

Safety of anti-TNF agents in pregnancy



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Activity Objectives:

1. To compare the pharmacology of different anti-TNF agents during pregnancy.
2. To recognize that anti-TNF agent exposure during pregnancy is not associated with increased maternal or infant adverse outcomes.
3. To state the vaccination recommendations for infants exposed *in utero* to anti-TNF biologics.

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Inflammatory bowel disease, rheumatoid arthritis, ankylosing spondylitis, psoriatic arthritis, and psoriasis are associated with adverse pregnancy outcomes. Active maternal disease during pregnancy is associated with additional negative outcomes. Anti-TNF agents are effective treatments for inflammatory bowel disease, rheumatoid arthritis, ankylosing spondylitis, psoriatic arthritis, and psoriasis. These agents cross the placenta starting in the second trimester, with levels detected for several months after birth. This has led to safety concerns, with continued therapy during pregnancy for both the mother and the infant. This review covers retrospective and prospective data published from various cohorts of pregnant women exposed to anti-TNF agents during pregnancy. It highlights the safety of anti-TNF drugs in pregnancy, breast-feeding, and during the first year of life of the infant. (*J Allergy Clin Immunol* 2021;148:661-7.)

Key words: Anti-TNF agents, pregnancy, safety, inflammatory bowel disease

Inflammatory diseases such as inflammatory bowel disease (IBD), rheumatoid arthritis (RA), ankylosing spondylitis (AS), psoriatic arthritis (PsA), and psoriasis affect women during their reproductive years.¹⁻⁴ This makes management of the inflammation of their underlying disease of particular importance before and during pregnancy. Active maternal disease has been associated with an increased risk in pregnancy complications and adverse outcomes.⁵⁻⁸ Therefore, treatment to control inflammation throughout pregnancy with ongoing medical therapy continues to be a risk-benefit discussion. Sustained remission of the underlying disease is ideal to prevent complications.

Anti-TNF agents including infliximab (IFX), etanercept (ETA), adalimumab (ADA), certolizumab pegol (CZP), and golimumab (GOL) are effective treatments for IBD, RA, AS, PsA, and psoriasis.⁹⁻¹³ Infection risk, including opportunistic infections, is increased in patients treated with anti-TNF agents.¹⁴⁻¹⁸

IFX is the most studied anti-TNF agent in pregnancy, followed by ADA, CZP, and ETA, with only limited data available for GOL. Anti-TNF agents, except CZP, are IgG₁ molecules that cross the placenta starting after week 20, with the highest transfer occurring in the third trimester.¹⁹ CZP has an Fc-free Fab fragment attached to a pegol ligand and does not cross the placenta. IFX, ADA, and ETA levels have been detected in infants during their first year of life.^{20,21} This has raised the concern for adverse pregnancy outcomes, congenital abnormalities, risk of infection,

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Abbreviations used

ADA:	Adalimumab
ARR:	Absolute relative risk
AS:	Ankylosing spondylitis
CZP:	Certolizumab
CD:	Crohn disease
ETA:	Etanercept
GOL:	Golimumab
IBD:	Inflammatory bowel disease
IFX:	Infliximab
LBW:	Low birth weight
OR:	Odds ratio
RA:	Rheumatoid arthritis
RR:	Relative risk
SAB:	Spontaneous abortion
PIANO:	Prospective US Pregnancy in Inflammatory Bowel Disease and Neonatal Outcomes
PsA:	Psoriatic arthritis
UC:	Ulcerative colitis

and development delay in infants born to women on anti-TNF agents during pregnancy. As a result, it has been common practice for clinicians who manage immunosuppressive agents and/or pregnant patients to stop or hold anti-TNF agents during pregnancy.

This review aimed to address these safety concerns of anti-TNF agents during pregnancy, breast-feeding, and during the first year of life of the infant. The majority and the most robust data come from the IBD literature.

