Management of the pregnant inflammatory bowel disease patient on antitumour necrosis factor therapy: State of the art and future directions

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Antitumour necrosis factor (anti-TNF) therapy has been a major advance in the treatment of inflammatory bowel disease (IBD) by improving rates of mucosal healing, steroid-free remission, and decreasing rates of hospitalization and surgery. Because IBD affects women in their reproductive years, clinicians have and will continue to be asked in the future about the safety profile of these agents and their potential impact on pregnancy, the developing fetus and newborn. Immunoglobulin G transfer from the mother to fetus begins in the second trimester, with an elevation starting at 22 weeks of gestation and the largest amount transferred in the third trimester. Although research investigating the long-term outcomes of children exposed to anti-TNF therapy in utero is limited, there is no known adverse effect on either pregnancy or newborn outcomes including infectious complications with this class of drugs. The World Congress of Gastroenterology consensus statement on biological therapy for IBD considered infliximab and adalimumab to be low risk and compatible with use during conception and during pregnancy in at least the first two trimesters. Based on a clinical algorithm used at the University of Calgary Pregnancy and IBD clinic (Calgary, Alberta), recommendations have been provided on the management of pregnant patients on anti-TNF therapy; particularly with regard to third-trimester dosing, taking into account disease characteristics of individual patients. When educated about the safety of anti-TNF therapy during pregnancy, patients often choose to continue on therapy during the third trimester.

Key Words: Antitumour necrosis factor therapy; Inflammatory bowel disease; Pregnancy

The impact of antitumour necrosis factor (anti-TNF) therapy in the treatment of inflammatory bowel disease (IBD) has changed our concept of disease remission from that of purely symptomatic remission to endoscopic healing, with a corresponding reduction in hospitalizations and surgeries for IBD. In Canada, the available anti-TNF agents for Crohn disease and ulcerative colitis are infliximab (IFX; Remicade, Janssen, USA), a chimeric immunoglobulin (Ig) G1 monoclonal antibody and adalimumab (ADA; Humira, Abbvie, USA), a recombinant human IgG1 monoclonal antibody; and, for ulcerative colitis, golimumab (Simponi, Janssen, USA), a recombinant human IgG1 monoclonal antibody. With the exception of certolizumab (not available in Canada), all Food and Drug Administration (FDA)-approved anti-TNF agents for IBD are IgG1 antibodies with an Fc portion (IFX, ADA and golimumab).

Because IBD affects women in their reproductive years, clinicians have and will continue to be asked in the future about the safety profile of these agents and their potential impact on the developing fetus and newborn. While experiments involving nonhuman primates suggest that TNF-α is not required for normal development of the immune system (1), there are limited data regarding the long-term impact of these drugs on children beyond the first year of life. Both IFX and ADA are FDA category B drugs, meaning there is no evidence of risk in humans. However, due to concerns of the potential implications of TNF blockade in the fetus' developing immune system, uncertainty from both patients and physicians exist on how to best manage patients undergoing anti-TNF therapy during pregnancy.

According to the World Congress of Gastroenterology on biological therapy for IBD, IFX and ADA are considered to be low risk and compatible with use during conception and during pregnancy in at least the first two trimesters (2). However, the second trimester of pregnancy ends at gestational week 27. With a full-term pregnancy duration spanning approximately 40 weeks, this poses a clinical dilemma for gastroenterologists and patients. Withholding an anti-TNF agent for the entire third trimester equates to a significant drug holiday, and has risks for disease flare and the development of anti-TNF antibodies.

