotides (6-TGN) are detectable in fetal red blood cells, whereas 6-methylmercaptopurine (6-MMP) is not [87]. Dosing 6-TGN at least once during pregnancy is recommended to avoid excessively high levels, which may cause myelosuppresson in mother and child [86]. Traditionally, breastfeeding is believed to be contraindicated under thiopurine treatment, but several recent studies have shown that 6-MP levels in breast milk are low, and conclude that breastfeeding during treatment with AZA seems safe [87–89].

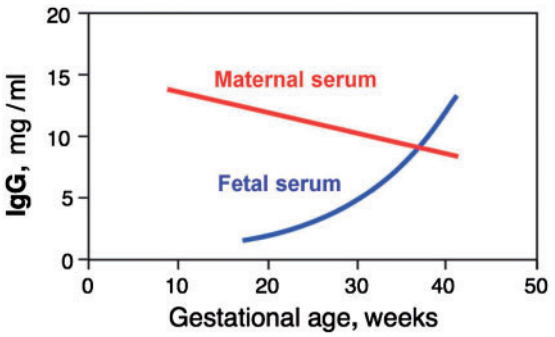
Anti-TNF therapies

The currently available TNF inhibitors (etanercept, infliximab, adalimumab, golimumab and certolizumab) are all classified as FDA Category B drugs, indicating that no teratogenic effects of these drugs were observed in animal reproduction studies, but adequate and controlled human safety data are still lacking.

TNF-α is a pleiotropic cytokine that, in addition to being a pivotal cytokine in the pathogenesis of immune-mediated inflammatory disorders, plays a role in various host defence mechanisms and in regulating and maintaining pregnancy. TNF-α and its receptors are expressed in the uterus, placenta and embryo, but surprisingly, pup morphology, litter size and growth of TNF-α knockout mice were not significantly different from wild-type controls [90]. When exposed to the teratogen CYC, however, fetuses from TNF-α knockout mice showed significantly higher proportions of malformations, indicating that TNF-α plays a role in protecting the fetus against teratogenic stress [91]. Administration of the TNF inhibitors during pregnancy and lactation did not influence the number or function of immune-competent cells in mice [92] or macaques [93], although another study reported growth retardation as well as atrophy of the thymus, spleen and lymph nodes in pups born to mice treated with anti-TNF antibodies [94].

Despite the roles of TNF in establishing and maintaining pregnancy and protecting the fetus, IgG anti-TNF antibodies can probably be safely administered during the first part of pregnancy, since IgG antibodies do not cross the placental barrier in the first trimester. Indeed, transplacental transport of IgG only starts after the first trimester and mainly increases during the third trimester of pregnancy [95]. IgG levels in the maternal circulation decrease during pregnancy, concomitant with a rise of IgG from maternal

Fig. 2 Evolution of maternal and serum IgG levels during pregnancy [94, 95]. IgG levels of maternal origin in the fetal circulation increase over the course of pregnancy. At the end of gestation, fetal IgG levels exceed those in the maternal circulation, which indicates that the placenta develops an active transport mechanism for IgG molecules. Adapted from Malek A, Sager R, Kuhn P, Nicolaides KH, Schneider H. Evolution of maternofetal transport of immunoglobulins during human pregnancy. Am J Reprod Immunol 1996;36:248–55, with permission from John Wiley & Sons Ltd.