DISEASE ACTIVITY AT CONCEPTION AND DURING PREGNANCY

Inflammatory bowel disease

Women with IBD experience higher rates of preterm delivery, low birth weight (LBW), and small-for-gestational-age infants, regardless of disease activity. Maternal IBD activity further compounds the risk of adverse pregnancy events and has been associated with preterm birth, small-for-gestational-age infants, spontaneous abortion (SAB), reduced weight gain in the mother, and complications of labor and delivery (cesarean section, preeclampsia, and placental abruption).²²⁻³¹

Two-thirds of patients with IBD with active disease at conception have persistent disease activity during pregnancy, whereas only one-third of patients with quiescent disease at conception experience a relapse during pregnancy.²⁶⁻²⁸ In contrast to patients with Crohn disease (CD), pregnant patients with ulcerative colitis (UC) have a higher risk of relapse during pregnancy (especially the first and second trimesters) and in the postpartum period compared with nonpregnant women with UC.²⁹

Results from the prospective US Pregnancy in Inflammatory Bowel Disease and Neonatal Outcomes (PIANO) cohort found that patients with UC had significantly increased disease activity compared with patients with CD during every trimester. Almost half the patients with UC were not on biologics or thiopurines despite their higher rates of disease activity. Disease flares were more likely in those women unexposed to biologics or thiopurines.²³

In a meta-analysis of 14 studies, there was a high risk of ongoing active disease during pregnancy in women with active

disease at conception compared with the risk of relapse in women in remission at conception for both UC (55% vs 29%; relative risk [RR], 2.0; 95% CI, 1.5-3; $P < .001$) and CD (46% vs 23%; RR, 2.0; 95% CI, 1.2-3.4; $P = .006$).³⁰

These data highlight the importance of control of inflammation at conception and the need to remain on adequate medical therapy throughout pregnancy with the goal of staying in remission to minimize complications.

Rheumatologic diseases

A recent meta-analysis of 237 pregnant patients with RA found that disease activity improved in 60% of patients during pregnancy and flared in 46.7% in the postpartum period. This study did not account for pharmacotherapy before, during, or after pregnancy.³¹

Women with RA have babies with lower birth weights that are exacerbated by disease activity during pregnancy.³² A prospective study ($n = 152$) of pregnant women with RA found that pregnancy outcomes in well-controlled RA are comparable with those in the general population. RA disease activity during pregnancy was independently associated with LBW.⁸

A recent systematic review of 21 studies assessed pregnancy outcomes in AS. Disease flare occurred in 25% to 80% of patients during pregnancy and in 30% to 100% during the postpartum period. Based on 2 case-control studies, there was an increased risk for prematurity and small-for-gestational-age infants in AS pregnancies, with pooled odds ratio (OR) of 1.99 (95% CI, 1.30-3.05) and 2.41 (95% CI, 1.22-4.77), respectively.³³ Compared with healthy controls, women with AS had an increased risk of delivering infants who require intensive care (absolute relative risk [ARR], 1.67; 95% CI, 1.05-2.67). Disease activity during pregnancy was associated with cesarean delivery (ARR, 5.82; 95% CI, 1.06-31.78).⁷

One hundred thirty-six pregnant patients with RA and AS were prospectively followed before, during, and after pregnancy. Disease flares during pregnancy occurred in 29% of patients with RA and in 25% of patients with AS. In both diseases, active disease and early discontinuation of anti-TNF agents were identified as risk factors for disease flares during pregnancy. The RR of flare in patients with RA who stopped anti-TNF treatment was 3.33 (95% CI, 1.8-6.1). Reinitiation of anti-TNF or glucocorticosteroid treatment in 60% of these patients resulted in disease improvement in the second and third trimesters. In patients with AS who stopped anti-TNF treatment, the RR of flare was 3.08 (95% CI, 1.2-7.9). Despite reinitiation of anti-TNF or glucocorticosteroid treatment in 62.5% of these patients, disease activity remained elevated throughout pregnancy.³⁴

A prospective multicenter study of 108 pregnancies in patients with PsA found that disease activity was low and stable during pregnancy, with an increase at 6 months postpartum. Those women who used anti-TNF agents during pregnancy had significantly lower disease activity.³⁵

Compared with healthy controls, women with PsA were at an increased risk for preterm delivery (32-36 weeks' gestation) (ARR, 1.81; 95% CI, 1.01-3.26), oligohydramnios (ARR, 3.79; 95% CI, 1.34-10.74), and cesarean delivery (ARR, 1.63; 95% CI, 1.26-2.12). Disease activity was associated with preterm delivery (ARR, 3.82; 95% CI, 1.51-9.67).⁷

Consistent with the IBD literature, the underlying disease itself is associated with adverse pregnancy outcomes, with additional negative outcomes caused by uncontrolled disease activity.

