

## Tumor necrosis factor- $\alpha$ inhibitor therapy and fetal risk: A systematic literature review

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### Abstract

Tumor necrosis factor- $\alpha$  inhibitors (anti-TNFs) are effective in the treatment of inflammatory bowel disease (IBD) recalcitrant to conventional medical therapy. As the peak incidence of IBD overlaps with the prime reproductive years, it is crucial to establish pharmacologic regimens for women of childbearing age that achieve effective disease control without posing significant fetal harm. A systematic literature review was performed to identify all human studies with birth outcomes data after maternal exposure to infliximab, adalimumab, or certolizumab pegol within 3 mo of conception or during any trimester of pregnancy. Live births, spontaneous abortions or stillbirths, preterm or premature births, low birth weight or small for gestational age infants, and congenital abnormalities were recorded. Fifty selected references identified 472 pregnancy exposures. The subsequent review includes general information regarding anti-TNF therapy in pregnancy followed by a summary of our findings. The benefits of biologic modalities in optimizing disease control during pregnancy

must be weighed against the potential toxicity of drug exposure on the developing fetus. Although promising overall, there is insufficient evidence to prove absolute safety for use of anti-TNFs during pregnancy given the limitations of available data and lack of controlled trials.

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**Key words:** Tumor necrosis factor- $\alpha$  inhibitors; Pregnancy; Congenital abnormalities; Safety; Infliximab; Adalimumab; Certolizumab

**Core tip:** A systematic literature review was performed to identify all human studies with birth outcomes data after maternal exposure to infliximab, adalimumab, or certolizumab pegol within 3 mo of conception or during any trimester of pregnancy. After systematic literature review investigating tumor necrosis factor- $\alpha$  inhibitor therapy and fetal risk, there is insufficient evidence to prove absolute safety for the use of biologics (specifically infliximab, adalimumab, and certolizumab pegol) during pregnancy.

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### INTRODUCTION

Inflammatory bowel disease (IBD) encompasses the diagnoses of Crohn's disease (CD) and ulcerative colitis (UC). These are chronic relapsing gastrointestinal illnesses that involve proinflammatory molecules. The onset of IBD has a bimodal distribution with a higher peak in the younger population aged 15-30 years; fifty percent of patients afflicted by IBD are diagnosed before the age

of 35<sup>[1]</sup>. Hence, the peak incidence for developing these conditions overlaps with the prime reproductive years<sup>[2,3]</sup>.

Effective control of IBD is essential during pregnancy. Active disease or disease flares have been associated with adverse obstetrical outcomes<sup>[4]</sup>. About 50% of the pregnancies in North America are unplanned, and less than half of females realize their pregnancy status by week four of gestation<sup>[5]</sup>. Inadvertent fetal exposure to medications during the crucial stages of organogenesis is thus possible and common. For these reasons, preconception discussions addressing risks and benefits of pharmacologic therapy during pregnancy are clinically warranted for all patients of childbearing potential.

The decision to pursue or maintain certain drug regimens throughout the prenatal and pregnancy periods may pose a significant challenge; the risks of disease activity must be weighed against the potential side effects of medical therapy. Untreated disease may create greater risks to a pregnancy than the drugs themselves<sup>[2]</sup>. Identifying the safest management strategy is crucial, as medication use during pregnancy impacts maternal disease activity, fetal development, and pregnancy outcomes.

Tumor necrosis factor- $\alpha$  (TNF- $\alpha$ ) is a pleiotropic cytokine that plays a role both in pregnancy and in the pathophysiology of inflammatory conditions including IBD. Mouse models have demonstrated that TNF- $\alpha$  is one of several cytokines bearing a potent regulatory effect on early development<sup>[6]</sup>. It controls cyclooxygenases that affect blastocyst implantation, vascular permeability of the endometrium, and uterine decidualization<sup>[7]</sup>. TNF- $\alpha$  also contributes to the process of labor by stimulating uterine contractions in conjunction with other inflammatory cytokines<sup>[8]</sup>. The production of TNF- $\alpha$  increases throughout pregnancy and reaches a peak at the onset of labor. High levels of TNF- $\alpha$  have been implicated in such pregnancy complications as infection and fetal growth retardation and have even been linked to early and unexplained spontaneous abortions<sup>[8,9]</sup>.

There is a characteristic abundance of gut inflammation in IBD originating *via* various mechanisms at the cellular and subcellular levels. TNF- $\alpha$  is a key cytokine in the development and perpetuation of this abnormal immune response<sup>[10]</sup>. Several studies support the heightened production of TNF- $\alpha$  in the intestinal mucosa of patients with CD, and the levels are increased in both inflamed and histologically normal mucosa<sup>[11-13]</sup>. Increased TNF- $\alpha$  has also been linked to such rheumatologic and dermatologic conditions as rheumatoid arthritis, ankylosing spondylitis, psoriatic arthritis, and psoriasis.

