

Use of biologic agents for rheumatic diseases in pregnancy

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Abstract

Biologic agents have ushered a new era in the treatment of inflammatory rheumatic diseases. In recent years, several biologic agents have been approved by food and drug administration and have significantly improved outcomes for patients with immune mediated

inflammatory disorders including rheumatic and inflammatory bowel diseases. The most common used biologic therapeutic agents are tumor necrosis factor inhibitors (etanercept, infliximab, adalimumab, certolizumab pegol, and golimumab), an interleukin (IL)-6 inhibitor (tocilizumab), an IL-1 receptor antagonist (anakinra), an anti-CD-20 antibody (rituximab), and a T cell co-stimulation modulator (abatacept). Their use during pregnancy has been controversial because of absence of controlled studies which have enrolled pregnant women. This brief overview provides published data on use of biologic agents for the treatment of rheumatic diseases in pregnancy.

Key words: Ankylosing spondylitis; Rheumatoid arthritis; Pregnancy; Disease-modifying antirheumatic drugs

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Core tip: Biologic agents are increasingly being used in the treatment of rheumatic diseases. This article presents published data on use of biologic agents in pregnant women with rheumatic diseases.

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INTRODUCTION

Most of the women with rheumatic diseases experience clinical remission during pregnancy, however in some cases, it is needed to continue the treatment throughout pregnancy^[1,2]. Few studies have suggested that high disease activity in rheumatic diseases throughout pregnancy may lead to increased risks for preeclampsia^[3], cesarean delivery^[4], prematurity^[5], low birth weight^[6,7], and intrauterine growth restriction^[4]. Owing to the fact

that important antirheumatic agents such as methotrexate and leflunomide have teratogenic effects, the treatment options are limited, and biological agents may be therapeutic alternative in pregnant women with high disease activity.

Since cytokines play a crucial role in host defense against infections, cytokine blockade is associated with increased risk of opportunistic infections. Previous studies have suggested an increased risk of bacterial, viral and fungal infections due to mycobacterium^[8], salmonella, listeria^[9], hepatitis B and C, herpes^[10], histoplasma, cryptococcus, coccidioides, candida, aspergillus and pneumocystis^[11]. Pregnancy is a period of relative immunosuppression, thus use of biologic agents during pregnancy may further increase the risk of infections^[12].

Since no drug trials have been performed in pregnant women to assess the risk of administration of biologic agents, safety of these agents during pregnancy is still a matter of debate. However, cumulative data suggest that frequency of birth defects after prenatal exposure to biologic agents does not seem to be higher than that occurs in the general population^[13].

Search strategy

A PubMed literature search (2000-2015) was performed to identify studies with human data on pregnancy outcomes after exposure to biologic agents during pregnancy. Search strategy was restricted to the articles published in English and Turkish and included the following search terms "tumor necrosis factor (TNF) inhibitors", "etanercept", "infliximab", "adalimumab", "certolizumab", "golimumab", "tocilizumab", "anakinra", "rituximab", "abatacept", and "pregnancy". First, titles and abstracts of all 931 references were screened; articles which have insufficient data or do not address the topic of the interest were excluded. Inclusion criteria were data on pregnancy outcomes in patients who were exposed to biologic agents before conception and throughout pregnancy. Additionally a hand-search was made looking for the reference lists of the applicable publications. Adequate documentation was found in 10 reviews, 10 registries, 17 case series and 18 case reports. Published data on reports of biologic therapies are summarized in Table 1.

USE OF ANTI-CYTOKINES DURING PREGNANCY

Tumor necrosis factor inhibitors

Efficacy of TNF inhibitors has been demonstrated in reducing disease activity and joint damage and improving health-related quality of life in the patients with rheumatoid arthritis (RA), psoriatic arthritis (PsA), juvenile idiopathic arthritis (JIA), and ankylosing spondylitis^[14]. Most frequently used TNF inhibitors include etanercept, a soluble p75 TNF-receptor and IgG1 Fc fusion protein; infliximab, a human-murine IgG1 anti-TNF monoclonal antibody; adalimumab, a human IgG1

anti-TNF monoclonal antibody; certolizumab pegol, a pegylated Fab fragment of humanized anti-TNF monoclonal antibody; and golimumab, fully humanized TNF-alpha monoclonal antibody^[15].