Dermatologic diseases

A prospective study of 47 women with psoriasis found that disease activity improved in 55%, remained stable in 21%, and worsened in 23% during pregnancy. In the postpartum period, 9% of patients reported improvement, 26% reported no change, and 65% reported worsening of disease.³⁶

Studies suggest that psoriasis may adversely affect maternal pregnancy outcomes, both as an independent risk factor and as a result of comorbidities. Psoriasis is associated with various comorbidities including psoriatic arthritis, anxiety, depression, obesity, gestational diabetes, preeclampsia, hypertension, and polycystic ovary syndrome.^{6,37-41}

A systematic review found statistically significant increases in SAB, cesarean delivery, LBW, macrosomia, large-for-gestational age infants, and prematurity. However, these associations were not always consistent across studies.⁴²

In a population-based study of 8097 births from 6103 women with psoriasis, an increased risk of gestational diabetes, gestational hypertension, preeclampsia, and cesarean delivery was found when compared with that in women without psoriasis. These risks were higher in patients with severe disease. Disease severity was also associated with preterm birth and LBW.⁶

A nationwide population-based study of 1463 mothers with psoriasis also found an increase in lower birth weight in patients with severe psoriasis. No adverse birth outcomes were found in patients with mild psoriasis.⁴³

Similar to the IBD and rheumatology data, women with psoriasis are at increased risk for adverse pregnancy outcomes that are exacerbated by disease activity.

ANTI-TNF PLACENTAL TRANSFER AND DRUG LEVELS

During pregnancy, maternal antibodies are transported across the chorionic villi by the neonatal Fc receptor to provide immunity to the newborn. IFX, ADA, ETA, and GOL are IgG₁ antibodies with Fc portions that are actively transported across the placenta starting early in the second trimester until delivery. CZP does not have an Fc portion and does not cross the placenta.¹⁹

Inflammatory bowel disease

In the general IBD population, interindividual and intra-individual differences in bioavailability and pharmacokinetics contribute to the variability seen in serum anti-TNF drug concentrations. Antidrug antibodies, male sex, IBD activity, body mass index, albumin, C-reactive protein, and concomitant immunomodulator use are known factors to influence the pharmacokinetics of anti-TNF agents.⁴⁴

In pregnancy, plasma volume expansion results in a decrease in albumin and hemoglobin. Body mass index increases, and C-reactive protein remains stable (in the absence of active disease).⁴⁵

IFX clearance is decreased in the second and third trimesters of pregnancy, raising maternal serum IFX levels. IFX transportation over the placenta increases exponentially in the third trimester, whereas ADA transportation is limited and increases in a linear fashion.⁴⁶ IFX cord levels rise during pregnancy, whereas ADA cord levels remain stable after accounting for changes in albumin, body mass index, and C-reactive protein.⁴⁵ The pharmacokinetic differences between IFX and ADA during pregnancy are not well understood.

In a prospective study (N = 80; 36 ADA and 44 IFX pregnant patients with IBD), drug levels were measured in the mother's serum at delivery, umbilical cord, and every 3 months in the infant. IFX and ADA levels were detected up to age 12 months. There was an inverse correlation between the time from last exposure during pregnancy and drug concentration in the umbilical cord. IFX was cleared more slowly than ADA from the infants.²⁰

In the PIANO registry, IFX had the highest infant and cord serum concentrations. There was no difference in risk of serious or any infant infection in the first 12 months by birth drug concentration for all of the biologics studied, including anti-TNF agents.²³

Rheumatologic diseases

In 2 case reports, etanercept was found to have a low transplacental transmission in mothers who continued etanercept throughout pregnancy.^{21,47}

PREGNANCY OUTCOMES IN PATIENTS ON ANTI-TNF AGENTS

Inflammatory bowel disease

Safety data from prospective studies, large nationwide cohorts, observational studies, systematic reviews, and meta-analysis of women with IBD on anti-TNF agents during pregnancy have not shown an increased risk of adverse pregnancy outcomes.⁴⁸⁻⁵⁷

