Reumatismo, 2014; 66 (4): 304-317

Are biological drugs safe in pregnancy?

A. Calligaro, A. Hoxha, A. Ruffatti, L. Punzi
Rheumatology Unit, Department of Medicine-DIMED, University of Padua, Italy

SUMMARY

The introduction of biological therapies has significantly improved the outcome of inflammatory rheumatic diseases. As most of these diseases affect women and men in childbearing age, some concerns have been voiced as to the safety of these drugs in relation to reproduction and pregnancy.

Data from many hundreds of pregnancies in patients affected by inflammatory bowel disease and inflammatory arthritis have suggested that exposure to anti-TNF therapies at conception and/or during pregnancy is not associated with adverse pregnancy outcomes or any increase in congenital abnormalities. However, the exposure to anti-TNFα agents, particularly to monoclonal antibodies, in late pregnancy is associated with high drug levels in the newborn and their long-term effects on children remain unknown. Therefore, limiting the use of anti-TNFα to the first 30 weeks of pregnancy is recommended to reduce fetal exposure. Live-virus vaccines should be given only when levels of anti-TNFα drugs are undetectable in the serum of infants. Studies suggest that many of these drugs do enter breast milk in small amounts, but the extent to which the infant absorbs them is less clear. Limited reports have not suggested adverse pregnancy outcomes in women whose partners were exposed to anti-TNF therapies at the time of conception. Pregnancy data for rituximab, abatacept, anakinra, tocilizumab and belimumab are limited and their use in pregnancy cannot currently be recommended.

Key words: *Biological drugs; anti-TNFα therapy; rituximab; tocilizumab; abatacept; anakinra; belimumab; pregnancy outcome; breastfeeding.*

Reumatismo, 2014; 66 (4): 304-317

INTRODUCTION

The introduction of biological therapies has significantly improved the outcome of inflammatory rheumatic diseases. As most of these diseases affect women and men in childbearing age, some concerns have been voiced as to the safety of these drugs in relation to reproduction and pregnancy.

Currently, ten biological agents have been approved for rheumatic diseases. These include anti-tumor necrosis factor α (TNFα) inhibitors (etanercept, infliximab, adalimumab, golimumab and certolizumab pegol), an anti-CD20 antibody (rituximab), an IL-6 inhibitor (tocilizumab), an IL-1 receptor antagonist (anakinra), a T cell costimulation modulator (abatacept) and an anti-Blys antibody (belimumab).

Albeit the efficacy and safety of these agents have been studied in both clinical trials and increasingly often in long-term observational studies, little attention in literature has been given to their use in pregnancy. According to the United States Food and Drug Administration (FDA) classification concerning the use of medications in pregnancy, anti-TNFα inhibitors and anakinra are classified in category B, while the others in category C. (1) However, this classification and the presumed safety of these drugs are based on limited data.

Given primarily to the lack of controlled studies, the current manufacturers' guidelines in Italy (2) recommend that all licensed biological therapies be discontinued prior to conception for variable time intervals (Table I).

Besides registry data, some case reports (3-37) and small case series (38-53) have been published reporting exposure to biologics and pregnancy outcomes. However, large population-based studies are limited, and there is a lack of prospective data in pregnant women. The increasing use of antibody-based therapy prompts the need

Corresponding author:
Antonia Calligaro
U.O.C di Reumatologia, Policlinico Universitario
Via Giustiniani, 2 - 35128 Padova, Italy
E-mail: antonia.calligaro@gmail.com

Table I - Biological drugs and current Italian summary of product recommendations on use during pregnancy.

Drug	Current Italian summary of production recommendations for use during pregnancy
Etanercept	Discontinue at least 3 weeks prior to conception
Infliximab	Discontinue at least 6 months prior to conception
Adalimumab	Discontinue at least 5 months prior to conception
Golimumab	Discontinue at least 6 months prior to conception
Certolizumab pegol	Discontinue at least 5 months prior to conception
Rituximab	Discontinue at least 12 months prior to conception
Anakinra	Not recommended during pregnancy-no details on cessation advice
Abatacept	Discontinue at least 14 weeks prior to conception
Tocilizumab	Discontinue at least 3 months prior to conception
Belimumab	Discontinue at least 4 months prior to conception

for further studies in this group of patients. This review aims to summarize the current information available regarding the use of biological drugs during conception, pregnancy and breastfeeding.

BIOLOGICAL THERAPIES IN THE PREGNANT PATIENT

The use of biological therapies is associated with an increased risk of serious and opportunistic infection (54, 55). The survival of the foetus in the womb is subject to an altered Th1/Th2 cytokine balance with Th2 predominance and T-cell transient anergy during pregnancy, in order to ensure a maternal tolerance to paternal allo-antigens expressed by the foetus (56, 57). Moreover, it has recently been reported that regulatory T lymphocyte cells are increased in normal pregnancy and play a critical role in embryo implantation and in the maintenance of the maternal immune tolerance to the semi-allogenic fetal antigens (58). Therefore pregnancy is a state of relative immunosuppression with the theoretical risk that the use of biological therapies during pregnancy could increase this risk of infection. Maternal IgG antibodies cross the placenta via Fc receptors expressed by syncytiotrophoblasts (59) to provide immunity to the neonate. IgG concentrations in fetal blood increase steadily from the early second quarter until delivery and most antibodies are transferred in the third quarter. At the end of pregnancy, fetal levels of IgG often exceed maternal levels (60).

All licensed biologics are complete, or in part, IgG molecules, if constituted both by the Fc and F'ab fragment, or the F'ab fragment alone, respectively. Most of them are monoclonal antibodies and, as suggested by animal studies, are handled like naturally occurring maternal antibodies. A small number of human studies and some case reports have assessed drug transfer in a direct manner by measuring the drug levels in newborns and breast milk in women exposed to anti-TNFα therapy (infliximab or adalimumab) during pregnancy (3, 4, 61). Mahadevan et al. confirmed these data in a prospective study on 31 pregnant women with Crohn's disease who gave birth to 33 infants (62). Infliximab and adalimumab showed significant placental transfer as measured by cord blood levels at birth with a concentration ratio of the cord/mother blood ranging from 87 to 400% depending on the day when the last dose was taken (62). Interestingly, the concentration ratio of the cord/mother blood was not different when the last drug was taken from 2 to 77 days before, whereas it was significantly lower if it was taken up to 91 days before (62). These data suggest that the continuation of infliximab and adalimumab through the third quarter until delivery imply a higher exposure of the foetus/infant to them. Due to the amount of proteolytic

digestion of these proteins in the infant's digestive tract and to the maturation of the reticuloendothelial systems of the newborn, these levels declined in the baby, despite breastfeeding and repeated infusions in the mother.