TNF- $\alpha$  inhibitors (anti-TNFs) are drugs that block the action of TNF- $\alpha$  and neutralize its biologic effect. This class has demonstrated efficacy in controlling disease activity associated with various inflammatory conditions. Infliximab (IFX), adalimumab (ADA), and certolizumab pegol (CTZ) are three such synthetic antibodies available in the United States for the treatment of IBD. Of these, infliximab has been the most highly studied.

Recognizing the effects of maternal drug use on fetal

development is an important aspect of providing care to pregnant patients and women of childbearing age with IBD. There is limited data, though, pertaining to the safety of biologic agents when used during pregnancy. The United States Food and Drug Administration (FDA) lists anti-TNF agents as category B drugs<sup>[14-16]</sup> (category B specifies that animal studies do not indicate fetal risk and there are no controlled studies in women or that animal studies have demonstrated adverse effects but controlled studies in women have failed to demonstrate risk). A recent consensus statement declared anti-TNF agents to be low risk during certain stages of pregnancy<sup>[17]</sup>. Some case reports and small case series reporting anti-TNF exposure and pregnancy outcomes have been published. However, large population-based studies are sparse, and there is a lack of prospective data in pregnant women. In addition, there is a relatively short number of post-marketing years since the advent of biologics, thus narrowing the safety information pool even further. The increasing use of antibody-based therapeutics fosters the need for further study in this group of patients.

A systematic literature review was performed to investigate fetal risks associated with maternal exposure to TNF- $\alpha$  inhibitors (IFX, ADA, and CTZ) during pregnancy.

## SEARCH STRATEGY

The search strategy was developed with the assistance of a medical librarian. Databases searched included MEDLINE, EMBASE, SCOPUS, and BIOSIS Previews through November 2011 and were restricted to studies published in English and performed in humans. Structured searches were conducted using both medical subject heading terms and keyword/exploded terms as follows: (“congenital abnormalities” OR “congenital disorders” OR “pregnancy” OR “safety”) AND (“infliximab” OR “adalimumab” OR “certolizumab”). Titles and abstracts were screened for relevance; reference lists of the applicable publications were hand-searched to identify additional studies.

## ELIGIBILITY CRITERIA

Case reports, case series, or observational studies published in article or abstract form were eligible for inclusion if there was documented female exposure to IFX, ADA, or CTZ within three months of conception or during any trimester of pregnancy and if > one of the following birth outcomes was assessed: live births, spontaneous abortions (SA), stillbirths (SB), preterm or premature births (PTB/PMB), low birth weight (LBW)/small for gestational age (SGA), or congenital abnormalities (CA). Studies were excluded if there was insufficient detail to link specific anti-TNF exposure with birth outcomes. One investigator independently performed the searches described above and reviewed the citations (titles and abstracts) to determine eligibility. Discrepancies were

resolved by the second investigator.

## DATA EXTRACTION

A standardized form was used to abstract the following data points from each study: anti-TNF drug exposure, indication for anti-TNF agent, pregnancy stage(s) of exposure by trimester, live births, and birth outcomes as aforementioned. Spontaneous abortions were defined as fetal death at < 20 wk, stillbirths as fetal death at > 20 wk or at weight > 350-500 g if gestational age unknown, preterm deliveries as < 37 wk gestation, premature deliveries as < 37 wk gestation and prior to completion of organ development, and low birth weight newborns as < 2500 g. Small for gestational age infants were described by authors as smaller than average size given the number of pregnancy weeks.

## SEARCH RESULTS

The initial search yielded 11452 citations. Fifty studies (Table 1)<sup>[18-68]</sup> met inclusion criteria for full review, including 13 case series, 36 case reports, and 2 prospective studies with control groups. Reports in Table 1 are categorized by biologic agent and study type, and details of maternal anti-TNF exposures and pregnancy outcomes are presented.

The total number of patients exposed to anti-TNFs was 472 (IFX 194/ADA 261/CTZ 17). Table 2<sup>[69-73]</sup> displays anti-TNF exposures and birth outcomes for the following categories: live births, spontaneous abortions, stillbirths, preterm/premature births, low birth weight/small for gestational age, and congenital abnormalities. Outcomes in Table 2 have been listed by anti-TNF exposure (IFX, ADA, and CTZ) and indication (for all medical conditions and for IBD patients alone), and results are compared to the general United States population.

