A Narrative Review on Anti-Tumor Necrosis Factor α Therapies in Inflammatory Bowel Disease During Pregnancy: Immunoglobulin Placental Translocation and its Impact

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ABSTRACT
Introduction: Inflammatory bowel disease activity is associated with adverse pregnancy outcomes. Anti-tumor necrosis factor α therapy is often required to treat flares and to maintain disease remission. However, there are concerns regarding treatment with these agents during pregnancy, as they actively cross the placental barrier.

Material and Methods: Studies regarding anti-tumor necrosis factor α therapy during pregnancy were identified from PubMed from 1958 to January 2018. The reference lists of the selected studies were reviewed to identify complementary publications.

Results and Discussion: Anti-tumor necrosis factor α agents are efficient treatments for moderate-to-severe inflammatory bowel disease and may ensure remission during pregnancy. Although these drugs cross the placenta, they are considered safe for both the mother and the fetus. Furthermore, up-to-date guidelines support therapy continuation during pregnancy aiming for disease control. The same guidelines also consider stopping treatment during the third trimester to limit maternal-fetal drug transfer. However, data shows that this strategy does not completely prevent fetus exposure. In addition, stopping treatment incurs in risk of disease flare and threatens subsequent therapy response. Fetus drug exposure has not showed an association with adverse childhood development. However, as infant drug levels could be detected up to seven months after birth, postponement of live virus vaccination is recommended.

Conclusion: There should be no disagreement among the medical community as to the need to maintain therapy aiming for disease remission during gestation in inflammatory bowel disease. Anti-tumor necrosis factor α agents are safe for both the mother and the fetus.

Keywords: Adalimumab; Infliximab; Inflammatory Bowel Disease; Pregnancy; Tumor Necrosis Factor-alpha

INTRODUCTION
Biological therapies, namely anti-tumor necrosis factor-alpha (anti-TNFα) agents, have become part of the effective treatment armamentarium for moderate-to-severe and difficult-to-treat inflammatory bowel disease (IBD). Fifty percent of patients with IBD are women, many of whom are diagnosed during adolescence and early adulthood, making pregnancy an expected scenario at some point. For pregnant women, there is a recognized increased risk of...
adverse pregnancy outcomes in the setup of active IBD.\textsuperscript{2-6} Therefore, current guidelines recommend that maintenance of disease remission is the most important factor for a successful pregnancy.\textsuperscript{7,8}

Anti-TNFα drugs, such as infliximab and adalimumab, are immunoglobulin (Ig) G antibodies, and can therefore actively cross from the maternal to the fetal blood compartment during pregnancy.\textsuperscript{9,10} Indeed, infliximab and adalimumab concentrations may be up to fourfold higher in infant circulation compared to maternal peripheral blood\textsuperscript{9-14} and can still be measurable up to 7 months after birth.\textsuperscript{15}

Despite maternal-fetal drug transfer, anti-TNFα treatment during gestation has not been shown to result in adverse pregnancy outcomes.\textsuperscript{15} Moreover, studies suggest that TNFα blockade does not appear to affect the development of the fetus either.\textsuperscript{15} However, the long-term effect on the emerging immune system remains unknown. The theoretical influence of anti-TNFα treatment on the fetus is a major concern for parents and clinicians.

It is the clinician’s role to rationally balance this dual concern: IBD relapsing risk threatening pregnancy outcome and requiring maintenance therapy versus infant’s theoretical immune system disruption risk, calling for therapy discontinuation.

Basic epidemiology, interventional trials, and real-world evidence on pregnancy outcomes among patients with IBD who have been exposed to anti-TNFα agents are lacking, making quantitative data scarce. Therefore, we conducted a narrative review, aiming to assess the best evidence on anti-TNFα agent’s safety during pregnancy in patients with IBD.