Certolizumab pegol differs from the other anti-TNFα monoclonal antibodies as the Fc region is missing. Therefore, as evidenced by studies with a surrogate pegylated antibody in rats, it is not actively transported through the placenta (63). This data are confirmed by Mahadevan *et al.* showing a minimal transplacental transfer when patients were treated with certolizumab pegol up to 5 days before delivery (62). Certolizumab pegol levels in mothers ranged from 1.87 to 59.57 μg/mL, while, those in the cord blood ranged from below detection level (<0.41 μg/mL) to 1.66 μg/mL (62). It is to be noted that levels in the cord blood were undetectable in 4 out of 12 infants; this minimal transplacental transfer is probably due to a passive diffusion, even if the mechanism is not currently understood (62).

Case reports on etanercept have also found drug levels in the newborns, although they were lower than the levels in the mother's blood stream, in fact the concentration ratio of the cord/mother blood ranged from 3.6 to 7% (5, 6).

A study of macaque monkeys treated with golimumab during pregnancy and lactation showed that foetuses were exposed to high concentrations of golimumab from the end of the second quarter, and the neonates had high levels of golimumab after birth. Golimumab was detectable in the infant serum for up to 6 months after birth (64).

Belimumab was detected in umbilical cord blood and amniotic fluid in a study on cynomolgus monkeys treated with belimumab throughout pregnancy, confirming

Table II - Summary of reports of maternal exposure to anti-tumor necrosis factor agents during pregnancy.

Reference	Anti-TNFα	Diagnosis	Patients (n)	Trimester exposure	Live births (n)	Pregnancy outcome	Congenital abnormalities (n)
Chambers et al. (38)	IFX	RA	4	T1	3	1 SA, 2 PTB	
Mahadevan et al. (39)	IFX	CD, UC	5	T2/T3 other exposure details NS	5		
Berthelot et al. (40)	IFX	RA, JIA, SpA	3	C/T1:1, C/T1/T2:2	3		
	ADA	RA, JIA	2	C/T1:1, C1/T1/T2/T3:1	2		
	ETN	RA, JIA, PsA, SpA	10	C/T1/T3	7	2 SA	
Chakravarty et al. (41)	IFX	RA	1	Pregnancy, not otherwise specified	1		
	ETN		8		6	1 SA (also MTX)	
Correira et al. (37)	IFX	CD	2	C/T1/T2/T3	2	1 PTB due to placental detachment (acute respiratory failure healthy at 8 mo follow-up), 1 SGA	
Hyrich et al. (42)	IFX	Rheumatologic diseases	3	C/T1	2	1 SA	
	ADA		3	C/T1	2	1 SA	
	ETN		17	C/T1:15, C/T1/T2: 1, C/T1/T2/T3:1	13	4 SA, 1PTB, 1 SGA 1 patient who continued ETN into T2 had an emergency caesarean section for fetal distress	
Kane et al. (43)	IFX	CD	3	C/T1/T2/T3:2, T1/T2/T3:1	3	1 PTB	

Katz et al. (IFX Safety Data-Base) (44)	IFX	CD, UC, RA, JIA	96	C:25, C/T1:28, T1:30, >3 mo before conception:7	64	13 SA, 1 SB, 1 PTB, 1 SGA 1 complicated neonatal course: respiratory distress/jaundice/seizure	1 Tetralogy di Fallot, 1 Intestinal malrotation, 1 Developmental delay and hypothyroidism
Mahadevan et al. (45)	IFX	CD	10	C/T1/T2/T3:8, T1:1, T3:1	10	3 PTB, 1 SGA 1 neonatal jaundice 1 complicated neonatal course: 39 wk with respiratory distress/ desaturation/gastric ulcer day 5; healthy at 6 mo follow-up	
Rosner et al. (46)	IFX	RA, JIA	4	C/T1/T2/T3	4	1 PTB, 2 premature rupture of membranes	
Schnitzler et al. (47)	IFX	CD, UC	35	C/T1/T2	27	6 SA, 1 SB due to cord strangulation; 1 child develop necrotizing enterocolitis and died at 13 d, 6 PTB, 4 SGA	
	ADA		7		5	2 PTB, 2 SGA	
Weber-Schoenderfer et al. (48)	IFX	NS	25	C/T1	22	2 SA, 4 PTB	1 VSD, 1 Hemangiomas
	ADA		28		24	2 SA, 4 PTB	
Zelinkova et al. (3)	IFX	CD, UC	4	C/T1/T2:3, C/T1/T2/T3:1	4	1 PTB	1 Polydactyly left hand
Srinivasan et al. (7)	IFX	CD	1	C/T1	1	1 PTB(24 w) complicated by intracerebral and intrapulmonary haemorrhages; neonate died at 3 d. Mother also exposed to metronidazole, azathioprine and mesalamine for fistuling CD	
Carter et al. (8)	ETN	PsO	1	C/T1/T2/T3	1		1 Tracheal atresia, Tracheoesophageal fistula, Esophageal atresia, Imperforate anus, Hypospadia, Vertebral body abnormality, and Patent foramen ovale
Vasiliauskas et al. (4)	IFX	CD	1	C/T1/T2/T3	1		
Cheent et al. (9)	IFX	CD	1	C/T1/T2/T3	1	1 PTB Infant develop disseminated BCG after vaccination at 3 mo and died at 4.5 mo	
Stengel et al. (10)	IFX	CD	1	C/T1/T2/T3	1		
Johnson et al. (49)	ADA	RA	34	T1 other exposure NS	29	5 SA, 3 PTB	1 Undescended testicle 1 Microcephaly