TNF inhibitors have been rated as Food and Drug Administration (FDA) category B (No evidence of a risk to the fetus was found in animal toxicity studies; however there are no controlled studies which have enrolled pregnant women). TNF inhibitors do not actively cross the placenta during the first trimester and organogenesis, but they are transferred across the placenta during the late second and third trimester^[12]. These can be found in newborn's cord blood in levels that exceed those of the corresponding maternal serum^[16,17]. Additionally, they are detectable in blood of the infant for more than six months after the birth, reducing the safety of vaccination^[16]. Certolizumab does not contain Fc region, thus it does not actively cross the placenta^[18].

Use of TNF inhibitors has been reported in almost 2000 pregnancies of the patients with rheumatic diseases, inflammatory bowel diseases and psoriasis. Based on the published data from case reports^[19-29], case series^[30-34] and registries on etanercept, infliximab, adalimumab, golimumab and certolizumab^[35-37], it has been found that preconception exposure to biologic agents or use of them during pregnancy including first, second and third trimesters is not associated with increased risk of adverse pregnancy outcomes, malformations or birth defects compared with general population.

An FDA database review revealed 61 birth defects in 41 children born to mothers receiving TNF inhibitors^[38]. Of these mothers, 22 received etanercept and 19 received infliximab. The most common congenital anomalies were heart defects, spinal deformities, imperforate anus, tracheoesophageal fistula, renal anomalies and limb defects, which were the features of vertebral defects, anal atresia, cardiac defects, tracheo-esophageal fistula, renal anomalies, and limb abnormalities association. These anomalies were found to be linked with use of TNF antagonists and it was suggested that these agents should not be administered during pregnancy.

British society for rheumatology biologics register (BSRBR) is a database which keeps information about RA patients taking TNF antagonists. Between 2005 and 2006, 11473 patients were registered with the BSRBR. Of these patients, 17 received etanercept, 3 received infliximab and 3 received adalimumab. No congenital malformation was observed^[37]. After this report, another BSRBR report which assesses the outcomes of 118 pregnancies in patients who were exposed to TNF antagonists was published in 2008^[39]. The rate of miscarriage was 27% in the patients who received anti-TNF at the time of conception (group 1), 17% in those with prior exposure to anti-TNF (group 2) and 10% in those who were never exposed to anti-TNF (group 3). The rate of premature delivery was 26% in group 1, 17% in group 2, and 20% in group 3. A perinatal death causing from hypoxia was reported in a patient who was

Table 1 An overview of published data from case reports, case series and registries on biologic agents