In the large prospective PIANO registry, there were no differences in rates of pregnancy complications (congenital malformations, LBW, SAB, preterm, intrauterine growth restriction, cesarean section, neonatal intensive care unit stay at birth) between the unexposed, biologics, thiopurine, and combination therapy groups. Maternal IBD activity was an independent risk factor for SAB. Biologics and combination therapy had higher rates of cesarean sections, most likely due to the severity of the underlying IBD rather than the medications themselves.²³

Similarly, a retrospective 3-center study from the Czech Republic found that anti-TNF agents are effective and safe during pregnancy without a signal for congenital malformations.⁵⁸

In the earlier Therapy Resource Evaluation and Assessment Tool registry, pregnancy outcomes in patients with CD were similar in the gestational IFX exposure group when compared with the unexposed group. Lower live birth rates were reported among IFX-exposed women, which was thought to be related to those patients having more severe CD.⁵⁹

In the general IBD population, discontinuation of anti-TNF therapy when in remission has been associated with an up to 50% relapse rate within 2 years.^{60,61}

In pregnant women with IBD in remission, discontinuation of anti-TNF therapy (before week 30) was associated with relapse rates of 8% in a small case series (N = 25) and 14% in a case-control study (n = 85).^{52,62} In the case-control study, an additional 32% of patients in remission who discontinued therapy during pregnancy flared in the first 3 postpartum weeks.

In a prospective study of women with IBD, there was no difference in relapse rates after week 22 among women in sustained remission who stopped anti-TNF therapy at week 25 compared with the remaining women who continued therapy beyond week 30 (9.8% vs 15.6%; *P* = .14).⁶³

A retrospective cohort study in France found that exposure to anti-TNF treatment during pregnancy increased the risk for maternal complications (adjusted OR, 1.49; 95% CI, 1.31-1.67)

TABLE I. Safety of anti-TNF agents during pregnancy

Anti-TNF agent	Pregnancy outcome	Infections	Lactation	Vaccines	Milestones
Infliximab (IFX) Adalimumab (ADA) Certolizumab (CZP) Golimumab (GOL)	No adverse outcomes ^{23,48-59,64-78}	No increase in infant infections ^{23,48,81,83}	Compatible ^{64,65,79,80,85-89}	Avoid live vaccines in the first 12 mo (except for CZP) ^{64,65,74,79,80,91}	Normal development ^{23,92}
Etanercept (ETA)	No adverse outcomes ⁶⁶⁻⁷⁴	No increase in infant infections ⁸³	Compatible ^{21,47,74,88}	Avoid live vaccines in the first 12 mo ⁷⁴	No data

and infections (adjusted OR, 1.31; 95% CI, 1.16-1.47) but not infant infections (adjusted OR, 0.89; 95% CI, 0.76-1.05). However, maintaining anti-TNF agents after 24 weeks did not increase the risk of maternal complications, but discontinuation before week 24 increased the risk of disease flare.⁴⁹

Based on the reassuring safety data of continuation of anti-TNF agents throughout pregnancy and the clear association of active disease with adverse pregnancy outcomes, current North American guidelines and expert opinion do not support early discontinuation of anti-TNF agents in pregnancy.^{64,65}

Rheumatologic diseases

Safety data from small prospective studies, retrospective studies, case series, registries, and observational studies of women with rheumatologic diseases on anti-TNF agents during pregnancy have not shown an increased risk of adverse pregnancy outcomes.⁶⁶⁻⁷⁰

A systematic review of 143 recent publications (January 2015 to July 2019) found no difference in the rates of miscarriages and congenital malformations when comparing patients with inflammatory autoimmune diseases treated with biologics (including anti-TNF agents) and the general population.⁷¹

A large series of pregnant women with CD and RA (n = 96) exposed to IFX throughout pregnancy found no difference in pregnancy outcomes compared with the US population of pregnant women and pregnant women with CD not exposed to IFX.⁵¹

The European League Against Rheumatism task force described 10 cohort studies of 2492 pregnancies (1734 followed prospectively) exposed to anti-TNF agents during pregnancy. They found no differences in the rate of miscarriages or congenital defects between the exposed and unexposed controls.⁷²

The Organization of Teratology Information Services registry is a prospective cohort study of pregnant women (n = 100) with inflammatory arthritis including RA, AS, and PsA exposed to ETA compared with 54 unexposed controls. Similar rates of live birth (94% ETA vs 87% controls) and rate of congenital anomalies (8% ETA vs 5.7% controls) were found.⁷³