### MATERIAL AND METHODS

A search of literature was conducted to identify papers regarding anti-TNFα therapy during pregnancy in patients with IBD. The authors identified sources (abstracts and full text articles) from the PubMed database from 1958 to January 2018. Full texts published during 2018, referring to abstracts presented prior to January 2018 were also identified and analyzed. The search was narrowed to articles written in English, Portuguese, and French. MeSH terms were used in the search including: ‘inflammatory bowel diseases’; ‘colitis, ulcerative’; ‘crohn disease’; ‘pregnancy’; ‘pregnancy outcome’; ‘adalimumab’; ‘infliximab’; ‘tumor necrosis factor-alpha’; ‘immunoglobulins’; ‘placenta’; ‘maternal-fetal exchange’. In addition, the reference lists of the identified studies were manually reviewed to identify complementary publications.

Approximately 160 articles were screened in the first round. Studies were included in this review if they met the following criteria: (1) meta-analysis revisions, editorials or expert reviews; (2) observational design (prospective, retrospective, case control and case series); (3) interventional design. Studies that did not report outcomes for an IBD-only and female-only population were excluded. Errata and commentary were also excluded. Insufficient data for extraction was recorded in 6 studies. Data extraction was carried out independently by two investigators (Roseira J, Ramos J) with discrepancies resolved by the senior author (Ramos J).

The results and discussion section in this narrative review were organized in two main subtopics to obtain a more pleaded narration: (1) a physiology segment aiming to explore placental immunoglobulin translocation, and maternal-fetal exchange according to gestational week; (2) a clinical impact segment aiming to analyze the exposure of mothers, fetuses, and newborns to anti-TNFα agents.

### RESULTS AND DISCUSSION

#### 1) Physiology

**Anti-TNFα agents during pregnancy in IBD – explaining immunoglobulin maternal-fetal transfer**

Crohn’s disease (CD) and ulcerative colitis (UC), the main forms of IBD, are chronic and disabling diseases of the digestive tract.\textsuperscript{17} The introduction of biological therapies, in particular anti-TNFα agents, has dramatically changed the natural history of the disease. TNFα agents are primarily used to treat moderate-to-severe IBD in patients with inadequate response to standard medications.\textsuperscript{18} By inhibiting TNFα, these agents can restrict the inflammatory pathway by inhibiting cellular proliferation, migration, adhesion, and cytokine response.\textsuperscript{19}

Currently, four anti-TNFα agents are approved by the United States Food and Drug Administration (USFDA) for the treatment of IBD, namely golimumab, certolizumab pegol, infliximab, and adalimumab (Table 1).

Available information concerning golimumab and certolizumab use during pregnancy is scarce and these agents will only be briefly reviewed here. Golimumab is a fully human IgG1-kappa monoclonal antibody approved in the United States and in European Union (EU) for moderate-to-severe UC.\textsuperscript{20} The potential negative effect of golimumab during pregnancy has not been studied in humans yet. However, animal studies (pregnant cynomolgus monkeys) showed no evidence of harm to the fetus.\textsuperscript{21} Certolizumab pegol is a recombinant antigen-binding fragment (Fab’) antibody against TNFα, which is conjugated with polyethylene glycol.

<table>
<thead>
<tr>
<th>Name</th>
<th>Structure</th>
<th>Dosage form</th>
<th>Half-life</th>
<th>Approval</th>
</tr>
</thead>
<tbody>
<tr>
<td>Infliximab (Remicade\textsuperscript{8})</td>
<td>IgG1</td>
<td>intravenous</td>
<td>9.5 days</td>
<td>1998</td>
</tr>
<tr>
<td>Adalimumab (Humira\textsuperscript{8})</td>
<td>IgG1</td>
<td>subcutaneous</td>
<td>10 - 20 days</td>
<td>2005</td>
</tr>
<tr>
<td>Golimumab (Simponi\textsuperscript{8})</td>
<td>IgG1</td>
<td>subcutaneous</td>
<td>7 - 20 days</td>
<td>2009</td>
</tr>
<tr>
<td>Certolizumab pegol (Cimzia\textsuperscript{8})</td>
<td>Fab’</td>
<td>subcutaneous</td>
<td>14 days</td>
<td>2008</td>
</tr>
</tbody>
</table>