La prise en charge de la patiente enceinte atteinte d’une maladie inflammatoire de l’intestin traitée par un inhibiteur du facteur de nécrose tumoral : mesures de pointe et futures orientations

L’inhibiteur du facteur de nécrose tumoral (anti-TNF) est un progrès important dans le traitement des maladies inflammatoires de l’intestin (MII), car il améliore le taux de guérison des muqueuses et de rémission sans stéroides et réduit le taux d’hospitalisations et d’opérations. Puisque les MII touchent des femmes en âge de procréer, les cliniciens doivent connaître le profil d’innocuité de ce traitement et ses répercussions possibles sur la grossesse, le fœtus et le nouveau-né. Le transfert d’immunoglobuline G de la mère au fœtus s’amorce au deuxième trimestre, l’élévation commençant à 22 semaines de grossesse et le transfert le plus important s’observant au troisième trimestre. Même si les recherches sur les effets à long terme du traitement anti-TNF in utero chez les enfants qui y sont exposés sont limitées, cette catégorie de médicaments ne s’associe à aucun effet indésirable connu sur la grossesse ou le nouveau-né, y compris les complications infectieuses. D’après la déclaration consensuelle du Congrès mondial de gastroentérologie sur le traitement biologique des MII, l’infliximab et l’adalimumab sont peu à risque et peuvent être utilisés pendant la période périconceptionnelle et au moins les deux premiers trimestres de la grossesse. Selon un algorithme clinique utilisé à la clinique de grossesse et de MII de l’université de Calgary, en Alberta, des recommandations ont été formulées sur la prise en charge des patientes enceintes sous traitement anti-TNF, notamment la posologie au troisième trimestre, compte tenu des caractéristiques de la maladie de chaque patiente. Lorsqu’elles sont informées de l’innocuité du traitement anti-TNF pendant la grossesse, les patientes choisissent souvent de le poursuivre au troisième trimestre.
The present review focuses on the latest research investigating transplacental passage of anti-TNF agents, the safety data on anti-TNF therapy during pregnancy, the optimal use of anti-TNF agents during pregnancy and highlight future areas requiring research.

HOW DO IGs CROSS THE PLACENTA IN A NORMAL PREGNANCY?

IgG is the only antibody class that significantly crosses the human placenta and, by doing so, provides short-term passive immunity to the newborn. This crossing is mediated by the neonatal Fc receptor (FcRn) that is expressed on syncytiotrophoblast cells of the placenta (3). Syncytiotrophoblasts on the maternal side of the placenta internalize IgG in endosomes (Figure 1). FcRn is expressed on the internal surface of endosomes. The endosomes then fuse with the fetal side of the syncytiotrophoblast, where the IgG dissociates from the FcRn to the fetal circulation (4). Preferential transport occurs for IgG1, followed by IgG4, then IgG3, with IgG2 having the lowest affinity for binding. IgG transfer from the mother to fetus begins in the second trimester, with an elevation starting at 22 weeks’ gestation, with the largest amount transferred in the third trimester (Figure 2) (4-6). Accordingly, there are significantly lower levels of IgG and corresponding seroprotection to diphtheria, tetanus, pertussis, Haemophilus influenzae type b and Neisseria meningitides serogroup C in preterm compared with full-term infants (7).

PLACENTAL TRANSFER OF ANTI-TNF AGENTS

Placental transfer of IFX was first published as a case report in 2006 (8). An infant born to a mother receiving IFX 10 mg/kg with the last infusion two weeks before delivery was found to have higher than expected levels at six weeks of age. Because IFX was not detected in the breast milk, this case provided the first evidence in humans of transplacental transfer of an anti-TNF agent. The authors of this case report and subsequent reviews and guidelines suggested terminating IFX at gestational week 30 (9,10). Zelinkova et al (11) then tested this guideline by determining the IFX levels in cord blood at delivery and the mothers’ peripheral blood at delivery in four patients. All four patients received IFX between gestational weeks 21 and 30. Of the four infants, three had IFX levels in cord blood that were two- to threefold higher than in the peripheral blood of their mothers (mothers received IFX at gestational weeks 26, 26 and 30). The patient who received IFX at gestational week 21 gave birth to a newborn with no detectable IFX in the cord blood.