Ben-Horin et al. (11)	ADA	CD	1	C/T1/T2/T3	1		
Kraemer et al. (12)	ADA	Takayasu's arteritis	1	C/T1/T2/T3	1		
Mishkin et al. (13)	ADA	CD	1	C/T1/T2/T3	1	1 PTB	
		RA	1	C/T1	1		
Vesga et al. (14)	ADA	CD	1	C/T1/T2/T3	1		
Wibaux et al. (15)	IFX	AS	1	C/T1	1		1 Primary cranisynostosis
	ADA	AS	1	C/T1/T2	1		
Mahadevan et al. (62)	IFX	CD	11	C/T1/T2/T3	11	1 infant had hand-mouth-foot disease at 9 mo; respiratory distress 11 mo, 1 infant had upper respiratory infection at 2 wk, 1 infant oral candida 10 wk; GERD 4 mo	
	ADA		10	C/T1/T2/T3	10	1 brief pulmonary oedema at birth	
	CZP		10	C/T1/T2/T3:7, T2/T3:2, T3:1	12 (2 set of twins)	5 PTB and SGA	
Johnson et al. (50)	ETN	RA, PsA, AS, PsO	100	Throughout pregnancy	94	6 SA	1 Congenital hypothiroidism, 1 Microcephaly, 1 Pyloric stenosis, 1 Cystic adenomatoid malformation 1 Hypospadia, 1 Esotropia, Inguinal hernia and VSD, 1 Displacement of the stomach, Epispadia and Specified abnormalities of the retina, 1 VSD and mild peripheral pulmonic stenosis
Murashima et al. (5)	ETN	RA	1	Throughout pregnancy	1		
Berthelsen et al. (6)	ETN	AS	1	Throughout pregnancy	1		
Clowse et al.. (51)	CZP	CD, RA, other condition NS	190	Pregnancy, not otherwise specified	132	38 SA, 11 PTB, 2 SGA 1 neonatal death from brain damage and pneumoperitoneum in one set of twins	1 Vescicoureteric reflux, 1 Right aortic arc with aberrant left subclavian artery, 1 Unilateral hydronefrosis

TNF, tumor necrosis factor; IFX, infliximab; ADA, adalimumab; ETN, etanercept; CZP, certolizumab pegol; RA, rheumatoid arthritis; CD, Crohn's disease; UC, ulcerative colitis; JIA, juvenile idiopathic arthritis; SpA, spondyloarthritis; PsA, psoriatic arthritis; PsO, psoriasis; C, within <3 months prior to conception; T1, first trimester; T2, second trimester; T3, third trimester; NS, not specified; SA, spontaneous abortion; SB, stillbirth; MTX, methotrexate; PTB, preterm birth (<37 wk gestation); SGA, small for gestational age; wk, week; mo, month; GERD, gastro-esophageal reflux disease; VSD, ventricular septal defect.

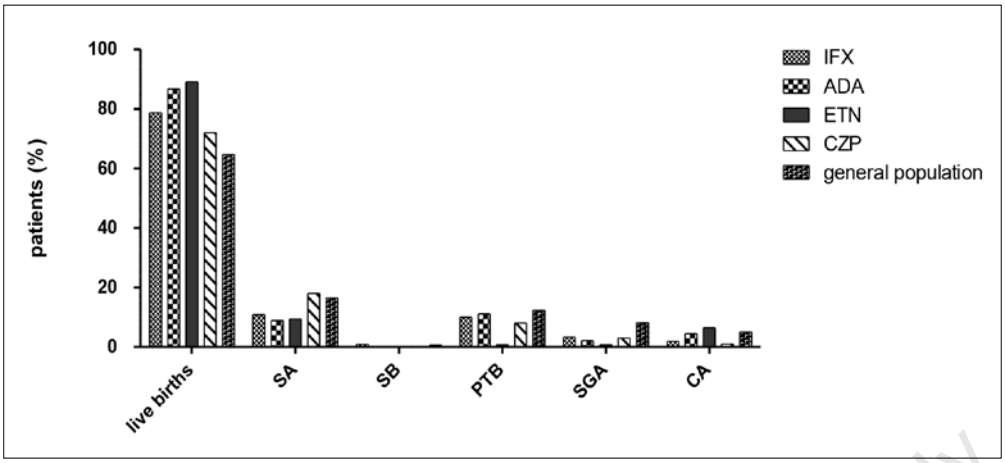

Figure 1 - Anti-tumor necrosis factor-α exposure and pregnancy outcome. IFX, infliximab; ADA, adalimumab; ETN, etanercept; CZP, certolizumab pegol; SA, spontaneous abortion; SB, stillbirth; PTB, preterm birth (<37 wk gestation); SGA, small for gestational age; CA, congenital malformation.

that transplacental transfer resulted in fetal exposure (65).

Case reports on rituximab given during the second and third quarter showed cord blood levels similar to or higher than maternal levels at delivery (16-19).

To the best of our knowledge there are no published studies of abatacept, anakinra or tocilizumab drug levels in newborns.

SAFETY EXPERIENCE OF BIOLOGICAL DRUGS DURING PREGNANCY

Anti-TNFα

There is now growing evidence on the use of anti-TNFα in pregnancy. Table II summarizes the reports of maternal exposure to anti-TNFα agents during pregnancy (3-15, 37-51). The majority of women with inflammatory arthritis (IA) discontinued the therapy during the first trimester (13, 15, 42, 44, 49) although there are reports of women continuing the therapy throughout pregnancy (5, 6, 40, 42, 46). Much of the evidence on the third trimester exposure to anti-TNFα treatment comes from women with inflammatory bowel diseases (IBDs). The total number of patients exposed to anti-TNFα drugs was 639 (infliximab 211, adalimumab 90, etanercept 138, certolizumab 200). The pregnancy outcome during anti-TNFα exposure was compared with that of the general population of the United States evaluating the following parameters: live births, spontaneous abortions, stillbirths, premature births, small for gestational age and congenital malformations (Figure 1) (66). These investigations found that, in most of cases, the exposure at conception or during pregnancy, including the second and third trimesters, was not associated with an increase in the risk of adverse neonatal outcome or congenital malformations compared with the general population. It should be noted that major congenital malformations have been reported less than in the general population, additionally no specific pattern of birth defects was identified (67).

Carter *et al.* described a case of an association of vertebrae abnormalities, anal abnormalities, tracheal problems, esophageal problems, radius or renal defects (VATER) without renal or limb abnormalities in an infant exposed to etanercept in utero (8). A review of the FDA safety database reported 61 types of congenital abnormalities in 41 children born to 40 mothers taking a TNFα antagonist (68). Specifically, 24 (59%) of those children had one or more congenital abnormalities that are part of a spectrum including vertebral defects, anal atresia,

cardiac defects, trachea-esophageal fistula, renal abnormalities, and limb abnormalities (VACTERL), thus raising concerns of a possible causative effect of the anti-TNFα agents. However, due to the nature of voluntary reporting to FDA, the denominator of pregnant mothers treated with anti-TNFα is not known and therefore it is not clear if the rate of occurrence is higher than expected. Moreover, because the most common abnormality reported was a cardiac defect (one of the most common abnormalities in the general population), the association is only speculative.

