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Concise Report

Pregnancy in rheumatology patients exposed to anti-tumour necrosis factor (TNF)-α therapy

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***Objectives*. Anti-tumour necrosis factor (TNF)-α therapies are considered category B drugs for pregnancy. Although sometimes prescribed to women of reproductive age, data in humans are limited with regard to safety for a developing fetus. The objectives of the present article are to report experience of anti-TNF-α use in pregnancy, and review the international literature.**
***Methods*. Since 1999 the present authors have used anti-TNF-α (infliximab ,etanercept ,adalimumab) to treat patients with various chronic rheumatic conditions. All patients were prospectively followed during their treatment time and data were systematically collected.**
***Results*. In a group of 442 patients treated with anti-TNF, three women with RA unexpectedly became pregnant One treated with etanercept chose a therapeutic termination at two and a half months, despite of any ultrasound anomaly, and satisfactory fetal growth. The other two patients (one with adalimumab exposure and one with etanercept exposure) delivered healthy infants. The following perinatal complications were observed: prematurity, neonatal jaundice, neonatal urinary *Escherichia coli* infection and adrenal congenital hyperplasia of probable hereditary origin.**
***Conclusions*. To date, there is no evidence that TNF-α antagonists are associated with embryo toxicity, teratogenicity or increased pregnancy loss. However, caution should be taken when anti-TNF agents are used during pregnancy, as human experience is still extremely limited, particularly in patients with rheumatic diseases among whom there are several alarming reports. The potential risk should be balanced against the known risks associated with DMARDs and steroid therapy. Large registries will be necessary before firm conclusions can be drawn.**

KEY WORDS: Rheumatoid arthritis, Pregnancies, Anti-TNF-α treatment.

Tumour necrosis factor (TNF)-α has an important role in pregnancy. Mouse models have shown it to be one of several cytokines with a potent modulatory effect on early development [1]. By inducing cyclo-oxygenase 2 gene expression in early pregnancy [2], TNF-α controls cyclo-oxygenases, thereby affecting blastocyst implantation, endometrial vascular permeability and uterine deciduation. It plays a role in the induction of labour, in synergy with other inflammatory cytokines to induce uterine contractions [3]. Levels in amniotic fluid and serum are high at the onset of labour and in pathological conditions such as infection and fetal growth retardation. TNF-α production is low in the first gestational trimester, but increases thereafter, reaching a peak at the onset of labour [3]. It may mediate recurrent spontaneous abortion, and higher concentrations of serum TNF-α and of serum soluble TNF receptor 1 have been observed in women with unexplained early spontaneous abortion [4]. Anti-TNF-α is often prescribed to women of reproductive age who have rheumatological disorders, raising questions about its effect on pregnancy.

Patients

Since 1999, the present authors have used anti-TNF-α to treat 442 patients with various chronic rheumatic conditions [5]. Three women treated with anti-TNF for rheumatoid arthritis (RA) inadvertently became pregnant.

Case 1

RA diagnosed at the age of 37 in a woman in 1999 and treated with sulfasalazine (3 g/day) until the end of 2001, followed by leflunomide (20 mg/day). The patient became pregnant in May 2002, leflunomide was discontinued and she opted for a therapeutic termination. Methotrexate (15 mg/week) was started in August 2002 but failed to control the disease. Etanercept (25 mg twice a week) was prescribed between February and August 2003, followed by adalimumab (40 mg twice a month) in October. The treatment appeared to be effective and well-tolerated. The patient had been counselled about using adequate contraception, but in November 2003 she discovered she was pregnant at about 5 weeks of gestation, and after a single injection of adalimumab since conception. The patient decided to continue her pregnancy. Fetal growth was satisfactory and diagnostic ultrasound detected no abnormality. A healthy infant weighing 2.6 kg and 47 cm long was delivered at 32 weeks. No neonatal abnormality was noted, and the child is now 25 months old, and growing and developing normally.