Similar to the IBD literature, anti-TNF exposure during pregnancy has not been associated with adverse pregnancy outcomes. The American College of Rheumatology guideline supports the continuation of anti-TNF agents throughout pregnancy in a mother with active disease. It recommends discontinuation of anti-TNF agents (except CZP) in the third trimester if maternal disease activity is in remission to minimize transfer of drug to the infant.⁷⁴

Dermatologic diseases

Case reports and small case series have not found any adverse pregnancy outcomes in patients with psoriasis treated with anti-TNF agents.^{75,76}

In the Psoriasis Longitudinal Assessment and Registry, 298 pregnancies occurred. Of the 298 pregnancies, 168 were exposed to biologic within 1 year of birth. Eight percent (14 of 168) of patients were exposed to IFX or GOL. There was 1 SAB (1 of 14) and 13 healthy newborns without any congenital anomalies. Overall, pregnancy outcomes were similar in the women exposed to all biologics compared with the unexposed women.⁷⁷

In a small case series, 50% (6 of 12) of women with psoriasis were exposed to an anti-TNF in the first trimester only. One woman elected to undergo an abortion. One woman switched from IFX to CZP and continued therapy throughout pregnancy. There were no congenital abnormalities at birth or any negative effects on growth and physiological development at last follow-up.⁷⁸

The safety data in the dermatology literature are very limited, with most exposures to anti-TNF drugs in the first trimester only. Systematic reviews and consensus statements do not routinely support continuation of anti-TNF agents throughout pregnancy; however, they do support an individualized approach taking into account risks and benefits to the mother and the infant.^{79,80}

RISK OF INFECTIONS IN PREGNANT PATIENTS ON ANTI-TNF AGENTS

Anti-TNF agents are associated with an increased risk of infection in patients with IBD, rheumatologic diseases, and psoriasis.¹⁴⁻¹⁷ Therefore, the risk of maternal and infant infections when anti-TNF agents are used during pregnancy has been of great concern. This has been mostly studied in the IBD literature.

Inflammatory bowel disease

An earlier small study of 80 pregnant women with IBD found that infants born to mothers treated with combination anti-TNF and thiopurine therapy during pregnancy had a 3-fold increased risk of infantile infection compared with infants born to mothers treated with anti-TNF monotherapy.²⁰ A large cohort study (n = 1457) of women with IBD found that biologics during pregnancy were associated with an increased risk of maternal, but not infantile, infections.⁴⁹

A recent meta-analysis of 8013 women with IBD who gave birth to 8490 infants found that biologic use during pregnancy was not associated with an increased risk of all infantile infections (OR, 0.91; 95% CI, 0.73-1.14). The majority of biologic exposure was with anti-TNF agents. In a subgroup analysis, biologic use was associated with an increased risk for upper respiratory tract infections but not infantile antibiotic use or infection-related hospitalizations. The investigators also showed that the risk of infantile infections was comparable between CZP and other anti-TNF agents. Continuing biologics in the third trimester did not increase infection risk.⁸¹

In the PIANO registry, preterm birth was the only risk factor for infection. Controlling for preterm birth, maternal age, and disease activity, the use of biologics (OR, 0.92; 95% CI, 0.70-1.20), thiopurine (OR, 0.90; 95% CI, 0.64-1.28), or combination therapy (OR, 0.93; 95% CI, 0.66-1.32) was not associated with an increased risk of any infection in the first year of life. Infection rates did not differ by the type of biologic use. In addition, exposure to biologic use in the third trimester was not associated with increased infant infection rates.²³

Similar to the PIANO study, a retrospective multicenter cohort (TEDDY) of 841 children born to mothers with IBD, *in utero* exposure to anti-TNF agents did not appear to be associated with increased short-term or long-term risk of severe infections in children. Preterm delivery was the only variable associated with a higher risk of severe infection (OR, 2.5%; 95% CI, 1.5-4.3).⁴⁸

Children of mothers with IBD who attend day care in their first year of life have an increased risk of any infection compared with those not in day care. There is no difference in serious infections. Biologic use was not found to increase infections in those who attend day care.⁸²