The PIANO registry, a prospective registry of pregnant women with IBD (326 unexposed, 204 exposed to thiopurine, 291 exposed to anti-TNFα agents and 75 exposed to a combination of anti-TNFα agents and thiopurine) did not find an increase in congenital abnormalities associated with drug exposure (69). In addition, the use of a combination therapy was not associated with an increase in *any complication* (spontaneous abortion, preterm birth, intrauterine growth restriction, caesarean section, or admission to neonatal intensive care unit), even when adjusted for the type or the activity of the disease. It should be noted that, at 12 months of age, infants exposed to a combination therapy with any thiopurine drugs plus either infliximab or adalimumab had a significant increase in infections compared with infants exposed to monotherapy, however the same did not occur in infants exposed to a certolizumab pegol combination therapy, thus suggesting a role of anti-TNFα that cross the placenta in the development of the immune system. A study of macaque monkeys treated with golimumab during pregnancy and lactation did not report any differences in the development or maturation of the immune system compared with standard saline injections (64).

Because infants may have therapeutic levels of anti-TNFα for several months from birth, response to vaccines is also a concern. There is a case report of an infant exposed in utero to infliximab who received the bacillus Calmette-Guèrin (BCG) vaccine at 3 months of age (9). This infant became ill and, due to disseminated BCG, died at 4.5 months of age. This case emphasized the importance of deferring live vaccines in infants after 6 months of age when exposed to anti-TNFα in utero. On the other hand, infants exposed to infliximab in utero had an appropriate response to standard vaccinations (70). In this respect the London Position Statement of the World Congress of Gastroenterology on the Biological Therapy for IBD stated that vaccination of infants exposed to biological therapy in utero should be given according standard schedules, except for live-virus vaccines, which are not recommended if biological agents are detectable in the infant bloodstream (71).

Rituximab

Table III summaries the reports of maternal exposure to rituximab either prior to or during pregnancy (16-34).

Rituximab has various indications. The majority of patients receive the drug for non-rheumatic conditions, including severe hematologic disorders. In the literature the cases of exposure to Rituximab range from 22 months prior conception in a patient with systemic lupus erythematosus (SLE) (20) to the third quarter in a patient with idiopathic thrombocytopenic purpura (18). Two case series have shown that the use of rituximab before pregnancy, or even close to conception, is not associated with adverse effects in the child (20, 21).

The rituximab global drug safety database reported 153 pregnancies with known outcomes (72). These mothers were treated with rituximab and often a concomitant therapy for malignancies or various types of autoimmune diseases with an exposure to this drug ranging from 7 weeks of gestation until the third quarter. These data showed an increased rate of spontaneous abortion (22%) and prematurity (24%). Moreover, in full-term pregnancies neonatal deaths or congenital malformations (2.2%) were not higher than in the general population. Hematological abnormalities at birth including neutropenia and B cell depletion have been reported in 12% of the neonates; most of these abnormalities were

Table III - Summary of case reports of maternal exposure to rituximab either prior to or during pregnancy.

References	Diagnosis	Patients (n)	Trimester exposure	Live births (n)	Pregnancy outcome	Congenital abnormalities (n)
Ostensen et al. (23)	SLE	3	Pre (12, 6 and 4 mo)	2	1 PTB	
Pellkofer et al. (24)	Neuromyelitis optica	1	Pre (1 wk)	1		
Ton et al. (22)	RA	1	Pre (6 wk)	2 (twins)		1 Clubfoot
Ojeda-Uribe et al. (25)	TTP	1	Pre (1 wk)	1		
	RA	1	T1 (wk 2 and 4)	1		
Ojeda-Uribe et al. (26)	AIHA	1	T1	1		
Sangle et al. (20)	GPA	1	Pre (10 mo)	1		
	SLE	1	Pre (10 mo)			
	SLE	1	Pre (12 mo)	1	1 PTB	1 Esophageal atresia
	SLE	1	Pre (18 mo)	1	1 PTB, 1 SGA	
	SLE	1	Pre (22 mo)	1		
	SLE	1	Pre (8 mo)	1		
Kimby et al. (27)	NHL	1	Pre and T1	1		
Ponte et al. (28)	Atopic dermatitis	1	T1	1		
Rey et al. (29)	NHL	1	T2	1	1 PTB	
Gall et al. (19)	ITP	1	T2 (wk 26)	1		
Martinez-Martinez et al. (30)	ITP	1	T2	1	1 PTB	
Alkaabi et al. (31)	SLE/ thrombocitopenia	1	T2	1	1 PTB	
Daver et al. (32)	Hairy cell leukaemia	1	T2	1		
Herold et al.. (33)	NHL	1	T2/T3	1	1 PTB	
Friedrichs et al. (17)	NHL	1	T2/T3	1		
Decker et al. (16)	NHL	1	T2/T3	1	1 PTB	
Perez et al. (34)	NHL	1	T2/T3	1	1 PTB	
Klink et al. (18)	ITP	1	T3	1		
Pendergraft et al. (21)	PAN	1	Pre (2 wk)	1	1 PTB, 1 SGA	
	GPA	1	Pre (16.5, and 7.5 mo)	1	1 SA	1 Beckwith-Wiedemann syndrome
	GPA	1	Pre (1 and 2 wk)	2	1 PTB	
	GPA	1	Pre (13.5 mo)	1		
	GPA	1	Pre (2.8 mo)	1	1 PTB	
	MPA	1	Pre (1 wk)	1		

SLE, systemic lupus erythematosus; RA, rheumatoid arthritis; TTP, thrombotic thrombocytopenic purpura; AIHA, autoimmune haemolytic anaemia; GPA, granulomatosis with polyangiitis; NHL, non-Hodgkin lymphomas; ITP, idiopathic thrombocytopenic purpura; PAN, polyrteritis nodosa; MPA, microscopic polyangiitis; T1, first trimester; T2, second trimester; T3, third trimester; SA, spontaneous abortion; SB, stillbirth; PTB, preterm birth (< 37 wk gestation); SGA, small for gestational age; wk, week; mo, month.

Table IV - Biologics with no or anecdotal human pregnancy experience.