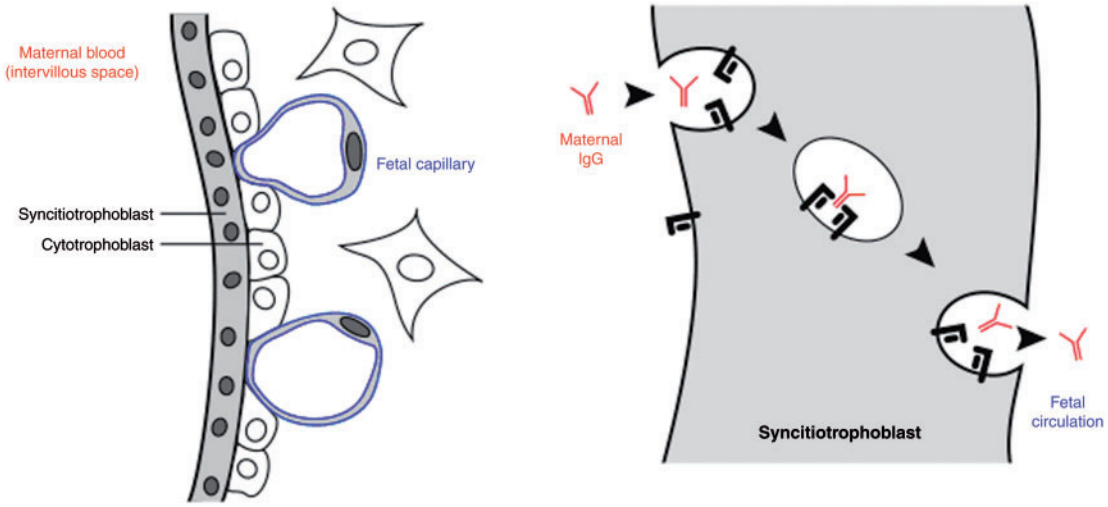


origin in the fetal circulation starting from Week 13 onwards. At term, IgG levels in the fetus exceed the levels in the maternal circulation, which is indicative of an active transport mechanism (Fig. 2) [96]. Transplacental transport was shown to be most efficient for the IgG1 and least efficient for the IgG2 subclass [96]. IgG is transported over the placenta via pH-dependent receptor-mediated transcytosis, in which maternal IgG binds to the so-called neonatal immunoglobulin constant fragment (Fc fragment) receptor expressed on the syncytiotrophoblast membrane, followed by transcytosis and release of bound IgG in the fetal circulation (Fig. 3) [97–99].

Certolizumab is a PEGylated Fab′ fragment of an anti-TNF mAb without Fc fragment. Certolizumab would therefore be expected not to be transferred across the placental barrier according to the mechanism described above. Indeed, animal studies report much lower placental transfer of PEGylated Fab′ antibodies; data in humans are not yet available, but a case of certolizumab administration as rescue therapy in the third pregnancy trimester of an IBD patient had a favourable outcome [100].

A review of more than 120 000 adverse events recorded in the FDA drug surveillance database revealed 61 congenital anomalies in 41 children born to women treated with etanercept or infliximab during pregnancy. These anomalies could be classified into 34 different types, 19 of which were associated with the so-called VACTERL syndrome [101]. VACTERL is an acronym for congenital syndromes characterized by the following birth defects: vertebral, anal atresia, cardiac abnormalities, tracheoesophageal fistula, oesophageal atresia, renal abnormalities and limb abnormalities. This study was criticized for the inherent selection bias in the reporting of anomalies, the lack of sensitivity analysis taking into account co-existing

FIG. 3 Active transplacental transport mechanism for IgG. Fc receptors on syncytiotrophoblast cells at the feto-maternal interface bind IgG from the maternal circulation in a pH-dependent way, transport it over the syncytiotrophoblast cells via transcytosis, and release the bound IgG in the fetal circulation.



risk factors, the fact that the congenital anomalies reported were among the most common in the population and the fact that none of the reported cases showed three anomalies, necessary for formal VACTERL diagnosis. These criticisms cast doubts on the validity of the assumption that TNF inhibitors cause congenital defects of the VACTERL type [102, 103].

Apart from the VACTERL controversy, accumulating data on anti-TNF treatment in RA during pregnancy has not yielded any indications of teratogenicity or adverse outcomes [104–111]. Although the indications that anti-TNF therapy is not teratogenic are growing as the number of pregnancies exposed to anti-TNF during preconception and early pregnancy increases, experience with anti-TNF therapy in pregnant arthritis patients is still quite limited [58, 112].