Mahadevan et al (12) studied maternal peripheral blood, and newborn cord and peripheral blood of 11 IFX-treated patients and 10 ADA-treated patients. The median time from the last dose of IFX to delivery was 35 days (range two to 91 days). In every case, the cord or infant level of IFX was higher than the mother’s at the time of delivery, and took two to seven months to become undetectable. The median cord drug level was 160% of the maternal drug level (range 87% to 400%). The median time from the last dose of ADA to delivery was 5.5 weeks (range 0.14 to 8 weeks). Again, in every case, the cord or infant level of ADA was higher than the mother’s at the time of delivery, with the median cord drug level 179% of the maternal drug level (range 98% to 293%). Levels in newborns were detectable for at least 11 weeks from birth. There were no significant complications to newborns during the follow-up period in both IFX and ADA groups.

WHAT HAPPENS WHEN PATIENTS DISCONTINUE ANTI-TNF THERAPY DURING PREGNANCY?

In the same study published by Zelinkova et al (13), data regarding discontinuation of anti-TNF therapy during pregnancy demonstrated the risk for disease relapse. In the ADA group, therapy was discontinued at gestational weeks 21 and 26 in 11 patients. Two patients relapsed: one flared at gestational week 30 and required corticosteroids; the second flared at gestational week 36 and underwent an elective Caesarean section at week 37. In the IFX group, of 12 patients with early discontinuation of the therapy, one developed an allergic reaction postpartum on resumption of IFX. In total, this patient had a drug holiday of 22 weeks because of postpartum concerns about mastitis. In Leuven (Belgium), of patients taken off anti-TNF by week 22 of pregnancy, 12.5% of patients flared in the third trimester and 20.6% flared postpartum (14). In the series published by Mahadevan et al (12), 60% of patients flared when ADA was stopped >35 days before delivery.
More importantly, there are no prospective controlled data to dem-
strate that corticosteroid use is safer for maternal and neonatal out-
comes in the third trimester than anti-TNF therapy. Reddy et al (15)
published a case control study demonstrating that pregnant women
with IBD requiring hospitalization for active disease were at significant
risk for preterm delivery compared with pregnant IBD patients with
stable disease (mean 35.0 weeks versus 38.7 weeks; P < 0.05) and were
also at risk for delivering a low birthweight infant (mean 2001 g versus
3018 g; P < 0.05) (15). This highlights the importance of stringent
disease control during pregnancy.

SAFETY OF ANTI-TNF AGENTS DURING
PREGNANCY

Although there is evidence that newborns exposed to anti-TNF ther-
apy during gestation are born with higher levels of IFX and ADA than
the mother, there are no data that these agents are associated with
short-term adverse newborn outcomes. To put risks into perspective, in
the general Canadian population, the rate of congenital anomalies is
6.0%, preterm birth is 7.7% and Caesarean section is 27.1% (16).

The largest prospective registry of 1052 pregnant women with
IBD is the Pregnancy and Neonatal Outcomes in Women with
Inflammatory Bowel Disease (PIANO) registry. In an abstract
presented at Digestive Diseases Week in 2012, 797 patients had
completed their pregnancy with no reported increase in congenital
anomalies by drug exposure (17). Of these patients, 337 were unex-
posed to a biologic or a thiopurine, 265 were thiopurine exposed,
102 were biologic (IFX, ADA or certolizumab) exposed, and 59 exposed
to combination biologic and thiopurine therapy. The proportion of
congenital anomalies overall was 4.6%. There was no increase in preterm birth, intrauterine growth retardation, Caesarean
section or neonatal intensive care unit associated with drug exposure.