References	Biological type	Diagnosis	Patients (n)	Trimester exposure	Pregnancy and neonatal outcome
Ojeda-Uribe et al. (25)	Abatacept	RA	1	T1	Healthy term infant
Rubbert-Roth et al. (52)	Tocilizumab	RA	32 (33 pregnancy)	C/T1	11 term delivery, 7 SA, 2 unknown outcome
Ishikawa et al. (53)	Tocilizumab	RA	6	C/T1	5 full term infant, 1 SA
Berger et al. (36)	Anakinra	Adult-onset Still disease	1	Throughout pregnancy	Healthy term infant
Fischer-Betz et al. (35)	Anakinra	Adult-onset Still disease	2	Throughout pregnancy	Healthy term infant
GlaxoSmithKline database (75)	Belimumab	SLE	117	Pre-C/C	45 term delivery, 27 SA, 2 SB, 5 CA and 21 unknown outcome

RA, rheumatoid arthritis; SLE, systemic lupus erythematosus; C, within <3 months prior to conception; T1, first trimester; SA, spontaneous abortion; SB, stillbirth, CA, congenital abnormalities.

mild and transient and recovered spontaneously after a period ranging from 2 weeks to 18 months. Three neonatal infections were recorded (febrile illness at 3 weeks of age, bronchiolitis and vertical transmission of cytomegalovirus); no infection occurred in infants with cytopenias.

The response to vaccination was studied in cynomolgus monkeys (73). The offspring showed a normal ability to induce T cell-dependent antibody responses, following vaccination or after antigenic challenge (73, 74). Moreover, normal vaccination response to routine childhood vaccines has been observed in several 8-20 month old children exposed to rituximab in utero (16, 17, 22).

Anakinra, abatacept, tocilizumab and belimumab

Published experience on pregnancy and exposure to anakinra, abatacept, tocilizumab and belimumab is extremely limited (Table IV) (25, 35, 36, 52, 53, 75).

Anakinra was administered throughout pregnancy to three patients with adult-onset Still's disease and the children born at term were healthy (35, 36).

First quarter exposure to abatacept in combination with methotrexate (MTX) was reported in a 33-year-old woman with rheumatoid arthritis (RA); she delivered a healthy infant who was performing well at the age of 3.5 years (25).

Embryonic and fetal developmental toxicity of tocilizumab was studied in animals without evidence of a teratogenic/dysmorphogenic effect regardless of the dose (74). Two case series reported the outcome of 39 pregnancies in RA patients exposed to either tocilizumab monotherapy (31.6%) or combination therapy with MTX or other disease modifying antirheumatic drugs (DMARDs) (68.4%) during conception and the first quarter (52, 53). Outcomes included 41% of live births, 20.5% of spontaneous abortion (71.4% receive also MTX), 33.3% of elective terminations and 5% were unknown. No congenital abnormalities have been recorded.

To our knowledge there are no published data on belimumab. However, data from ongoing belimumab trials report a total of 117 pregnancies (75). Outcomes include 38.5% of live births, 23% of spontaneous abortion, 1.7% of stillbirths, 4.2% of congenital abnormalities, 18.8% of elective terminations and 17.9% were unknown.

Studies on pregnant cynomolgus monkeys that were administered belimumab intravenously or subcutaneously throughout gestation have shown a transplacental passage, but no congenital abnormalities in the offspring (65).

Biological therapies and breastfeeding

Information on the use of biological therapy during breastfeeding is limited to an-

ti-TNFα therapies. Case reports and case series show that detectable levels of anti-TNFα in breast milk during breastfeeding was significantly lower than in the maternal bloodstream (4-6, 10, 11, 62, 76). Drug levels in the newborn gradually decreased until they became undetectable despite breastfeeding. To date, in the few case reports of women receiving anti-TNFα therapies (primarily etanercept and infliximab) who breastfed, no adverse effects have been reported in the infants (4-6, 10, 76).

Biological therapies and fathers

The experience in men exposed to biological drugs at the time of conception is limited to anti-TNFα therapies. The first two case series suggested semen abnormalities in men exposed to infliximab (77, 78). One of these reported asthenozoospermia in two of four men with ankylosing spondylitis receiving infliximab (77). The other study regarding 10 men with Crohn's disease reported a significant increase in semen volume with a trend towards decreased sperm motility and normal forms after infliximab infusion (78). However, another study on 25 men with spondyloarthritis (SpA), including 15 patients receiving anti-TNFα therapies (infliximab, adalimumab or etanercept), found no differences in sperm quality between anti-TNFα-treated patients and healthy controls. Interestingly, patients with SpA who did not receive anti-TNFα were more likely to have poor motility compared with those on treatment (79). This findings have been recently confirmed by a prospective case-control study on 10 patients with SpA treated with adalimumab showing that the anti-TNFα therapy is safe on testicular function and fertility; in addition the authors suggest that discontinuation of treatment before conception is probably unnecessary (80).

Published clinical experience on pregnancy outcome after paternal exposure to biological drugs remains limited. A total of 25 pregnancies involving 20 men resulted in 23 healthy babies, 1 miscarriage and 1 therapeutic first quarter termination following the development of hydrocephaly in the fetus (it should be noted that the father was also receiving MTX for psoriasic arthritis at the time of conception) (81, 82). The UCB Pharma global safety database reports 24 pregnancies from fathers exposed to certolizumab pegol, which resulted into 13 live births, 4 miscarriages, 1 termination and an 6 unknown outcomes.[51] Data on paternal exposure to other biological therapies are limited. The rituximab global drug safety database reports 8 cases of men exposed to rituximab at the time of conception. Outcomes included 7 healthy term infants and 1 spontaneous miscarriage (72).

CONCLUSIONS

The differences in transplacental passage of biological drugs depend on their molecular structure. In fact it is greater for monoclonal antibodies and more limited for fusion proteins or F'ab fragments. On the whole, the data regarding maternal exposure to anti-TNFα at conception and/or during pregnancy do not show a worse outcome with respect to the general population. Moreover, they do not show an increase in congenital abnormalities and seem to be compatible with breastfeeding. Exposure to anti-TNFα agents in late pregnancies, particularly to monoclonal antibodies, is associated with high drug levels in the newborn, however the long-term effects on the child remain unknown. Therefore, in the clinical practice we suggest that the anti-TNF-α therapy be continued through conception and during pregnancy until the first 30 weeks of gestation, when there is a moderate-high activity of the disease. Live-virus vaccines should be given only when levels of anti-TNFα drugs are undetectable in the serum of infants. Pregnancy data for *non anti-TNF*α biologics are lacking and their use in pregnancy cannot be currently recommended.