Ref.	Study design	No. of pregnancies	Diagnosis	Biologic agent	Time of exposure	Reported outcomes
Bortlik <i>et al</i> ^[6]	Case series	41	27 CD 14 UK	INF ETA	NR	5 spontaneous abortion 2 elective termination 1 congenital malformation (mild hip dysplasia) Healthy infant at 36 wk of gestation
Burt <i>et al</i> ^[9]	Case report	1	CD	INF	T1	Healthy term delivery
Sinha and Patient ^[20]	Case report	1	RA	ETA	C + T1 + T2 + T3	Healthy term delivery
Takayama <i>et al</i> ^[21]	Case report	1	BD	INF	T2 + T3 (discontinued at 32 wk of gestation)	Healthy term delivery
Coburn <i>et al</i> ^[22]	Case report	1	CD	ADA	T2 + T3	Healthy term delivery
Akinci <i>et al</i> ^[23]	Case report	1	AS	INF	T2 + T3	Healthy term delivery
Kraemer <i>et al</i> ^[24]	Case report	1	Takayasu arteritis	ADA	C + T1 + T2 + T3	Healthy term delivery
Hou <i>et al</i> ^[25]	Case report	1	CD	INF	T1 + T2 + T3 (discontinued at 33 wk of gestation)	Healthy term delivery
Umeda <i>et al</i> ^[26]	Case report	1	RA	ETA	T2 + T3	Healthy term delivery
Puig <i>et al</i> ^[27]	Case report	1	Psoriasis	INF	T1 + T2 + T3 (last infusion at 29 wk of gestation)	Healthy term delivery
Jang <i>et al</i> ^[28]	Case report	1	CD	INF	C + T1	Healthy term delivery
Vesga <i>et al</i> ^[29]	Case report	1	CD	ADA	C + T1 + T2 + T3	Healthy term delivery
Mahadevan <i>et al</i> ^[30]	Case series	10	CD	INF	NR	10 live birth
Berthelot <i>et al</i> ^[31]	Case series	15	SpA, RA, IIA, PsA	3 INF 2 ADA 10 ETA	NR	3 premature delivery 0 spontaneous abortion 0 elective termination 0 congenital malformation 2 spontaneous abortion (ETA) 1 elective termination (ETA)
Rump <i>et al</i> ^[33]	Case series	8 pregnancies in 5 women	4 RA 1 AS	ETA	NR	1 spontaneous abortion 1 megacolon congenitum 1 premature delivery
Arguelles-Arias <i>et al</i> ^[34]	Case series	12	8 CD 4 UK	INF	1 C 2 T1 3 T1 + T2 6 T1 + T2 + T3	No congenital malformation, IUGR, SGA
Diav-Citrin <i>et al</i> ^[35]	Registry	83	CD, RA, UK, UndA, PsA, AS, BD	35 INF 25 ETA 23 ADA	81 T1 2 T2 or T3	67 live birth 9 spontaneous abortion 5 elective termination 0 congenital malformation 1 spontaneous abortion (ETA) 1 elective termination (ETA)
Chakravarty <i>et al</i> ^[36]	Registry	17	RA	15 ETA 2 INF	NR	No congenital malformation, IUGR, SGA 14 live births
Hyrich <i>et al</i> ^[37]	Registry	23	RA	17 ETA 3 INF 3 ADA	NR	6 spontaneous abortion (4 ETA, 1 INF, 1 ADA) 3 elective termination (all in patients receiving ETA, 2 also receiving MTX)
Carter <i>et al</i> ^[38]	Registry	41	Autoimmune diseases	22 ETA 19 INF	NR	24 (59%) children had one or more congenital deformities such as vertebral deformities, anal atresia, cardiac anomalies, tracheoesophageal fistula, renal anomalies and limb defects, which were the features of VACTERL

Offiah <i>et al</i> ^[40]	Case report	1	PsA	INF	C + T1 + T2 + T3	Transient colloid membrane
Guiddir <i>et al</i> ^[41]	Case series	4	UK	INF	T1 + T2 + T3	4 neonatal neutropenia
Grosen <i>et al</i> ^[44]	Case report	1	UK	INF	T3	Ten days after INF infusion serum sickness-like reaction in the mother
Ergaz <i>et al</i> ^[45]	Case report	1	RA	ETA (also receiving prednisone and hydroxychloroquine)	C + T1 + T2 + T3	Preterm infant without any congenital anomaly
Hultzsich <i>et al</i> ^[46]	Case series	26	19 RA 6 AS 1 PsA	ETA	T1	Congenital fulminant kaposiform hemangioendothelioma 19 live birth 5 premature delivery 5 spontaneous abortion 2 elective termination
Weber-Schoendorfer <i>et al</i> ^[47]	Case series	53	Autoimmune diseases	28 ADA 25 INF	T1	1 congenital renal agenesis 1 hypoplastic left heart syndrome + hypospadias 1 Wolff Parkinson White syndrome 46 live birth (24 ADA, 22 INF) 8 premature delivery (4 ADA, 4 INF) 4 spontaneous abortion (2 ADA, 2 INF) 3 elective termination (2 ADA, 1 INF) 1 autosomal disease inherited from his father (ADA)
Johnson <i>et al</i> ^[48]	Case series	34	RA	ADA	T1	29 live birth 5 spontaneous abortion 1 undescended testicle
Katz <i>et al</i> ^[49]	Registry	64	82 CD 8 RA 2 JRA 1 UK	INF	53 within 3 mo of C 25 within 3 mo prior to C28 within 3 mo prior to C + T1 30 T1 7 > 3 mo prior to C 6 unknown	1 microcephaly 64 live birth 14 spontaneous abortion 18 therapeutic termination 0 congenital malformation
Cheent <i>et al</i> ^[50]	Case report	1	CD	INF	C + T1 + T2 + T3	No congenital malformation, IUGR BCG vaccination at age of 3 mo
Mahadevan <i>et al</i> ^[51]	Registry	190	124 CD 56 other diseases	CZP	NIR	Died from disseminated BCG disease at age of 4.5 mo 132 live birth 36 spontaneous abortion 22 elective termination
Lau <i>et al</i> ^[56]	Case series	40	24 RA 1 PsA 5 AS 10 UK	GLM	NIR	vesicoureteral reflux, congenital morbus, congenital megacolon, congenital talipes equinovarus, aortic arch anomaly, and unilateral hydronephrosis in four infants 19 live birth 13 spontaneous abortion 7 induced abortion 1 ectopic pregnancy
Berger <i>et al</i> ^[57]	Case report	1	AOSD	Anakinra	C + T1 + T2 + T3	1 unspecified congenital malformation leading to intrauterine death and induced abortion Term delivery complicated with placental retention