\textsuperscript{Fab’} = recombinant antigen-binding fragment antibody
The drug is approved in the United States and in Switzerland for the treatment of CD in adults but is not approved for IBD in the EU. Clinical experience with certolizumab pegol during pregnancy is sparse and there is little available information concerning fetal serum levels. Placental transport of fab’ fragments has been demonstrated in animal studies (pregnant rats). However, a recent pharmacokinetic study looking at infants born to mothers exposed to certolizumab pegol (last dose at 35 days or less prior to delivery), found that 93% had no quantifiable drug levels at birth, and one newborn had an insignificant level of 0.042 µg/mL. As such, certolizumab data during pregnancy needs further clarification. Infliximab and adalimumab were the first anti-TNFα agents to be approved for IBD and they are the best studied agents so far. Both drugs are widely used for UC and CD in adult patients who have not responded to a full course of corticosteroids or immunosuppressant therapy. Infliximab is an engineered chimeric IgG1 monoclonal antibody, and adalimumab is a fully human IgG1 monoclonal antibody. These drugs both represent a clear advance in the treatment of IBD, offering the chance for clinical remission and mucosal healing in severe disease. However, once inflammation is controlled, the question of when to consider stopping anti-TNFα treatment frequently occurs. Reasons for stopping treatment most often include patients’ concerns about adverse events, costs, or particular situations such as pregnancy.

However, anti-TNFα treatment is indicated for moderate-to-severe disease to prevent disease flares. Continued prevention of flares is also crucial during pregnancy.

Several studies have revealed that women with active IBD at conception and during pregnancy have a higher risk of miscarriage, preterm delivery, and fetal growth restriction compared with women in disease remission. Anti-TNFα agents, such as infliximab and adalimumab are efficient for moderate-to-severe IBD and may ensure remission during pregnancy.

Maternal-fetal interface development

For decades it was presumed that the human placenta served as a barrier, protecting the fetus from xenobiotics that mothers could be exposed to. But as appropriate placental perfusion studies and placental villi cultures developed, it has become apparent that the placenta allows maternal-fetal drug transfer.

The human placental barrier consists of a layer of multinucleated cells, known as syncytiotrophoblast. The syncytiotrophoblast layer is already formed 4 to 5 days after conception, when the blastocyst is implanted. Within the syncytiotrophoblast layer, lacunae emerge from the decidua where maternal arterial and venous blood circulates. These lacunae, or blank spaces, are filled with maternal blood from the endometrial vessels. Among the lacunae, fetal chorionic tissue perfused by fetal vessels, develops. Together with the maternal blood lacunae, the fetal chorionic tissue forms a tree-like structure called villi, where the maternal-fetal interface is formed.

Placental xenobiotic transfer

Most drugs cross the placenta by simple diffusion. However, other mechanisms of placental transfer may be involved, such as plasma membrane carriers, biotransformation enzymes, and export pumps. Factors that affect the drug transport include molecular weight, degree of ionization, lipid solubility, protein binding capacity, and fetal and placental blood flow. Nonionized, nonprotein-binding, lipid soluble drugs, with molecular weight below 600 Da, freely cross the placental barrier. On the other hand, high molecular weight drugs, such as insulin, are not transported in significant amounts. There are a few exceptions though, such as IgG, which can cross the placental barrier despite a large molecular mass of approximately 160 kDa.

Placental immunoglobulin transport

Fetal immunity is acquired during pregnancy by transfer of IgG antibodies from the maternal to the fetal circulation. Of the five major classes of antibodies, only IgG is transferred across the placenta. Analysis of cord sera has shown that all IgG subclasses are transmitted to the fetus but a preferential transport of IgG1 was found.