Acknowledgements

The authors would like to thank Prof. S. Todesco for his knowledgeable contribution to this article.

REFERENCES

1. Food Drug Administration. Regulations. Federal Register 1980; 44: 37434-67.
2. Agenzia Italiana del Farmaco (AIFA). Banca Dati Farmaci. Available from: https://farmaci.agenziafarmaco.gov.it/bancadatifarmaci/Accessed: 7 July 2014.
3. Zelinkova Z, de Haar C, de Ridder L, Pierik MJ, Kuipers EJ, Peppelenbosch MP, et al. High intrauterine exposure to infliximab following maternal anti-TNF treatment during pregnancy. Aliment Pharmacol Ther. 2011; 33: 1053-8.
4. Vasiliauskas EA, Church JA, Silverman N, Barry M, Targan SR, Dubinsky MC. Case report: evidence for transplacental transfer of maternally administered infliximab to the newborn. Clin Gastroenterol Hepatol. 2006; 4: 12558-8.
5. Murashima A, Watanabe N, Ozawa N, Saito H, Yamaguchi K. Etanercept during pregnancy and lactation in a patient with rheumatoid arthritis: drug levels in maternal serum, cord blood, breast milk and the infant's serum. Ann Rheum Dis. 2009; 68: 1793-4.
6. Berthelsen BG, Fjeldsoe-Nielsen H, Nielsen CT, Hellmuth E. Etanercept concentrations in maternal serum, umbilical cord serum, breast milk and child serum during breastfeeding. Rheumatology. 2010; 49: 2225-7.
7. Srinivasan R. Infliximab treatment and pregnancy outcome in active Crohn's disease. Am J Gastroenterol. 2001; 96: 2274-5.
8. Carter JD, Valeriano J, Vasey FB. Tumor necrosis factor alpha inhibition and VATER association: a causal relationship. J Rheumatol. 2006; 33: 1014-7.
9. Cheent K, Nolan J, Shariq S, Kiho L, Pal A, Arnold J. Case Report: Fatal case of disseminated BCG infection in an infant born to a mother taking infliximab for Crohn's disease. J Crohns Colitis. 2010; 4: 603-5.
10. Stengel JZ, Arnold HL. Is infliximab safe to use while breastfeeding? World J Gastroenterol. 2008; 14: 3085-7.
11. Ben-Horin S, Yavzori M, Katz L, Picard O, Fudim E, Chowers Y, Lang A. Adalimumab level in breast milk of a nursing mother. Clin Gastroenterol Hepatol. 2010; 8: 475-6.
12. Kraemer B, Abele H, Hahn M, Rajab T, Kraemer E, Wallweiner D, Becker S. A successful pregnancy in a patient with Takayasu's arteritis. Hypertens Pregnancy. 2008; 27: 247-52.
13. Mishkin DS, Van Deinse W, Becker JM, Farraye FA. Successful use of adalimumab (Humira) for Crohn's disease in pregnancy. Inflamm Bowel Dis. 2006; 12: 827-8.
14. Vesga L, Terdiman JP, Mahadevan U. Adalimumab use in pregnancy. Gut. 2005; 54: 890.
15. Wibaux C, Andrei I, Paccou J, Philippe P, Biver E, Duquesnoy B, et al. Pregnancy during TNFalpha antagonist therapy: beware the rifampin-oral contraceptive interaction. Report of two cases. Joint Bone Spine. 2010; 77: 268-70.
16. Decker M, Rothermundt C, Holländer G, Tichelli A, Rochlitz C. Rituximab plus CHOP for treatment of diffuse large B-cell lymphoma during second trimester of pregnancy. Lancet Oncol. 2006; 7: 693-4.
17. Friedrichs B, Tiemann M, Salwender H, Verpoort K, Wenger MK, Schmitz N. The effects of rituximab treatment during pregnancy on a neonate. Haematologica. 2006; 91: 1426-7.
18. Klink DT, van Elburg RM, Schreurs MW, van Well GT. Rituximab administration in third trimester of pregnancy suppresses neonatal B-cell development. Clin Dev Immunol. 2008; 2008: 271363.
19. Gall B, Yee A, Berry B, Birchman D, Hayashi A, Dansereau J, et al. Rituximab for management of refractory pregnancy-associated immune thrombocytopenic purpura. J Obstet Gynaecol Can. 2010; 32: 1167-71.
20. Sangle SR, Lutalo PM, Davies R, Khamashta MA, D'Cruz DP. B-cell depletion therapy and pregnancy outcome in severe, refractory systemic autoimmune diseases. J Autoimmun. 2013; 43: 55-9.
21. Pendergraft WF 3rd, McGrath MM, Murphy AP, Murphy P, Laliberte KA, Greene MF, et al. Fetal outcomes after rituximab exposure in women with autoimmune vasculitis. Ann Rheum Dis. 2013; 72: 2051-3.
22. Ton E, Tekstra J, Hellmann PM, Nuver-Zwart IH, Bijlsma JW. Safety of rituximab therapy during twins' pregnancy. Rheumatology. 2011; 50: 806-8.
23. Østensen M, Lockshin M, Doria A, Valesini G, Meroni P, Gordon C, et al. Update on safety during pregnancy of biological agents and some immunosuppressive anti-rheumatic drugs. Rheumatology. 2008; 47: 28-31.
24. Pellkofer HL, Suessmair C, Schulze A, Hohlfeld R, Kuempfel T. Course of neuromyelitis optica during inadvertent pregnancy in a patient treated with rituximab. Mult Scler. 2009; 15: 1006-8.
25. Ojeda-Uribe M, Afif N, Dahan E, Sparsa L, Haby C, Sibilia J, et al. Exposure to abatacept or rituximab in the first trimester of pregnancy in three women with autoimmune diseases. Clin Rheumatol. 2013; 32: 695-700.
26. Ojeda-Uribe M, Gilliot C, Jung G, Drenou B, Brunot A. Administration of rituximab during the first trimester of pregnancy without consequences for the newborn. J Perinatol. 2006; 26: 252-5.
27. Kimby E, Sverrisdottir A, Elinder G. Safety of rituximab therapy during the first trimester of pregnancy: a case history. Eur J Haematol. 2004; 72: 292-5.