Table 3 summarizes the reported congenital abnormalities associated with live births (4.1%). Among 19 congenital anomalies (IFX 9/ADA 10/CTZ 0), no specific pattern of birth defects was identified<sup>[74-76]</sup>.

## DISCUSSION

We performed a systematic literature review to assess the risk of adverse birth outcomes after maternal exposure to IFX, ADA, or CTZ and identified 50 references with a total of 472 fetal exposures.

The subsequent discussion highlights each biologic agent in the context of pregnancy and provides a summary of our data.

### Infliximab

Infliximab (Remicade) is a human-murine chimeric monoclonal antibody that neutralizes the activity of TNF- $\alpha$ . It is composed of a human immunoglobulin G1 (IgG1) constant region and a murine variable region. Its efficacy in IBD has been documented in randomized

controlled trials in the treatment of moderate to severe CD refractory to conventional therapy as well as enterocutaneous fistulae<sup>[77,78]</sup>. The drug can reduce the need for corticosteroids and, in patients who respond to initial dosing, IFX is effective for the maintenance of response and prolonged remission in CD<sup>[79,80]</sup>.

IFX is classified by the United States FDA as pregnancy category B. Murine models show no evidence of teratogenicity or embryotoxicity. However, anti-TNF- $\alpha$  antibodies vary among species; data cannot simply be paralleled to human pregnancy outcomes. Infliximab does not cross-react with TNF- $\alpha$  in species other than humans and chimpanzees, and it has not been tested in animal reproduction studies<sup>[14]</sup>.

IFX is not thought to cross the placenta in the first trimester due to its human IgG1 constant region<sup>[81]</sup>, but this subclass is known to efficiently cross in the late second and third trimesters<sup>[26]</sup>. Given this timing, the infant is somewhat shielded from drug exposure during the critical period of organogenesis. IFX levels can be detected in newborns of exposed mothers, and the drug remains in the system for up to six months after delivery<sup>[19,50]</sup>. This bears important consequences in terms of newborn infection risks and vaccination responses<sup>[17]</sup>. Discontinuing infliximab in the third trimester is an option to decrease late placental transport to the newborn.

### Adalimumab

Adalimumab (Humira) is a fully human monoclonal IgG1 antibody against TNF- $\alpha$ . It has proven effective for inducing and maintaining remission in CD<sup>[82,83]</sup>, especially in those who have lost response to or have become intolerant of infliximab<sup>[84]</sup>.

ADA is classified as an FDA pregnancy category B drug. In an embryo-fetal perinatal developmental toxicity study, cynomolgus monkeys were administered ADA at extreme dosages of up to 100 mg/kg [266 times human area under the curve (AUC) when dispensed as 40 mg subcutaneously with methotrexate weekly or 373 times human AUC when dispensed as 40 mg subcutaneously without methotrexate]. No evidence of fetal harm due to ADA was recorded. Adequate and well-controlled studies have not been conducted in pregnant women. Again, animal reproduction and developmental studies are not always indicative of human response, and ADA must be used with caution in pregnancy<sup>[15]</sup>. There is no long-term data regarding effects of adalimumab on the developing fetus.

Less information exists on the transplacental diffusion of ADA throughout the trimesters compared to infliximab. Determining the time course of drug administration and when to potentially discontinue ADA during pregnancy is not well-defined due to shorter dosing intervals and limited ability to commercially measure ADA levels. Withholding the drug in the third trimester may be considered to reduce late placental transport to the newborn. Mahadevan *et al*<sup>[17]</sup> suggests discontinuation 8-10 wk prior to estimated date of delivery.

Table 1 Summary of reports of maternal exposure to anti-tumor necrosis factor agents during pregnancy