Author	Case series	9	CAPS	Anakinra	C + T1 + T2 + T3	Fetal loss of a twin due to renal agenesis. DNA testing revealed the same NLRP3 c.785T > C, p.V262A mutation as the mother	No preterm birth or serious complication
Chang <i>et al</i> ^[59]	Registry	33	RA	TCZ	NR	11 term delivery (1 infant died from ARDS 3 d after emergency cesarean section for intrapartum fetomaternal hemorrhage due to placenta previa)	7 spontaneous abortion 13 elective termination
Rubbert-Roth <i>et al</i> ^[60]	Case series	3	Autoimmune diseases	2 RTX 1 abatacept	T1	3 healthy term delivery	90 live birth 33 spontaneous abortion 28 elective termination 22 premature delivery
Ojeda-Urbe <i>et al</i> ^[61]	Registry	153	Autoimmune diseases	RTX	NR	1 maternal death from autoimmune thrombocytopenia	1 perinatal death 11 perinatal hematologic anomalies 4 perinatal infections 1 congenital talipes equinovarus 1 cardiac malformation
Chakravarty <i>et al</i> ^[64]	Case series	6	5 SLE 1 WG	RTX	8-22 mo prior to C	4 healthy term delivery (3 SLE, 1 WG) 1 preterm low birth weight (SLE)	1 esophageal atresia (SLE)
Sangle <i>et al</i> ^[65]	Case report	1	Autoimmune vasculitis	RTX	7.5 mo prior to C	Spontaneous abortion (Beckwith-Wiedemann Syndrome)	

CD: Crohn's disease; RA: Rheumatoid arthritis; BD: Behcet disease; AS: Ankylosing spondylitis; SpA: Spondyloarthritis; JIA: Juvenile idiopathic arthritis; PsA: Psoriatic arthritis; UndA: Undifferentiated arthritis; JRA: Juvenile rheumatoid arthritis; SLE: Systemic lupus erythematosus; WG: Wegener granulomatosis; AOSD: Adult onset Still's disease; CAPS: Cryopyrin associated periodic syndromes; INF: Infliximab; ETA: Etanercept; ADA: Adalimumab; CZP: Certolizumab; GLM: Golimumab; RTX: Rituximab; TCZ: Tocilizumab; C: Conception; T1: First trimester; T2: Second trimester; T3: Third trimester; IUGR: Intrauterine growth restriction; SGA: Small for gestational age; BCG: Bacille Calmette-Guérin; ARDS: Acute respiratory distress syndrome; NR: Not reported; VACTERL: Vertebral defects, anal atresia, cardiac defects, tracheo-esophageal fistula, renal anomalies, and limb abnormalities; UK: Ulcerative colitis; MITX: Methotrexate.

exposed to etanercept at the time of conception. Additionally four cases of congenital anomalies were reported. In group 1, congenital hip dysplasia and pylorostenosis, and in group 2 Marcus Gunn syndrome and infantile hemangioma were observed. The authors suggested that treatment with TNF inhibitors might be linked with an increased risk of spontaneous abortion, however the effects of disease activity and other antirheumatic agents could not be eliminated.

Offiah *et al*^[40] reported a transient colloid membrane in a 2-d-old infant born to mother receiving infliximab for severe psoriasis and PsA throughout pregnancy in United States. The skin turned to normal at age 1 year with mineral oil treatment.