Rheumatologic and dermatologic diseases

A population-based cohort study in Denmark, Finland, and Sweden compared 1,027 children born to women with RA, psoriasis, psoriatic arthritis, AS, or IBD treated with anti-TNF agents, and 9,346 children born to similar women with nonbiologic systemic treatment, with 1,617,886 children of the general population. Children were followed for 3 years. Adjusted by maternal age, parity, smoking, body mass index, country, and calendar year, the incidence rate ratios with 95% CI for hospital admissions for infection in the first year were 1.43 (1.23-1.67) for anti-TNF and 1.14 (1.07-1.21) for nonbiologic systemic treatment. There was a slight increase in antibiotic prescriptions in the second year for anti-TNF, 1.19 (1.11-1.29), and for nonbiologic systemic treatment, 1.10 (1.07-1.13). There was no difference among anti-TNF agents, treatment in the third trimester, or between mono/combination therapies compared with nonbiologic systemic treatment.⁸³

LACTATION AND BREAST-FEEDING

Breast-feeding is beneficial for both mother and child. However, some women discontinue their medications because of fear of transmission into the breast milk.⁸⁴

In a study of women receiving treatment for IBD and their infants, low concentrations of IFX, ADA, and CZP were detected in breast milk samples. No GOL was detected in 1 patient. Breast-fed infants of mothers on biologics, immunomodulators, or combination therapies had similar risks of infection and rates of milestone achievement compared with infants not breast-fed or infants unexposed to these drugs.⁸⁵

In case reports, ETA was found in very low concentrations in breast milk.^{21,47}

Based on the current available data, worldwide consensus statements, and expert opinion, maternal use of anti-TNF agents is compatible with breast-feeding.^{64,65,80,86-89}

SAFETY AND RESPONSE TO VACCINES

All vaccines should be given according to the Centers for Disease Control and Prevention guidelines. However, current guidelines

recommend that infants born to mothers exposed to biologics during the third trimester (except for CZP) should avoid live vaccines during the first 12 months. In the United States, this includes the live rotavirus vaccine given at 2 and 4 months.⁶⁴ In other countries, this includes the live Bacillus-Calmette-Guerin vaccine.

Cheent et al⁹⁰ described a fatal case of severe, disseminated Bacillus-Calmette-Guerin infection after vaccination at 3 months in an infant exposed to maternal IFX.

In the PIANO registry, vaccine response to *Haemophilus influenzae* B and tetanus vaccines was not impacted by maternal exposure to thiopurines or biologic therapy. There was also no association between cord blood or infant serum concentrations of biologics and adequacy of vaccine titers. In a small group of women, administration of the live rotavirus vaccine to infants exposed to biologics *in utero* did not result in any significant adverse events.⁹¹

DEVELOPMENTAL MILESTONES

In the PIANO registry, no differences in developmental milestones (communication, fine motor, gross motor, personal-social, and problem solving) were found between the unexposed, biologic, thiopurine, and combination therapy groups at 12 months.²³

An observational study of 3 centers in the Czech Republic found that anti-TNF exposure *in utero* does not seem to have a negative impact on postnatal development of children with regard to infectious complications, vaccination response, allergy, growth, or psychomotor development when compared with unexposed children of women without IBD.⁹²

CONCLUSIONS

Anti-TNF agent exposure during pregnancy in women with IBD, RA, AS, PsA, and psoriasis is not associated with increased maternal or infant adverse outcomes. It is compatible with lactation and does not have a negative impact on postnatal development. Live vaccines should be avoided during the first year (except for in CZP). Table I summarizes the safety of all anti-TNF agents.

Active maternal disease has been associated with an increased risk in pregnancy complications and adverse outcomes. To prevent any pregnancy complications, physicians should have a risk-benefit discussion with their patients about the importance of remission at conception and the possibility of the need to continue anti-TNF therapy throughout pregnancy with the goal of achieving and maintaining remission.

What do we know?

- IBD, RA, AS, PsA, and psoriasis are associated with adverse pregnancy outcomes independent of disease activity.
- Active maternal disease during pregnancy is associated with additional negative pregnancy outcomes.
- Anti-TNF agent exposure during pregnancy in women with IBD, RA, AS, PsA, and psoriasis is not associated with increased maternal or infant adverse outcomes.

What is still unknown?

- Pharmacokinetics of different anti-TNF agents during pregnancy in women with IBD, RA, AS, PsA, and psoriasis.
- Comprehensive long-term effects on infants exposed to anti-TNF agents *in utero*.

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