Probably rheumatologists can learn from the more extensive experience with anti-TNF treatment during pregnancy that exists already for IBD. In the latter disease context, the need for effective treatment during pregnancy is higher than in RA, because IBD disease activity is less suppressed by pregnancy [113, 114]. Additionally, the abdominal location of the disease raises the stakes of maintaining disease remission during pregnancy in IBD, as IBD disease flares during pregnancy carry a high risk of adverse birth outcomes, including prematurity, low birthweight and congenital abnormalities [115]. These considerations have prompted gastroenterologists to build more extensive experience with anti-TNF treatment during pregnancy. A number of studies report intentional use of anti-TNF treatment during pregnancy [108, 116, 117], and the 2010 European Crohn's and Colitis Organisation (ECCO) guidelines state that 'medical treatment for Crohn's disease (except methotrexate) should generally continue during pregnancy, because the benefits outweigh the risk of medication' [118].

Although experience is still limited, the fact that anti-TNF antibodies do not cross the placenta in the first trimester of pregnancy together with the overall unremarkable outcome of pregnancies in women treated with TNF inhibitors lead us to the opinion that TNF blockers can be useful in RA patients to keep disease activity under control in the preconception period after withdrawal of teratogenic DMARDs and in the first trimester of pregnancy.

Abatacept

Abatacept is a cytotoxic T-lymphocyte antigen 4 (CTLA4) human immunoglobulin fusion protein that selectively blocks T-cell co-stimulation through the CD80/CD86 pathway. Abatacept crosses the placenta, but animal studies with abatacept have revealed no congenital abnormalities. Human pregnancy data are still lacking. Hence this drug received an FDA Category C classification and it is advised to discontinue therapy for 10 weeks before conception [58]. Since no data are available currently on the secretion of abatacept into milk, breastfeeding is contraindicated during abatacept treatment [119].

Rituximab

Animal reproduction studies did not observe fetotoxicity caused by the anti-CD20 mAb rituximab, which depletes B cells. Scant data are available on the outcome of human pregnancies exposed to rituximab. Consequently the FDA classifies this drug in Category C.

The eight case reports of rituximab treatment during pregnancy have reported reversible B-cell depletion and lymphopenia in the neonate, but no congenital malformations. Due to its long-lasting effects, it is recommended that rituximab treatment be stopped 1 year before conception [79]. Currently data on secretion of rituximab in breast milk are still lacking, hence the safety of this biological during lactation cannot be guaranteed [119].

Tocilizumab

Preclinical studies have not observed adverse effects of tocilizumab on fertility or fetal development. In cynomolgus monkeys, small increases in abortion rates and fetal mortality rates were observed, but these effects only occurred at tocilizumab doses >100-fold the dose used in humans. No pregnancies under tocilizumab therapy have been reported up to now [117]. Currently it is advised to discontinue tocilizumab therapy 3 months before planned pregnancy [58]. Data on excretion of tocilizumab in breast milk are not available at present [120].

Summary

Approximately two-thirds of RA patients experience a decrease in disease activity during pregnancy. Hormonal and immunological changes associated with pregnancy have been implicated to explain this effect, but its mechanisms remain largely elusive.

Treatment options for RA before conception and during pregnancy are limited because of the teratogenicity of DMARDs such as MTX and LEF. HCQ, SSZ and AZA are compatible with pregnancy, as are CSs in doses up to 15 mg/day (prednisolone equivalent) and NSAIDs in the first half of the pregnancy.

Current experience from IBD suggests that anti-TNF therapy is a safe and useful option to bridge the period between discontinuation of teratogenic DMARDs and conception, or during the first trimester of pregnancy for RA patients with aggressive disease. Clinical experience with the newer biologicals in pregnancy is scarce to non-existent, so it is safest to stop these drugs before conception.

Rheumatology key messages

- RA disease activity, measured by validated instruments, decreases during pregnancy in approximately two-thirds of patients.
- Anti-TNF is acceptable to control RA disease activity in the period directly preceding conception.

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