28. Ponte P, Lopes MJ. Apparent safe use of single dose rituximab for recalcitrant atopic dermatitis in the first trimester of a twin pregnancy. J Am Acad Dermatol. 2010; 63: 355-6.
29. Rey J, Coso D, Roger V, Bouayed N, Belmecheri N, Ivanov V, et al. Rituximab combined with chemotherapy for lymphoma during pregnancy. Leuk Res. 2009; 33: 8-9.
30. Martínez-Martínez MU, Baranda-Cándido L, González-Amaro R, Pérez-Ramírez O, Abud-Mendoza C. Modified neonatal B-cell repertoire as a consequence of rituximab administration to a pregnant woman. Rheumatology. 2013; 52: 405-6.
31. Alkaabi JK, Alkindi S, Riyami NA, Zia F, Balla LM, Balla SM. Successful treatment of severe thrombocytopenia with romiplostim in a pregnant patient with systemic lupus erythematosus. Lupus. 2012; 21: 1571-4.
32. Daver N, Nazha A, Kantarjian HM, Haltom R, Ravandi F. Treatment of hairy cell leukemia during pregnancy: are purine analogues and rituximab viable therapeutic options. Clin Lymphoma Myeloma Leuk. 2013; 13: 86-9.
33. Herold M, Schnohr S, Bittrich H. Efficacy and safety of a combined rituximab chemotherapy during pregnancy. J Clin Oncol. 2001; 19: 3439.
34. Perez CA, Amin J, Aguina LM, Cioffi-Lavina M, Santos ES. Primary mediastinal large B-cell lymphoma during pregnancy. Case Rep Hematol. 2012; 2012: 197347.
35. Fischer-Betz R, Specker C, Schneider M. Successful outcome of two pregnancies in patients with adult-onset Still's disease treated with IL-1 receptor antagonist (anakinra). Clin Exp Rheumatol. 2011; 29: 1021-3.
36. Berger CT, Recher M, Steiner U, Hauser TM. A patient's wish: anakinra in pregnancy. Ann Rheum Dis. 2009; 68: 1794-5.
37. Correira LM, Bonilha DQ, Ramos JD, Ambrogini O, Miszputen SJ. Inflammatory bowel disease and pregnancy: report of two cases treated with infliximab and a review of the literature. Eur J Gastroenterol Hepatol. 2010; 22: 1260-4.
38. Chambers CD, Johnson DL, Jones KL. Pregnancy outcome in women exposed to anti-TNF medications: the OTIS Rheumatoid Arthritis in Pregnancy Study. Arthritis Rheum. 2004; 50: S479.
39. Mahadevan U, Terdiman JP, Church J. Infliximab levels in infants born to women with inflammatory bowel disease. Gastroenterol. 2007; 132: A144.
40. Berthelot JM, De Bandt M, Goupille P, Solau-Gervais E, Lioté F, Goeb V, et al. Exposition to anti-TNF drugs during pregnancy: outcome of 15 cases and review of the literature. Joint Bone Spine. 2009; 76: 28-34.
41. Chakravarty EF, Sanchez-Yamamoto D, Bush TM. The use of disease modifying antirheumatic drugs in women with rheumatoid arthritis of childbearing age: a survey of practice patterns and pregnancy outcomes. J Rheumatol. 2003; 30: 241-6.
42. Hyrich KL, Symmons DP, Watson KD, Silman AJ. Pregnancy outcome in women who were exposed to anti-tumor necrosis factor agents: results from a national population register. Arthritis Rheum. 2006; 54: 2701-2.
43. Kane S, Ford J, Cohen R, Wagner C. Absence of infliximab in infants and breast milk from nursing mothers receiving therapy for Crohn's disease before and after delivery. J Clin Gastroenterol. 2009; 43: 613-6.
44. Katz JA, Antoni C, Keenan GF, Smith DE, Jacobs SJ, Lichtenstein GR. Outcome of pregnancy in women receiving infliximab for the treatment of Crohn's disease and rheumatoid arthritis. Am J Gastroenterol. 2004; 99: 2385-92.
45. Mahadevan U, Kane S, Sandborn WJ, Cohen RD, Hanson K, Terdiman JP, et al. Intentional infliximab use during pregnancy for induction or maintenance of remission in Crohn's disease. Aliment Pharmacol Ther. 2005; 21: 733-8.
46. Rosner I, Haddad A, Boulman N, Feld J, Avshovich N, Slobodin G et al. Pregnancy in rheumatology patients exposed to anti-tumour necrosis factor (TNF)-alpha therapy. Rheumatology. 2007; 46: 1508.
47. Schnitzler F, Fickler HH, Ferrante M, Noman M, Van Assche GA, Spitz B, et al. Intentional treatment with infliximab during pregnancy in women with inflammatory bowel disease. Gastroenterol. 2007; 132: A144.
48. Weber-Schoendorfer C, Fritzsche J, Schaefer. Pregnancy outcomes in women exposed to adalimumab or infliximab: the experience of the Berlin Institute for Clinical Teratology and Drug Risk Assessment in Pregnancy. Reprod Toxicol. 2011; 31: A267-8.
49. Johnson DJ, Jones KL, Chambers CD, Salas E. Pregnancy outcomes in women exposed to adalimumab: the OTIS autoimmune diseases in pregnancy project. Gastroenterol. 2009; 136: A27.
50. Johnson D, Jones KL, Chambers C, The OTIS Collaborative Research Group. Pregnancy outcomes in women exposed to Etanercept: The OTIS Autoimmune Diseases in Pregnancy Project. Arthritis Rheum. 2008; 58: S682.
51. Clowse M, Wolf DC, Förger F, Cush JJ, Stach C, Kosutic G, et al. Retrospective analysis of certolizumab pegol use during pregnancy: update of impact on birth outcomes. Arthritis Rheum. 2013; 65: 433.
52. Rubert-Roth A, Goupille Ph, Moosavi Sh, Hou A. First experiences with pregnancies in RA patients receving Tocilizumab therapy. Arthritis Rheum. 2010; 62: S161.
53. Ishikawa H, Hirano Y, Kaneka A, Kida D, Sato T, Kojima T, et al. Pregnancy in patients with