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Table 1. TNF-α-exposed RA pregnancies

Authors	Anti-TNF	Exposure	Number of pregnancies	Live births	Miscarriages	Therapeutic terminations	Malformations
Chambers *et al.* [6, 7]	Eta	T1	29	7	3	1	Trisomy 18 with miscarriage
Sills *et al.* [9]	Eta	Conception	1	1			
Chakravarty *et al.* [10]	Eta		15	6	1 (MTX)	1	
Joven *et al.* [12]	Eta	5–14 weeks	4	1		1	
Rump *et al.* [15]	Eta	Throughout pregnancy	1	1			
		First month	1	1			
Feyertag *et al.* [16]	Eta	Throughout pregnancy	1	1			
Our cases 2	Eta	Conception/T1	1			1	
3	Eta	Conception	1	1			
Chambers *et al.* [6, 7]	Inf	T1	4	2	1	1	
Chakravarty *et al.* [10]	Inf		2	1			
Katz *et al.* [11]	Inf	Conception/T1	8				Intestinal malrotation (LFN)
Joven *et al.* [12]	Inf	First month	2	1	1		
Kinder *et al.* [14]	Inf	Conception/first month	1		1 (MTX)		
Joven *et al.* [12]	Ada	6.5 months	1				
Our case 1	Ada	Conception/T1	1			1	

Eta, Etanercept; Inf, Infliximab; Ada, Adalimumab; MTX, Methotrexate; LNF, Leflunomide; T1, First trimester.

Table 2. TNF-α-exposed psoriatic arthritis (PsA), juvenile idiopathic arthritis (JIA) and rheumatoid arthritis (RA)

Authors	Disease	Anti-TNF-α	Exposure	Number of pregnancies	Live births	Miscarriages	Therapeutic terminations	Malformations
Joven *et al.* [12]	PsA	Eta	First month	1	1			
Carter *et al.* [19]	PsA	Eta	Throughout pregnancy	1				VATER association
Joven *et al.* [12]	PsA	Inf	First month	1	1			
Dechant *et al.* [18]	PsA	Inf	Conception	1				
Joven *et al.* [12]	JIA	Eta	9 weeks	1	1			
Katz *et al.* [11]	JIA	Inf	Conception/T1	2				
Joven *et al.* [12]	JIA	Inf	First month	1	1			
Koskvik *et al.* [8]	JIA+RA	Eta	Conception/3 weeks	5	3	2		
Hyrich *et al.* [20]	Rheumatic	Eta	Conception	16	13	6 (3 MTX,	3	
	diseases (mostly RA)	Inf		3		1 LFN)		
		Ada		3				

Eta, Etanercept; Inf, Infliximab; Ada, Adalimumab; MTX, Methotrexate; LFN, Leflunomide; T1, First trimester.

Case 2

Severe RA since 1996 in a woman initially treated unsuccessfully with hydroxychloroquine (400 mg/day). Subsequently, methotrexate (15 mg/week) was stopped because of gastro-intestinal side effects, and sulfasalazine (600 mg/day) was not tolerated. Infliximab was prescribed between February and August 2002 but discontinued because of allergic manifestations. Leflunomide was also not tolerated due to gastro-intestinal side-effects. Etanercept (25 mg twice a week) was started in October 2004. She discovered she was pregnant at about 2 months of gestation. Diagnostic ultrasound detected no abnormality and fetal growth was satisfactory, but the patient opted for therapeutic termination at two and a half months.

Case 3

Severe RA starting in 2000, in a 21-year-old woman initially treated with infliximab (200 mg every 8 weeks). Methotrexate (15 mg/week) was added in March 2002, poorly tolerated and discontinued in November 2002. Infliximab alone was effective, but discontinued (allergic manifestations) in November 2003. Etanercept (25 mg twice a week) initiated in December 2003 and given with prednisone 5 mg/day, was well-tolerated and controlled the disease effectively. She became pregnant, beginning gestation on 28 August 2004. Her last injection of etanercept was given on 22 September 2004. Fetal growth was normal. Amniocentesis and chromosomal investigation failed to detect any anomaly. A healthy male infant weighing 3.520 kg, 57 cm in length and with a cranial circumference of 37 cm was delivered on 1 June 2005. A neonatal urinary *Escherichia coli* infection was treated with ceftriaxone. Neonatal jaundice detected 3 days after birth resolved following phototherapy. Adrenal congenital hyperplasia with 21 hydroxylase deficiency, known in the father, was detected 5 days after birth and treated with prednisone (5 mg/day). The child is now 2 years old and is developing normally.