Data shows that maternal IgG concentrations increase in fetal blood from early in the second trimester through term, with most antibodies being acquired during the third trimester. As early as 1967, Hobbs et al., found an exponential relationship between total IgG and gestational age in preterm infants. Subsequent studies tried to address maternal-fetal IgG transfer per gestational trimester. Van den Berg et al., demonstrated that in the first trimester, very little IgG is transported to the fetus. In the second trimester, the fetal IgG rises from approximately 10% of the maternal concentration at weeks 17 - 22 of gestation to 50% at gestational weeks 28 - 32. In the third trimester, between gestational weeks 29 - 41, fetal IgG concentration is two times higher than between gestational weeks 17 - 28. By gestational weeks 37 - 40, infant cord blood concentration of maternal IgG often exceeds that of maternal serum (100% of maternal concentration) by the delivery time point in full-term healthy pregnancies. Similarly, other authors have demonstrated that the greatest rate of antibody transfer to the fetus is after gestational week 34. There are no reports showing that IgG is transferred back to the mother’s circulation once it has reached the fetus.

To be transferred from the maternal to the fetal blood compartment, IgG must overcome several anatomical barriers. Maternal IgG must cross the syncytiotrophoblast and cytotrophoblast cell layers and be transferred across the villous stroma to ultimately reach the lumen of the fetal endothelial vessels (Fig. 1). So far, the mechanism of IgG transplacental transfer across the distinct placental anatomical barriers is not completely elucidated. Early studies have demonstrated that the neonatal Fc receptor (FcRn) expressed on syncytiotrophoblast cells is a key contributor to IgG transplacental transfer. FcRn at the surface of the syncytiotrophoblast binds the Fc portion of IgG at acidic pH environment. It is believed that maternal IgG in the...
intervillous space undergoes fluid-phase endocytosis into acidic endosomes that protect the immunoglobulin from proteolysis. Thereafter, the endosome is transported to the basal plasma membrane, where intact IgG is released into the fetal circulation, inside the villous tree.51

Placental transfer of anti-TNFα IgG such as infliximab and adalimumab follow the same pathway and timing, as FcRn is not able to discriminate beneficial from potentially harmful IgG.52

2) Clinical Impact

Exposure to infliximab and adalimumab – demystifying the risk for the mother, the fetus, and the newborn

Only a residual amount of IgG1 antibodies, including infliximab and adalimumab, cross the placental barrier during the first trimester. Therefore, infliximab and adalimumab do not have a teratogenic effect.7,45 However, as already stated, transfer of these agents across the placental barrier becomes significant in the second and third trimester,9,10,42,45,47 which still raises concerns among parents, obstetricians and the pediatric community.

Although anti-TNFα agents cross the placental barrier, there must be caution when limiting these efficient therapeutic options based on anxieties that are not evidence-based. For example: if patients flare during pregnancy because maintenance therapy with anti-TNFα was discontinued, they will have to undergo treatment with corticosteroids to control active disease. Corticosteroids are generally believed to be safe during pregnancy. But this may be true only at doses up to 15 mg per day,53 which is an insufficient dose to induce remission in active moderate-to-severe IBD. Higher doses increase the risk of infection and premature delivery.54 Also, orofacial malformations are described in infants born to mothers exposed to corticosteroids in the first trimester.55 Indirectly, the risk of maternal complications such as hypertension, diabetes, and preeclampsia are also increased,56,57 which can be associated with unfavorable pregnancy outcomes. Based on these studies, it seems daring to say that corticosteroids are safer than infliximab or adalimumab during pregnancy. In fact, it seems to be the other way around.

It is well established that anti-TNFα agents themselves do not increase the risk of adverse pregnancy outcomes.16,58-60 Narula et al61 published the first meta-analysis

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**Figure 1 – Maternal-fetal interface**


reporting on the safety of infliximab, adalimumab and cer
tolizumab treatment during pregnancy. Later, Shihab et al.22
issued a second meta-analyses that, again, found no in
creased risk of adverse pregnancy outcomes for patients
on these anti-TNFα agents compared with matched con
trols. Optimizing disease control through anti-TNFα therapy
during pregnancy is in the best interest of both mother and
baby. Indeed, up-to-date practice guidelines recommend
ongoing therapy to maintain disease remission.7,8

Maternal-fetal transport of IgG starts at the beginning of
the second trimester, and is maximal during the third trimes
ter, around gestational week 37 to 41.45 Studies addressing
drug levels in the cord serum and blood of the newborn at the
time of birth found that concentrations of infliximab and adali
mumab were higher in infants than in the mothers – 160%
and 153% of maternal concentrations respectively. Further-
more, the drugs could be detected for as long as 6 months
after birth.63 Julsgaard et al.64 further investigated infliximab
and adalimumab washout timings and showed that the mean
time for drug disappearance in infants was 4 months for adali
mumab and 7.3 months for infliximab, and that no drug could
be detected in children after 12 months of age.