Guiddir *et al*^[41] reported four cases of severe neutropenia in newborn patients exposed to infliximab. High serum infliximab concentrations were detected several months after birth. It was suggested that the mononuclear phagocyte system of a newborn is inadequate to clear the antibody rapidly.

Tetralogy of Fallot, intestinal malrotation, hypothyroidism, intracranial and intrapulmonary hemorrhage, unilateral renal agenesis, serum sickness-like reaction (with infliximab)^[35,42-44], infantile kaposiform hemangioendothelioma, Kasabach-Merritt syndrome, renal agenesis, urethral defects, cardiac conduction system abnormalities, pylorostenosis, congenital megacolon (with etanercept)^[32,39,45,46], and ventricular-septal defect, congenital hip dysplasia, spina bifida with hydrocephalus, aortic valve disease, corpus callosum agenesis, and congenital hypothyroidism (with adalimumab)^[47,48] have been reported in the babies born to mothers directly exposed to TNF inhibitors during pregnancy. However rates of these anomalies have been found to be similar to those expected for the general population^[35,46,49].

Cheent *et al*^[50] reported use of infliximab during pregnancy in a 28-year-old patient with Crohn's disease. Newborn had no congenital malformation or intrauterine growth

retardation. He was healthy until bacillus calmette-guerin (BCG) vaccine administered at the age of three months. One point five months later he died from disseminated BCG disease which was a rare life-threatening complication of BCG administration.

Certolizumab is different from other TNF inhibitors, it does not contain Fc region, thus it is not actively transported through the placenta^[16]. It has only minimal transplacental transmission to newborn *via* passive diffusion during first, second and third trimesters^[17].

The Union Chimique Belge Pharma global safety database revealed 69.5% live birth rate in 190 pregnant women exposed to certolizumab^[51]. The rates of spontaneous abortions and elective terminations were 18.9% and 11.6%, respectively. Six birth defects were observed in four infants among all live births: vesicoureteral reflux, congenital morbus, congenital megacolon, congenital talipes equinovarus, aortic arch anomaly, and unilateral hydronephrosis. However these congenital anomalies were not thought to be associated with exposure to certolizumab. These pregnancy outcomes were comparable to those reported for united states general population (65% live births, 17% spontaneous abortions, and 18% elective abortions)^[52]. In Pregnancy in Inflammatory Bowel Diseases and Neonatal Outcomes study^[53] where women with inflammatory bowel disease exposed to certolizumab in the third trimester of pregnancy were compared with unexposed group, it was suggested that use of certolizumab in the third trimester was not associated with increase in infant infection rates.

Golimumab is a newer TNF inhibitor and there is limited data on its use during pregnancy^[54]. In a study by Martin *et al*^[55] performed in cynomolgus monkeys received 25-50 mg/kg golimumab twice weekly during pregnancy, no effect was observed on pregnancy outcomes or fetal immune system. Experience with use of golimumab during pregnancy has been limited to conference abstracts. Lau *et al*^[56] reported pregnancy outcomes of 40 women exposed to golimumab at the American College of Rheumatology (ACR) Annual Meeting in 2013. Outcomes included one unspecific congenital anomaly, 19 live births, 13 spontaneous abortions and 7 induced abortions. Of 13 mothers with spontaneous abortion, 4 had concomitant methotrexate use.

Anakinra

Anakinra is a human IL-1 receptor antagonist certified by FDA for the therapy of RA patients with intermediate/high disease activity^[14]. It has been rated as FDA pregnancy category B. It has a half-life of 4-6 h. Because of its short half-life, discontinuance of anakinra before conception is not necessary^[18]. Experiences with use of anakinra during pregnancy are limited. Three pregnancies in patients received anakinra for the treatment of adult onset Still's disease resulted in term live births^[57,58]. Chang *et al*^[59] described outcomes of fifteen pregnancies in nine women receiving anakinra for the treatment of cryopyrin-associated periodic syndrome. Outcomes included 14

healthy term infants and one intrauterine fetal demise resulting from renal agenesis.