Ref.	Study type	Disease	Anti-TNF- $\alpha$ agent	Exposure to other drugs	Exposures in pregnancies with documented outcome	Maternal exposure: Pregnancy stage	Live births (n)	SA/SB (n)	PTB/ PMB (n)	LBW/ SGA (n)	CA (n)	Pregnancy outcomes: Details/complications
Chambers <i>et al</i> <sup>[18]</sup>	Prospective	RA	IFX	NS	4	T1	3	1 SA	2			
Mahadevan <i>et al</i> <sup>[19]</sup>	Prospective	CD: (4) UC: (1)	IFX	NS	5	T2/T3 other exposure details	5					
Berthelot <i>et al</i> <sup>[20]</sup>	Case series	Rheumatologic disease	IFX	- <sup>1</sup>	3	NS C/T1: 1 C/T1/T2: 2	3					
Chakravarty <i>et al</i> <sup>[21]</sup>	Case series	RA	IFX	Some pts	1	Pregnancy, not otherwise specified	1					
Correia <i>et al</i> <sup>[22]</sup>	Case series	CD	IFX	Yes: 1 No: 1	2	C/T1/T2/T3	2	1	1	1	1	1 preterm/premature birth due to placental detachment (31 wk, 1.6 kg with acute respiratory failure requiring mechanical ventilation $\times$ 24 h and intensive care $\times$ 40 d; healthy at 8 mo follow-up)
Hyrich <i>et al</i> <sup>[23]</sup>	Case series	Rheumatologic disease	IFX	Some pts	3	C/T1	2	1 SA				
Kane <i>et al</i> <sup>[24]</sup>	Case series	CD	IFX	Some pts	3	T1/T2/T3: 2 T2/T3: 1	3		1			
Katz <i>et al</i> <sup>[25]</sup>	Case series	CD: (82) UC: (1) RA: (8) JRA: (2)	IFX	Some pts	100	C: 53 T1: 30 > 3 mo prior to C: 7	68	10 SA	1	1	3	CA (3): 1 full-term with tetralogy of Fallot 1 intestinal malrotation 1 developmental delay and hypothyroidism
		Unknown: (3)				Unknown: 6		1 SB				1 complicated neonatal course: Respiratory distress/jaundice/seizure. Mother was also exposed to several antibiotics for pulmonary and urinary infections, azathioprine, hydrocortisone, and total parental nutrition early in pregnancy
Mahadevan <i>et al</i> <sup>[26]</sup>	Case series	CD	IFX	Some pts	10	T1: 1 T3: 1 C/T1/T2/T3: 8	10		3	1		Miscarriages (14): 10 SA 1 SB (mother exposed to leflunomide) 3 unknown type 1 neonatal jaundice (resolved) 1 complicated neonatal course: term delivery at 39 wk with respiratory distress/desaturation/gastric ulcer day 5; healthy at 6 mo follow-up
Rosner <i>et al</i> <sup>[27]</sup>	Case series	Rheumatologic disease	IFX	Yes	3	C/T1/T2/T3	3		1			1 premature rupture of membranes
Schnitzler <i>et al</i> <sup>[28]</sup>	Case series	CD/UC/IC	IFX	NS	10	C/T1/T2	9	1 SB	2			

Weber-Schoenderfer <i>et al.</i> <sup>[29]</sup>	Case series	NS	IFX	NS	25	T1	22	2	4	2	CA (2): 1 ventricular septal defect 1 growing hemangioma requiring therapy CA (1): L hand polydactyly (Infant also had respiratory depression after anesthetics that resolved spontaneously. Mother was taking methotrexate 2 mo prior to conception without folic acid supplement.)
Zelinkova <i>et al.</i> <sup>[30]</sup>	Case series	CD: (3) UC: (1)	IFX	Some pts	4	C/T1/T2: 3 C/T1/T2/T3: 1	4	SA	1	1	
Akinci <i>et al.</i> <sup>[31]</sup>	Case report	Rheumatologic disease	IFX	Yes	1	C/T1/T2/T3	1				
Angelucci <i>et al.</i> <sup>[32]</sup>	Case report	CD	IFX	Yes	1	C/T1	1		1	1	LBW
Angelucci <i>et al.</i> <sup>[33]</sup>	Case report	CD	IFX	Yes	1	T1	1				
Antoni <i>et al.</i> <sup>[34]</sup>	Case report	Psoriatic Arthritis	IFX	NS	1	C/T1	1				
Arai <i>et al.</i> <sup>[35]</sup>	Case report	CD	IFX	Yes	1	C/T1/T2	1				
Aratari <i>et al.</i> <sup>[36]</sup>	Case report	CD	IFX	Yes	1	T2	1			1	SGA
Burt <i>et al.</i> <sup>[37]</sup>	Case report	CD	IFX	Yes	1	C/T1	1		1		
Chaparro <i>et al.</i> <sup>[38]</sup>	Case report	CD	IFX	NS	1	C/T1/T2/T3	1		1		
Cheent <i>et al.</i> <sup>[39]</sup>	Case report	CD	IFX	NS	1	C/T1/T2/T3	1		1		Infant developed disseminated BCG after vaccination at 3 mo and died at 4.5 mo
Epping <i>et al.</i> <sup>[40]</sup>	Case report	CD	IFX	Yes	1	C/T1/T2/T3	1				
Hou <i>et al.</i> <sup>[41]</sup>	Case report	CD	IFX	NS	1	C/T1/T2/T3	1				
James <i>et al.</i> <sup>[42]</sup>	Case report	CD	IFX	Yes	1	T2	1				
Kinder <i>et al.</i> <sup>[43]</sup>	Case report	RA	IFX	Yes	1	C/T1	0	1			
Østensen <i>et al.</i> <sup>[44]</sup>	Case report	RA	IFX	Yes	1	C/T1	1	SA			Oligohydramnios detected on 18 wk ultrasound that resolved with discontinuation of Nimesulide
Puig <i>et al.</i> <sup>[45]</sup>	Case report	Psoriasis	IFX	Yes	1	C/T1/T2/T3	1				
Srinivasan <i>et al.</i> <sup>[46]</sup>	Case report	CD	IFX	Yes	1 <sup>2</sup>	C/T1	1		1		Preterm premature birth (24 wk) complicated by intracerebral and intrapulmonary hemorrhages and neonate died at 3 d Mother was also exposed to metronidazole, azathioprine, and mesalamine for fistulizing CD
Steenholdt <i>et al.</i> <sup>[47]</sup>	Case report	UC	IFX	Yes	1	C/T1/T2/T3	1				
Stengel <i>et al.</i> <sup>[48]</sup>	Case report	CD	IFX	Yes	1	C/T1/T2/T3	1				
Tursi <i>et al.</i> <sup>[49]</sup>	Case report	CD	IFX	NS	1	C/T1/T2/T3	1		1		
Vasiltauskas <i>et al.</i> <sup>[50]</sup>	Case report	CD	IFX	NS	1	C/T1/T2/T3	1				
Wilbaux <i>et al.</i> <sup>[51]</sup>	Case report	AS	IFX	NS	1	C/T1	1				
Xirouchakis <i>et al.</i> <sup>[52]</sup>	Case report	CD	IFX	Yes	1	C/T1	1		1		Preterm (29 wk) birth with neonatal hospitalization $\times$ 30 d post-delivery. Baby in "good condition" at follow-up
Johnson <i>et al.</i> <sup>[53,54]</sup>	Prospective	CD and RA	ADA	NS	94	T1 Other exposure details NS	80	13 SA	12	7 (among live births)	CA (7) (live births): 1 undescended testicle 1 microcephaly 1 congenital hip dysplasia with inguinal hernia 1 congenital hypothyroidism 1 ventricular septal defect