Gisbert and Chaparro (18) systematically reviewed data from 21 stud-
ies involving 462 women with IBD exposed to anti-TNF agents during
pregnancy and also concluded that these therapies are low risk in the short
term. The overall proportion of spontaneous abortions (11%) and
congenital anomalies (1.7%) were similar to the control groups. There
was an increase in rate of preterm birth, intrauterine growth retarda-
tion or Caesarean section associated with drug exposure. Nielsen et al
(19) published a similar systematic review, with the inclusion of 58 stud-
ies. Due to the heterogeneity of studies, results could not be meta-
analyzed; however, there were four studies with a control population
that reported nonsignificant ORs or relative risks for spontaneous
abortion, preterm delivery, low birth weight and or congenital anom-
alies in patients exposed to anti-TNF therapy during pregnancy to
those without anti-TNF drug exposure.

The infliximab safety database and the The Crohn’s Therapy,
Resource, Evaluation, and Assessment Tool Registry (TREAT) were
also included in these two recent systematic reviews. The infliximab
safety database is a retrospective registry maintained by the manufac-
turers of IFX and relies on voluntary reporting of pregnancies of
women with rheumatoid arthritis (RA) or Crohn disease (20). There
were 96 pregnancies that resulted in 100 births. Only two major struc-
tural anomalies were reported: one Tetralogy of Fallot and one integ-
nal malrotation with no differences from the observed outcomes to
expected outcomes from the general population. The TREAT registry is
an ongoing, prospective, observational, multicentre, long-term registry
of North American patients with Crohn disease. In the TREAT regis-
try, there were 142 IFX-exposed pregnancies with no differences in the
rate of live births or congenital anomalies compared with IFX versus
non-IFX-treated patients (21). A review of the FDA database of
adverse events with etanercept (not used in IBD), IFX and ADA from
1999 to 2005 found a total of 61 congenital anomalies in 41 children
born to mothers taking anti-TNF agents (22). Fifty-nine percent of
the children had one or more congenital anomalies that were part of the
VACTERL spectrum (vertebral abnormalities, anal atresia, cardiac
defect, tracheoesophageal defects, renal defects, and limb defects).
However, there was no denominator available for the calculation of
incidence, and no child exhibited the full VACTERL syndrome, which
requires a minimum of three of the seven defects to be present.

SAFETY OF ANTI-TNF THERAPY IN LONG-TERM
OUTCOMES OF EXPOSED CHILDREN

Apart from data on congenital anomalies and data from PIANO on
outcomes up to one year, there are little long-term data regarding out-
comes of children exposed to anti-TNF therapy in utero. Borlik et al
(23) published outcomes on a series of 25 children with a median age
of 34 months at the last follow-up (range 14 to 70 months) exposed to
IFX or ADA. The mean gestational age of exposure to the anti-TNF
agent was 26 weeks (range 17 to 37 weeks). There was one case of
psychomotor delay in a boy born as a dizygotic twin and four cases of
serious infections requiring hospitalization. While circulating levels of
anti-TNF drug in the child were not measured, the infections occurred
between 10 and 29 months of age when, according to existing pharma-
okinetic data, the anti-TNF agent would likely have been cleared
from the infant’s circulation. There were no clinical signs of immuno-
deficiency or impaired cellular immunity. Mildly low levels of IgA
and/or IgG were observed in seven of 17 infants. In the absence of a
control group, the authors attributed the findings to transient hypo-
gammaglobulinemia of infancy. In the same study, 15 infants exposed
to IFX received the live Bacille Calmette-Guerin vaccine. Three of
these children experienced local skin reactions. Despite the absence
of systemic adverse effects in this study, there was a previous case report
of disseminated Bacille Calmette-Guerin in an infant exposed to anti-
TNF therapy in utero after receiving the live vaccine (24). Therefore,
we would strongly recommend avoidance of all live vaccines in chil-
dren who have had in utero exposure to anti-TNF therapy until at
least six months of age.