rheumatoid arthritis treated with biological agents: results of the 8-year of Japanese TBC registry. Ann Rheum Dis. 2012; 71: 501.
54. Galloway JB, Hyrich KL, Mercer LK, Dixon WG, Fu B, Ustianowski AP, et al. Anti-TNF therapy is associated with an increased risk of serious infections in patients with rheumatoid arthritis especially in the first 6 months of treatment: updated results from the British Society for Rheumatology Biologics Register with special emphasis on risks in the elderly. Rheumatology. 2011; 50: 124-31.
55. Ramiro S, Gaujoux-Viala C, Nam JL, Smolen JS, Buch M, Gossec L, et al. Safety of synthetic and biological DMARDs: a systematic literature review informing the 2013 update of the EULAR recommendations for management of rheumatoid arthritis. Ann Rheum Dis. 2014; 73: 529-35.
56. Tafuri A, Alferink J, Moller P, Hammerling G, Arnold B. T cell awareness of paternal alloantigens during pregnancy. Science. 1995; 270: 630-3.
57. Raghupathy R. Th1 immunity is incompatible with successful pregnancy. Immunol Today. 1997; 18: 478-82.
58. Alijotas-Reig J, Llurba E, Gris JM. Potentiating maternal immune tolerance in pregnancy: a new challenging role for regulatory T cells. Placenta. 2014; 35: 241-8.
59. Roopenian DC, Akilesh S. FcRn: the neonatal Fc receptor comes of age. Nat Rev Immunol. 2007; 7: 715-25.
60. Simister NE. Placental transport of immunoglobulin G. Vaccine. 2003; 21: 3365-9.
61. Fritzsche J, Pilch A, Mury D Schaefer C, Weber-Schoendorfer C. Infliximab and adalimumab use during breastfeeding. J Clin Gastroenterol. 2012; 46: 718-9.
62. Mahadevan U, Wolf DC, Dubinsky M, Cortot A, Lee SD, et al. Placental transfer of anti-tumor necrosis factor agents in pregnant patients with inflammatory bowel disease. Clin Gastroenterol Hepatol. 2013; 11: 286-92.
63. Wakefield I, Stephens S, Foulkes R, Nesbitt A, Bourne T. The use of surrogate antibodies to evaluate the developmental and reproductive toxicity potential of an anti-TNFalpha PEGylated Fab' monoclonal antibody. Toxicol Sci. 2011; 122: 170-6.
64. Martin PL, Oneda S, Treacy G. Effects of an anti-TNFalpha monoclonal antibody, administered throughout pregnancy and lactation, on the development of the macaque immune system. Am J Reprod Immunol. 2007; 58: 138-49.
65. Auyeung-Kim DJ, Devalaraja MN, Migone TS, Cai W, Chellman GJ. Developmental and peri-postnatal study in cynomolgus monkeys with belimumab, a monoclonal antibody directed against B- lymphocyte stimulator. Reprod Toxicol. 2009; 28: 443-55.
66. Martin JA, Hamilton BE, Sutton PD, Ventura SJ, Mathews TJ, Osterman MJ. Births: final data for 2008. Natl Vital Stat Rep. 2010; 59: 13-71.
67. Centers for Disease Control and Prevention (CDC). Update on overall prevalence of major birth defects - Atlanta, Georgia, 1978-2005. MMWR Morb Mortal Wkly Rep. 2008; 57: 1-5.
68. Carter JD, Ladhani A, Ricca LR, Valeriano J, Vasey FB. A safety assessment of tumor necrosis factor antagonists during pregnancy: a review of the Food and Drug Administration database. J Rheumatol. 2009; 36: 635-41.
69. Mahadevan U, Martin CF, Sandler RS, Kane SV, Dubinsky M, Lewis JD, et al. PIANO: a 1000 patient prospective registry of pregnancy outcomes in women with IBD exposed to immunomodulators and biologic therapy. Gastroenterol. 2012; 14: S149.
70. Mahadevan U, Kane S, Church J, Vasiliauskas E, Sandborn WJ, Dubinsky MC. The effect of maternal peripartum infliximab use on neonatal immune response. Gastroenterology. 2008; 134: A-69.
71. Mahadevan U1, Cucchiara S, Hyams JS, Steinwurz F, Nuti F, Travis SP, et al. The London position statement of the World Congress of Gastroenterology on Biological Therapy for IBD with the European Crohn's and Colitis Organisation: pregnancy and pediatrics. Am J Gastroenterol. 2011; 106: 214-23.
72. Chakravarty EF, Murray ER, Kelman A, Farmer P. Pregnancy outcomes after maternal exposure to rituximab. Blood. 2011; 117: 1499-506.
73. Vaidyanathan A, McKeever K, Anand B, Eppler S, Weinbauer GF, Beyer JC. Developmental immunotoxicology assessment of rituximab in cynomolgus monkeys. Toxicol Sci. 2011; 119: 116-25.
74. Pham T, Claudepierre P, Constantin A, de Bandt M, Fautrel B, Gossec L, et al. Tocilizumab: therapy and safety management. Joint Bone Spine. 2010; 77: S3-100.
75. GlaxoSmithKline. Use of intravenous (IV) benlysta in pregnant patients with systemic lupus erythematosus (SLE); 2014. Available from: http://ctr.gsk.co.uk/welcome.asp
76. Ben-Horin S, Yavzori M, Kopylov U, Picard O, Fudim E, Eliakim R, et al. Detection of infliximab in breast milk of nursing mothers with inflammatory bowel disease. J Crohns Colitis. 2011; 5: 555-8.
77. Montagna GL, Malesci D, Buono R, Valentini G. Asthenoazoospermia in patients receiving anti-tumour necrosis factor {alpha} agents. Ann Rheum Dis. 2005; 64: 1667.
78. Mahadevan U, Terdiman JP, Aron J, Jacobsohn S, Turek P. Infliximab and semen quality in men with inflammatory bowel disease. Inflamm Bowel Dis. 2005; 11: 395-9.
79. Villiger PM, Caliezi G, Cottin V, Förger F,

Senn A, Østensen M. Effects of TNF antagonists on sperm characteristics in patients with spondyloarthritis. Ann Rheum Dis. 2010; 69: 1842-4.
80. Ramonda R, Foresta C, Ortolan A, Bertoldo A, Oliviero F, Lorenzin M, et al. Influence of tumor necrosis factor α inhibitors on testicular function and semen in spondyloarthritis patients. Fertil Steril. 2014; 101: 359-65.
81. Saougou I, Markatseli TE, Papagoras C, Kaltsonoudis E, Voulgari PV, Drosos AA. Fertility in male patients with seronegative spondyloarthropathies treated with infliximab. Joint Bone Spine 2013; 80: 34-7.
82. Katz JA, Antoni C, Keenan GF, Smith DE, Jacobs SJ, Lichtenstein GR. Outcome of pregnancy in women receiving infliximab for the treatment of Crohn's disease and rheumatoid arthritis. Am J Gastroenterol 2004; 99: 2385-92.