Berthelot <i>et al</i> <sup>[20]</sup>	Case series	Rheumatologic disease	ADA	3	2	C/T1: 1 C/T1/T2/T3: 1	2	1 bicuspid aortic valve and agenesis of corpus callosum (twin sibling had patent ductus arteriosus) 1 congenital hydronephrosis
Hyrich <i>et al</i> <sup>[23]</sup>	Case series	Rheumatologic disease	ADA	Some pts	3	C/T1	2	CA (9) (all pregnancies): In addition to above 7 defects were: 1 spina bifida and hydrocephalus (resulted in elective termination) 1 ectopia cordis and caudal regression (twin pregnancy resulting in a spontaneous abortion)
Johnson <i>et al</i> <sup>[53,54]</sup>	Case series	CD and RA	ADA	NS	122	T1	122	5 CA (5): 2 chromosomal abnormalities 1 atrial septal defect and peripheral pulmonic stenosis 1 ventricular septal defect 1 congenital hip dysplasia 1 infant with autosomal dominant disease (not otherwise specified); paternal inheritance Twin-to-twin transfusion syndrome (1 small due to discordance)
Weber-Schoenderfer <i>et al</i> <sup>[29]</sup>	Case series	NS	ADA	NS	28	T1	24	1 infant reported as "normal" at 12 mo follow-up
Abdul Wahab <i>et al</i> <sup>[55]</sup>	Case report	CD	ADA	Yes	1	C/T1/T2/T3	2 (twins)	1
Ben-Horin <i>et al</i> <sup>[56]</sup>	Case report	CD	ADA	NS	1	C/T1/T2/T3	1	SGA
Bosworth <i>et al</i> <sup>[57]</sup>	Case report	CD	ADA	Yes	1	C/T1/T2/T3	1	1
Coburn <i>et al</i> <sup>[58]</sup>	Case report	CD	ADA	Yes	1	T2/T3	1	
Dessinioti <i>et al</i> <sup>[59]</sup>	Case report	Psoriasis	ADA	NS	1	C/T1	1	1
Jurgens <i>et al</i> <sup>[60]</sup>	Case report	CD	ADA	NS	1	C/T1	1	LBW
Kraemer <i>et al</i> <sup>[61]</sup>	Case report	Takayasu's Arteritis	ADA	Yes	1	C/T1/T2/T3	1	
Mishkin <i>et al</i> <sup>[62]</sup>	Case report	CD	ADA	Yes	1	C/T1/T2/T3	1	
Roux <i>et al</i> <sup>[63]</sup>	Case report	RA	ADA	NS	1	C/T1	1	1
Vesga <i>et al</i> <sup>[64]</sup>	Case report	CD	ADA	Yes	1	C/T1/T2/T3	1	
Witbaux <i>et al</i> <sup>[51]</sup>	Case report	AS	ADA	Yes	1	C/T1/T2	1	1
Kane <i>et al</i> <sup>[65]</sup>	Case series	CD	CTZ	NS	14	NS	5	CA (1): Primary craniostomosis requiring surgery
Mahadevan <i>et al</i> <sup>[66]</sup>	Case report	CD	CTZ	Yes	1	T2/T3	1	1
Ousallah <i>et al</i> <sup>[67]</sup>	Case report	CD	CTZ	NS	1	C/T1/T3	1	SGA
Steinberg <i>et al</i> <sup>[68]</sup>	Case report	CD	CTZ	Yes	1	T2	1	