Both the infliximab safety database (20) and the study by Carter et
al (22) included patients with RA. The British Society for Rheumatology
Biologics Register reported on 130 pregnancies to women with RA
exposed to anti-TNF therapy during conception and ce/pregnancy (25).
In the subgroup of patients exposed to anti-TNF monotherapy, the rate
of spontaneous abortion was 25% compared with 10% in the never-
exposed group; however, the cohort was small and results were only
presented descriptively. Reports of anti-TNF exposure in patients with
psoriasis have been limited to case reports/series (26,27).

HOW DO WE MANAGE PATIENTS ON ANTI-TNF
AGENTS DURING PREGNANCY?

At the University of Calgary (Calgary, Alberta), patients are seen
preconception to discuss the benefits and potential risks of continuing
therapy during pregnancy up to and including the third trimester. The
decision to continue or stop a treatment during pregnancy represents a
very difficult decision for gastroenterologists and patients. Given the
known half-lives of IFX (9.5 days) and ADA (10 to 20 days) and the
incremental rise in transplacental transfer of immunoglobulins after
gestational week 22, we aim to minimize anti-TNF exposure in the
final one-half of the third trimester because the results of studies inves-
tigating the long-term outcomes of children exposed to anti-TNF
therapy in utero are lacking. At this time, there are insufficient data to
support complete anti-TNF therapy cessation in the third trimester for
the reasons outlined above, namely increased risk for disease flare.
Therefore, our approach is to minimize both disease flare and neonatal
exposure by modifying the timing of the last dose of anti-TNF therapy,
giving it earlier in the third trimester where possible. This decision
needs to be individualized, taking into consideration the disease char-
acteristics of the patient (Figure 3).

The decision to stop anti-TNF treatment partway through
pregnancy only applies to patients in stable, steroid-free remission
with objective markers to confirm remission

The priority for any patient is induction and maintenance of steroid-
free remission, regardless of pregnancy status. Due to the risk of flare
with cessation of anti-TNF therapy, we also recommend that an
Objective measure of activity should be performed to confirm that the disease is in deep remission such as small bowel ultrasound, flexible sigmoidoscopy or fecal calprotectin.

Patients in steroid-free clinical remission who may be at risk for flare if there is a missed dose should continue therapy

Patients who are at risk for flare if there is a missed dose include individuals who feel clinically well, but are not in deep remission based on imaging (for example, patients at risk of ileal obstruction) or who have elevated biomarker levels such as fecal calprotectin.

Other factors to consider include the current dosing interval. For example, if a patient is on weekly ADA, withholding a dose in early third trimester would equate to eight to 10 missed doses, increasing the risk for flare. Finally, there is evidence that patients with ulcerative colitis are at higher risk for disease flare during pregnancy; therefore, missing multiple doses in this disease phenotype may increase their risk for flare (28).

Patients initiating anti-TNF therapy during pregnancy require special consideration

Patients initiating anti-TNF therapy while pregnant are very different from patients who enter pregnancy already on maintenance therapy. Depending on the disease severity at presentation and response to steroids, patients who are diagnosed with IBD during pregnancy may require initiation of anti-TNF therapy. Even in patients with known IBD, there is still a risk for disease flare during pregnancy (28) that may require initiation of anti-TNF therapy. Induction dosing of anti-TNF therapy depends on the stage of pregnancy (Figure 4). In patients who are at gestational week <22, anti-TNF therapy can be prescribed at standard induction-dose intervals similar to nonpregnant patients. Subsequent maintenance dosing should not be withheld in the third trimester. For patients who require anti-TNF therapy after 22 weeks’ gestation, the decision to initiate anti-TNF will depend on the patient’s disease activity and phenotype (similar to how nonpregnant patients are managed) with the added consideration of time to delivery. For example, in patients who are likely to imminently deliver, anti-TNF therapy can likely be delayed until after pregnancy. We recommend that all patients with a new diagnosis of IBD during pregnancy are comanaged with specialists from the high-risk obstetrics group and internists from the maternal fetal medicine group.