Discussion

Among those three women with RA who unexpectedly became pregnant one chose a therapeutic termination, and the other two delivered healthy infants. Perinatal complications were observed: prematurity, neo-natal jaundice, neonatal urinary infection and probably hereditary adrenal congenital hyperplasia.

Several papers report pregnancies in patients treated with anti-TNF-α for rheumatic conditions (Tables 1 and 2).

OTIS (Organization of Teratology Information Services) [6, 7] has data on 33 pregnant RA patients with first trimester exposure to etanercept (29) or infliximab (4). A trisomy 18 with spontaneous abortion occurred in one etanercept-exposed

pregnancy and spontaneous abortions were observed with both etanercept (3/28) and infliximab (1/4) as one therapeutic termination in the etanercept group. However, a comparison with two control groups failed to detect any significant differences in the rate of malformation. Five pregnancies in RA and juvenile idiopathic arthritis (JIA) patients resulted in three live births and two miscarriages [8], and one report [9] describes a case of normal delivery of a healthy infant after pre-ovulatory administration of etanercept for RA. In another series [10], 15 pregnancies were exposed to etanercept and two to infliximab resulting in one miscarriage and six normal deliveries with etanercept as the single known outcome with infliximab. Data concerning eight RA patients exposed to infliximab at the time of conception and during the first trimester [11] report one intestinal malrotation in a patient also taking leflunomide which is known to be teratogenic in animals.

The Spanish registry BIOBADASER includes seven pregnancies in RA patients exposed to anti-TNF-α. They were reviewed in two articles [12, 13]. The first reported two live births (one with etanercept and one with infliximab), one therapeutic termination and one miscarriage (infliximab).

Two cases of miscarriage are reported elsewhere, two involving etanercept exposure [8], and one in a patient exposed to infliximab and methotrexate [14]; neither treatment led to malformation.

Normal deliveries and live births have been reported in women with RA exposed to anti-TNF (etanercept) for the first trimester and throughout the pregnancy [15, 16].

Complicated neonatal courses occurred in two RA patients in the present series. Neonatal jaundice has been observed without significant increase in neonates from Crohn's disease patients exposed to anti-TNF-α [11, 17]. RA seems to be the causal factor of prematurity [6, 7]. Any link between urinary neonatal infection and TNF-α immunosuppression is speculative.

A few cases of JIA have been reported following exposure to anti-TNF (infliximab, etanercept) at conception and during the first trimester [8, 10, 12].

Uncomplicated pregnancies have been reported in psoriatic arthritis patients exposed to etanercept and infliximab at first month and conception [12, 18].

A recent report described a psoriatic patient treated with high doses etanercept throughout pregnancy. The child was born with tracheal atresia, tracheoesophageal fistula, oesophageal atresia, unperforata anus, hypospadias, T12 vertebral anomaly and patent foramina ovale. These manifestations fit the vertebral anomalies; anal atresia; tracheooesophageal fistula; radial and renal anomalies (VATER) pattern [19].

The British Society of Rheumatology Biologics Register [20] describes 22 pregnancies in patients with rheumatic diseases and exposed to anti-TNF at conception (16 etanercept, three infliximab, three adalimumab). They resulted in six first trimester miscarriages (three in patients also receiving methotrexate and one receiving leflunomide at conception), three elective terminations and 13 live births. One patient treated with adalimumab reported recurrent cystitis during pregnancy.

The largest series of Crohn's disease exposed to infliximab at conception time and/or during first trimester includes about 82 patients [11] in the infliximab safety database, partially published elsewhere [21–23]. It reports 58 live births, 11 miscarriages and 16 therapeutic terminations. They are part of a group of 96 pregnancies in women with Crohn's and other rheumatic diseases comprising 68 live births, 14 miscarriages and 18 therapeutic terminations. Five infants were born with complications. One born at 24 weeks (Crohn's disease) had intra-cerebral and intra-pulmonary bleeding and died; the second had a complicated neonatal course (respiratory distress, seizure, jaundice); the third had tetralogy of Fallot; the fourth, intestinal malrotation (RA); and the fifth, delayed development and hypothyroidism. Several concomitant treatments (including leflunomide, azathioprine and metronidazole) may have contributed to the anomalies.