<sup>1</sup>Specified no exposure to disease-modifying antirheumatic drugs, methotrexate, or non-steroidal anti-inflammatory drugs; <sup>2</sup>Case reported by Srinivasan *et al*<sup>[66]</sup> was also documented by Katz *et al*<sup>[23]</sup>; <sup>3</sup>Specified no exposure to disease-modifying antirheumatic drugs, methotrexate, or non-steroidal anti-inflammatory drugs. TNF: Tumor necrosis factor; CD: Crohn's disease; UC: Ulcerative colitis; IC: Indeterminate colitis; RA: Rheumatoid arthritis; JRA: Juvenile rheumatoid arthritis; AS: Ankylosing spondylitis; IFX: Infliximab; ADA: Adalimumab; CTZ: Certolizumab pegol; NS: Not specified; Pts: Patients; C: Within < 3 mo prior to conception; T1: First trimester (LMP to 13 wk); T2: Second trimester (14 to 27 wk); T3: Third trimester (28 to 40 wk); SA: Spontaneous abortion; SB: Stillbirth; Preterm birth (< 37 wk gestation); PMB: Premature birth (< 37 wk gestation and prior to organ development); LBW: Low birth weight (< 2500 g); SGA: Small for gestational age (smaller than average size given the number of weeks of pregnancy).

**Table 2** Summary of anti-tumor necrosis factor exposures and birth outcomes *n* (%)

Anti-TNF exposure	Birth outcomes, <i>n</i> (with relative percents)						
	Fetal exposures	Live births	SA	SB	PTB/ PMB	LBW/SGA	CA
IFX/ADA/CTZ total	472	405 (85.8)	32 (8.2)	2 (0.6)	41 (19.9)	8 (6.1)	19 (4.1)
IFX <sup>1</sup>	194	155 (79.9)	15 (10.6)	2 (1.1)	21 (26.9)	5 (4.4)	6 (4.0)
IFX in IBD <sup>2</sup>	151	117 (77.5)	11 (8.9)	2 (1.4)	16 (36.4)	5 (4.8)	4 (3.5)
ADA <sup>1</sup>	261	242 (92.7)	16 (6.9)	0 (0.0)	20 (15.9)	2 (28.6)	13 (5.4)
ADA in IBD <sup>2</sup>	224	210 (93.8)	13 (5.8)	0 (0.0)	15 (17.0)	2 (28.6)	12 (5.7)
CTZ <sup>1</sup>	17	8 (47.1)	1 (5.9)	0 (0.0)	0 (0.0)	1 (12.5)	0 (0.0)
CTZ in IBD <sup>2</sup>	17	8 (47.1)	1 (5.9)	0 (0.0)	0 (0.0)	1 (12.5)	0 (0.0)
Outcome percents in general US population <sup>[69-73]</sup>		64.60%	16.50%	0.60%	12.30%	8.20%	3.00%-5.00%

<sup>1</sup>Exposure in all reported medical conditions; <sup>2</sup>Exposure in inflammatory bowel disease (IBD) patients. TNF: Tumor necrosis factor; IFX: Infliximab; ADA: Adalimumab; CTZ: Certolizumab pegol; SA: Spontaneous abortion (fetal death at < 20 wk); SB: Stillbirth (fetal death at > 20 wk or > 350 g if gestational age unknown); PTB: Preterm birth (< 37 wk gestation); PMB: Premature birth (< 37 wk gestation and prior to completion of organ development); LBW: Low birth weight (< 2500 g); SGA: Small for gestational age (smaller than average size given number of pregnancy weeks).