Patients with a well-documented history of stable remission confirmed by objective markers, on anti-TNF therapy, may discontinue therapy earlier during the pregnancy to reduce transplacental transfer of drug to the fetus

In our clinic, patients are informed that transplacental passage of anti-TNF agents begins in early second trimester, with the largest amount transferred in the third trimester. Discontinuing therapy at the start of the third trimester can represent a significant drug holiday for IFX and ADA patients, and often it is the patients themselves who are hesitant to stop the drug this early given concerns of disease flare and its impact on pregnancy outcomes.

Role of therapeutic drug monitoring in pregnancy

Studies investigating anti-TNF levels and antidrug antibody levels during pregnancy are not available at this time. Immunogenicity or the presence of antidrug antibodies are associated with adverse reactions and reduced efficacy of therapy (29,30). Therefore, in our practice, we do not routinely discontinue thiopurines that are used in combination with anti-TNF therapy if the patient was on the thiopurine during preconception. In the case of a patient who wants to stop concomitant thiopurine therapy, we discuss the benefits and risks of monotherapy and combination therapy. Additionally, we discuss the extensive data on the safety of thiopurines in pregnancy (31-33). However, due to its FDA rating of D, despite education of its excellent safety profile during pregnancy, many patients are inclined to stop this class of drugs during pregnancy when used as a concomitant immunomodulator. For patients who are initiating anti-TNF therapy during pregnancy, we tend not to start thiopurines for the first time during pregnancy (as the concomitant immunomodulator) due to the small but possible risk of thiopurine-associated pancreatitis and hepatitis, and side effects such as nausea and malaise.

Methotrexate is a well known teratogen in women and should be stopped a minimum of six months before conception.

Unanswered questions

1. What are the long-term effects on the immune system of children born to mothers on anti-TNF agents? If there are implications for the immune system of children, does this change depending on trimester exposure?

Figure 3) Algorithm for management of patients on maintenance antitumour necrosis factor (anti-TNF) therapy

Figure 4) Algorithm for management of patients who need antitumour necrosis factor (anti-TNF) induction during pregnancy and subsequent maintenance

Both mother and child. Ongoing and open dialogue between physician and patient is fundamental and, when presented with the data, the majority of our patients choose to accept anti-TNF therapy during early third trimester. The majority of our patients on eight-weekly dosing for IFX and bi-weekly dosing of ADA receive their last dose of anti-TNF therapy at gestational week 32 for IFX and gestational week 34 for ADA.
2. Can anti-TNF therapeutic drug monitoring in the first trimester with subsequent modification of dose and dosing interval be used to optimize disease course for the remainder of the pregnancy and postpartum?

3. Can we individualize anti-TNF therapy based on an understanding of an individual’s pharmacokinetics and, therefore, tailor dosing during pregnancy to minimize placental transfer? In other words, change the dose but not stop therapy.

**FUTURE DIRECTIONS**

With the introduction of new therapeutic molecules on the market for the treatment of IB, the uptake of anti-TNF therapy and other biologics will likely continue to increase and, therefore, an increasing number of patients in their reproductive years will be on these agents. In response to the abovementioned clinical and research needs, a Maternofetal Outcomes Research in IB – Canadian Registry (MORE CaRe) has been started with two fundamental goals. The first goal is to optimize the clinical care of pregnant IB patients through education, continuing medical education of physicians, (family physicians, obstetricians and fertility experts, and gastroenterologists), and establishment of clinical care pathways and guidelines that apply to Canadian practitioners. The second goal is to establish a national biorepository with biospecimens from patients through education, continuing medical education of physicians, (family physicians, obstetricians and fertility experts, and gastroenterologists), and establishment of clinical care pathways and guidelines that apply to Canadian practitioners. The second goal is to establish a national biorepository with biospecimens from mother's peripheral blood, breastmilk, cord blood and infant peripheral blood to answer additional questions regarding the long-term safety and optimal use of biologics in pregnancy.

**REFERENCES**