No significant differences were observed in live births, miscarriages, therapeutic terminations, pre-term deliveries, low-birth weight babies, neonatal jaundice or respiratory difficulties when comparing patients with Crohn's disease exposed or not to infliximab [24].

The TREAT Registry reports pregnancies in 66 Crohn's disease patients [25], 36 of whom were exposed to infliximab. No fetal malformation occurred and the rates of miscarriage ($P = 0.53$) and neonatal complications ($P = 0.78$) did not differ between infliximab-treated and untreated patients. Another report [17] concerns 10 women who received infliximab during their pregnancies: eight were given maintenance infusions throughout; one began infliximab in the third trimester and one in the first trimester. All pregnancies ended in live births. There were three premature infants, one low-birthweight infant, one case of jaundice and one of respiratory distress with gastric ulcer.

Other patients treated throughout pregnancy with adalimumab [26] or infliximab [27] experienced normal live births. Five reports of pregnancies in women with Crohn's disease exposed to anti-TNF at conception and/or during the first month involved infliximab [28–31] and adalimumab [32]. Outcomes were three births, and one premature infant born at 24 weeks who died with intracerebral and intrapulmonary bleeding [28].

Non-selective Cox 1, selective Cox 2 and specific Cox 2 inhibitors interfere with normal blastocyst implantation in the rat model [33]. In theory, therefore, TNF-α antagonists may affect implantation and ovulation. However, there is no direct evidence that anti-TNF-α decreases fertility or induces miscarriages. The rate of miscarriage among exposed Crohn's disease patients is similar to that in non-exposed controls. Among those with rheumatic diseases, the level of spontaneous abortion is lower, possibly due to co-administration of methotrexate in several cases. In the controlled data from OTIS [6] the risk of spontaneous abortion among RA patients treated with anti-TNF-α did not differ significantly from that among those with RA not treated with anti-TNF-α, or from healthy controls.

No evidence of embryotoxicity or teratogenicity has been observed in animal studies. Fetal and neo-natal complications are sometimes reported after anti-TNF-α use. The following anomalies have been observed in anti-TNF-treated patients with Crohn's disease: prematurity, tetralogy of Fallot, intestinal malrotation, hypothyroidism and complicated neo-natal course [11]. In RA, a trisomy 18 has been reported [6, 7] and a 21 hydroxylase deficiency was observed in one of the present patients (probably transmitted by the father). The rate of major fetal complications in anti-TNF-α-treated patients, whether with Crohn's disease or RA, is similar to that expected in untreated populations. However, VATER association in a child born to a woman with psoriatic arthritis and treated with etanercept throughout her pregnancy is alarming [19] and may be attributable to TNF-α inhibition. Cardiac defects, intestinal malrotation and respiratory distress may could reflect an incomplete VATER association.

Interest has been expressed in the use of anti-TNF-α in infertility, and anecdotal cases are reported in patients with RA [9], Crohn's disease and psoriasis [30], and an unspecified diagnosis [34]. A possible beneficial effect of TNF-α lowering is proposed.

Anti-TNF-α agents are classified as category B (no documented human toxicity) by the US FDA. Animal studies [35] with a soluble TNF receptor/IgG heavy chain chimeric protein and [36] a monoclonal antibody report no maternal toxicity, embryotoxicity or teratogenicity. However, anti-TNF antibodies are species specific and only a few human studies are available. The molecular structures of adalimumab and infliximab (chimeric IgG1 anti-TNF antibodies) and etanercept (a soluble receptor fusion protein composed of dimers with a ligand binding portion of the p75 receptor linked to the Fc portion of human IgG1), permit little

placental transfer during the first trimester, but placental transfer cannot be excluded during the second and third trimesters [37].

Human experience of anti-TNF is still extremely limited, particularly in patients with rheumatic diseases, among whom there are several alarming reports. The potential risk of their use should be balanced against the known risks associated with DMARDs and steroid therapy. Large registries will be necessary before firm conclusions can be drawn.

The authors have declared no conflicts of interest.

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