**Table 3** Summary of congenital abnormalities reported

Congenital abnormalities ( <i>n</i> = 19)	Affected ( <i>n</i> )	Anti-TNF exposure
Ventricular septal defect	3	IFX (1), ADA (2)
Chromosomal abnormalities	2	IFX
Congenital hip dysplasia	2	IFX (1), ADA (1)
Intestinal malrotation	1	IFX
Congenital hypothyroidism	1	IFX
Hemangiomas	1	IFX
L hand polydactyly	1	IFX
Tetralogy of Fallot	1	IFX
Patent ductus arteriosus	1	ADA
Atrial septal defect and peripheral pulmonic stenosis	1	ADA
Bicuspid aortic valve and agenesis of corpus callosum	1	ADA
Primary craniostylosis	1	ADA
Microcephaly	1	ADA
Congenital hydronephrosis	1	ADA
Undescended testes	1	ADA

IFX: Infliximab; ADA: Adalimumab; TNF: Tumor necrosis factor.

### Certolizumab pegol

Certolizumab pegol (Cimzia) is a recombinant humanized anti-TNF- $\alpha$  fragment antigen binding (Fab') fragment. The antibody fragment is bound to a polyethylene glycol molecule that extends the drug's half-life to approximately two weeks in the plasma, thereby reducing dosing frequency<sup>[85]</sup>. Studies have demonstrated the efficacy of CTZ for induction and maintenance of remission in CD<sup>[86]</sup>.

CTZ is a pregnancy category B drug. It does not cross-react with mouse or rat TNF- $\alpha$ . Reproduction studies in rats have thus been performed using a rodent anti-murine TNF- $\alpha$  pegylated Fab' fragment (cTN3 PF) that is similar in function to CTZ. These studies have been conducted using doses up to 100 mg/kg and have revealed no evidence of impaired fertility or fetal adversities due to cTN3 PF. Adequate and well-controlled studies have not been performed in pregnant women. As animal reproduction studies are not always indicative of human response, this drug must be used with caution in pregnancy<sup>[16]</sup>.

The molecular structure of CTZ lacks an Fc portion, so its cross-placental transfer is different from that of IFX and ADA. The Fab' fragment may passively cross the placenta in low levels during the first trimester, an event that is not expected with the IgG1 antibody. Although CTZ therapy would likely not need to be discontinued in the third trimester, it is important to recognize that the transplacental transfer of this drug occurs during a critical period of organogenesis in the first trimester.

In an animal model, pregnant rats received a murinized IgG1 TNF- $\alpha$  antibody and a PEGylated Fab' fragment of the antibody. Lower levels of the drug were detected in the infant and in breast milk with the Fab' fragment versus the full antibody<sup>[87]</sup>. Mahadevan *et al*<sup>[66]</sup> demonstrated these findings in two human patients receiving certolizumab during pregnancy. The drug was administered to both women two weeks prior to delivery. Although the mothers' drug levels were higher on the date of delivery, newborn cord blood levels were low.

There are few published reports on the use of CTZ during pregnancy. As with the other anti-TNF agents, it is possible that the Fab' fragment passively crosses the placenta at low levels in the first trimester. The drug must be further studied in humans to fully appreciate the course of drug transfer during gestation and subsequent effects on fetal development and pregnancy outcomes.

## SUMMARY OF DATA

Our review indicates that rates of SA and CA in anti-TNF-exposed patients are similar to rates in the general United States population<sup>[69-73]</sup> and in women with IBD unexposed to anti-TNF agents<sup>[74-76]</sup>. The live birth rate in the anti-TNF-exposed group (85.8%) is higher than that of the general United States population (64.6%); this holds true for all patients exposed to IFX or ADA regardless of underlying inflammatory disease and perhaps reflects a state of controlled disease activity. The live birth rate for patients exposed to CTZ (47.1%) is lower than that of the general population, although there is a very small collective sample size. The rates of SA and

SB for all groups are similar to the general United States population<sup>[72]</sup> with the exception of IFX-exposed patients, in whom the rate of SB is just slightly higher. The PTB/PMB rate in the anti-TNF-exposed group (19.9%) is higher than in the United States population (12.3%)<sup>[72]</sup>, perhaps due to an underlying predisposition as in the setting of IBD<sup>[76]</sup>. LBW/SGA infants are more common in ADA- and CTZ-exposed patients than in the general United States population<sup>[73]</sup>, again possibly reflecting the underlying disease itself or the severity of disease activity.