Tocilizumab

Tocilizumab is a humanized IL-6 receptor inhibitor used in the therapy of moderate to severe RA and polyarticular and systemic JIA. It is categorized as FDA pregnancy category C. Tocilizumab should be discontinued three months before conception^[18]. Experiences with use of tocilizumab during pregnancy were reported by Rubbert-Roth *et al*^[60] at the ACR Annual Meeting in 2010. Of 33 pregnancies, 13 resulted in induced abortion, 7 resulted in spontaneous abortion and 11 resulted in live births. Of 7 mothers with spontaneous abortion, 5 had concomitant methotrexate use.

ANTI-CELLULAR THERAPY DURING PREGNANCY

Rituximab

Rituximab is a chimeric monoclonal antibody against the B cell surface antigen CD20^[61]. It is indicated for the treatment of severe refractory RA with inadequate response to TNF inhibitors, certain types of vasculitis, non-Hodgkin's lymphoma and chronic lymphoid leukemia^[42]. It is classified as FDA category C, meaning "it has not been studied on pregnant women, however animal developmental toxicity studies have shown an adverse effects on the fetus". It has no active transplacental passage during the first trimester and organogenesis, but actively crosses the placenta during the late second and third trimester^[62], and may affect fetal and neonatal B cell development, causing increased risk for infections^[63]. Chakravarty *et al*^[64] reported pregnancy outcomes in 153 patients exposed to rituximab. Of these pregnancies, 90 resulted in live births, 22 resulted in prematurity and one resulted in perinatal death. 11 infants had hematologic abnormalities at birth (peripheral B-cell depletion, neutropenia, lymphopenia, thrombocytopenia and anemia) and four had perinatal infections. Two infants had congenital defects (congenital talipes equinovarus and cardiac malformation). Sangle *et al*^[65] reported pregnancy outcomes in 5 patients with systemic lupus erythematosus exposed to rituximab before conception. One of the infants was born with esophageal atresia, while the others were healthy. Pendergraft *et al*^[66] reported a miscarriage at 15 wk in a mother exposed to rituximab 7.5 mo prior to conception. Histologic and genetic evaluation of fetus revealed Beckwith-Wiedemann Syndrome. Ojeda-Urbe *et al*^[61] reported two successful outcomes in two women with autoimmune diseases received rituximab in the first trimester of pregnancy.

Preconception and first trimester exposure to rituximab seems not to indicate an excess risk of adverse fetal outcomes. Exposure during second and third trimesters causes decrease in B cells in the fetus^[18]. Further studies, especially prospective registries are needed to explore immune response to vaccines and perinatal infections in

infants born to mothers received rituximab during second and third trimesters.

Abatacept

Abatacept (CTLA4-Ig) is a recombinant fusion protein that modulates T cell costimulatory signal mediated through the CD28-CD80/86 pathway^[67]. It has been approved for the treatment of refractory RA^[4]. Abatacept therapy should be stopped three months before conception^[18]. Ojeda-Urbe *et al*^[61] reported a healthy infant born to a 33-year-old mother exposed to abatacept in the first trimester.

CONCLUSION

Since TNF inhibitors are classified in FDA category B, they are safer than synthetic Disease Modifying Anti Rheumatic Drugs such as methotrexate and leflunomide. Although sporadic cases of congenital malformations have been reported in newborns born to mothers exposed to biologics, these rates appear to be comparable with those expected in the general population. Maternal exposure to TNF inhibitors at conception seems not to be related to adverse pregnancy outcomes. TNF inhibitors do not pass through the placenta during the first trimester, but they cross the placenta during the late second and third trimester. They can be used in the first trimester if no therapeutic alternative is available. But use of these agents in late second and third trimester should be reconsidered more carefully because of high placental transfer. Collected experience does not suggest an increased risk of opportunistic infections in pregnant patients and fetus. However, in case of exposure to these agents in the late second and third trimester, live vaccines should not be administered in the first six months of life because of increased risk for infections.

Abatacept and tocilizumab are classified as FDA pregnancy category C, and they should be discontinued three months before conception. Experiences with use of anakinra and rituximab during pregnancy are limited, larger studies are needed to bring further clarity.

The decision to use biologic agents during pregnancy is difficult. The benefits of biologic agents must outweigh the risks to the fetus/embryo or the mother. Larger and further studies are needed to demonstrate the safety of these agents during pregnancy.

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