In general, pregnancy does not increase the risk of disease exacerbation in CD or UC<sup>[88,89]</sup>. Approximately one-third of women with inactive IBD at the time of conception are expected to flare during pregnancy and the puerperium<sup>[90]</sup>. Alternatively, if pregnancy overlaps with a period of active IBD, the disease may be difficult to control<sup>[91]</sup>. Active disease at the time of conception has been associated with increased rates of PTB<sup>[89]</sup> and fetal loss<sup>[92]</sup>, and disease flares during pregnancy have been associated with PTB and LBW<sup>[4,93]</sup>. Studies are mixed regarding the risk of congenital malformations among IBD progeny, with some data showing an increased risk for both CD and UC patients<sup>[94]</sup> or for UC patients alone<sup>[95,96]</sup> and other data showing no increased risk in CD or UC<sup>[97,98]</sup>. Regardless of disease activity, women with IBD have an increased risk for such adverse pregnancy outcomes as PTB, SB, LBW, SGA, and delivery complications such as cesarean sections compared to the general population<sup>[97-101]</sup>. In our study, no discernible increased risks for SA or CA were identified. Overall, unless there is a clear risk of fetal harm (*i.e.*, an FDA category X drug) that dictates otherwise, maintenance therapy is conventionally continued throughout pregnancy to optimize maternal disease control and prevent relapse or progression<sup>[102]</sup>.

This systematic review has limitations. Pooling data from different studies yields inherent heterogeneity based on study designs, study populations, and recording of birth outcomes data. As evidenced, there are a limited number of reported pregnancy exposures to anti-TNF agents, many published as case reports or case series with small sample sizes; these do not necessarily reflect outcomes that can be extracted to the general population. Our review is affected by the limitations of the individual studies, including the inability to adjust for maternal disease activity and severity, concomitant medication or substance use, comorbidities, or other maternal characteristics. Additionally, there exist potential publication bias against negative outcomes and recall bias involving drug exposure and timing of administration during conception and pregnancy. The decision to exclude studies based on the English language and on the inability to link specific anti-TNF exposure with birth outcomes may have discounted pertinent publications. Although care was taken to account for evident overlap, it is possible that repeated data exists given the nature of our information (for example, a case report that has also been reported within drug registry data).

A growing body of evidence supports that IFX, ADA, and CTZ are low risk in pregnancy<sup>[17]</sup>, and studies beyond those included in our data set are underway to further elucidate fetal risk and optimal timing of biologic administration during pregnancy<sup>[103,104]</sup>. Thus far, it is believed that IFX and ADA are most compatible for use during conception and at least the first and second trimesters considering mechanisms of placental transport<sup>[17,102]</sup>; further human data are needed to generate safety guidelines for the use of CTZ. In a recent study of pregnant women receiving biologic therapy, IFX and ADA were shown to be transplacentally transferred to infants at birth, with high levels of drug in cord blood and detectable drug levels up to six months after birth. CTZ was found to be least detectable in both cord blood and infant serum after birth. Of note, no CA or significant fetal complications were reported in this study<sup>[104]</sup>.

Future efforts are promising and include the expansion of drug safety data registries and the development of larger prospective trials to help definitively quantify fetal risk and to facilitate clinical decision-making in treating women with IBD during their childbearing years. One such project is the highly anticipated Pregnancy IBD and Neonatal Outcomes study, a prospective data collection from multiple IBD centers in the United States<sup>[105]</sup>. This large cohort registry not only accounts for maternal factors including IBD activity, medication use, delivery methods, and pregnancy complications but also tracks data over time from the neonatal period through children's first year of life. Similarly, post-marketing surveillance data may uncover additional consequences of fetal exposure to biologic agents over time.

While evidence in the field is mounting, caution should indefinitely be exercised. Given the limitations of the available data and lack of controlled trials, there is insufficient evidence to prove absolute safety for use of anti-TNFs during pregnancy. Although the benefits of therapy in optimizing disease activity during gestation may lend to more favorable pregnancy outcomes based on a controlled disease state, definitive safety of drug exposure on the developing fetus has not been confirmed.

Medical management decisions during the preconception and pregnancy periods will inevitably vary by case based on respective risk-to-benefit ratios, details of disease activity, response to alternative therapies, and individual preferences. Women and men of childbearing age should be educated about the effects of IBD on pregnancy and the potential implications of treatment on fetal development. In addition, patients should be encouraged to discuss reproductive plans with their physicians in order to achieve remission prior to conceiving. Ideally, the primary preconception goal should be quiescent disease, as this lends to the most favorable pregnancy outcomes.

## CONCLUSION

After systematic literature review investigating TNF- $\alpha$  inhibitor therapy and fetal risk, there is insufficient evi-



dence to prove absolute safety for the use of biologics (specifically infliximab, adalimumab, and certolizumab pegol) during pregnancy.

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