There is no known safe level of infliximab or adalimumab
in a newborn child. The worry is that exposure to these
drugs may disrupt the babies’ immune system maturation.
Also, the high infant drug levels raise concerns regarding
infant infection susceptibility. This speculative risk has led
to recommendations to stop treatment to limit the newborn’s
exposure to anti-TNFα and avoid live virus vaccines for the
first 6 - 9 months in children who were exposed to anti-TNFα
treatment during pregnancy.7,8 To limit the fetus exposure to
anti-TNFα treatment, the therapy can be stopped around
gestational week 24 - 26 or as early as possible in the third
trimester7,8 as infant drug levels negatively correlate with the
timing of the last dose during pregnancy.64 However, Ma
hadevan et al.65 published data suggesting that interrupting
anti-TNFα therapies during the third trimester, namely inflix
imab and adalimumab, does not completely prevent placen
tal drug transfer and high infant drug levels at birth. The rec
ommendation to stop treatment with anti-TNFα agents only
applies to very specific cases, as the benefit of maintaining
remission by treatment continuation exceeds the risks of fe
tal exposure. However, even for the specific cases, disease
flares during pregnancy and early post-partum after anti-
TNFα discontinuation have been reported.60,66 Furthermore,
the consequences of treatment interruption may lead to lack
of response later.66

For newborns exposed to anti-TNFα agents, the theo
retical infection risk and the recommended vaccination pol
icy has been extensively studied so far. In 2010, a healthy
newborn from a mother who received infliximab throughout
the pregnancy died unexpectedly after receiving the bacillus
Calmette-Guérin (BCG) vaccine at 3 months of age.67 Sub
sequently, minor reports of skin infections and neutropenia
in neonates that had been exposed to infliximab followed.68
No cases like these were ever reported again. Currently,
there is no data that meets the theoretical risk for neonatal
derangement of normal immunological function. In fact,
follow-up of a series of infants born to mothers exposed to
infliximab and adalimumab ensured healthy infants and
demonstrated normal response to haemophilus influenzae
and tetanus vaccines, along with regular levels of IgA and
IgG.1,19-70 This data is consistent with the results from the
PIANO registry. In this multicenter prospective study, the
authors found that infant infections during the first year of
life were not related to anti-TNFα exposure.72 Preliminary
data published earlier, reported an increased risk of infec
tion for newborns exposed to a combination of tiopurines
and anti-TNFα, but not for anti-TNFα alone.73 Finally, two
meta-analysis found that there is no data that demonstrates
a risk of increased infection or neonate immune system dis
order due to anti-TNFα exposure.61,62

Current guidelines recommend avoiding live vaccines,
such as BCG and rotavirus, during the first 6 - 9 months
for infants exposed to anti-TNFα treatment in utero. Other
vaccination strategies follow the recommendations from
national guidelines, as the infants can adequately respond
to non-live vaccines.71 However, according to the author’s
professional experience, live vaccines may be inadvertently
administered to infants before they reach 9 months of age.
To avoid this, it is the author’s opinion that parents should
be handed a medical leaflet informing that live vaccines
should be postponed in newborns exposed to anti-TNFα
during pregnancy. This would easily make parents, physi
icians, and public health authorities aware of this recom
mendation.

Novel findings have demonstrated that anti-TNFα phar
macokinetics may be altered during pregnancy, and cur
rent guidelines do not address how to handle this.64,74, 75
Julsgaard et al.64 found that infliximab half-life was longer
than adalimumab in exposed infants. In addition, Seow et
al.74 reported that maternal levels of infliximab increased
during pregnancy even when keeping the non-pregnant
weight adjustment, while adalimumab levels remained sta
ble. In line with this, Seow et al.74 showed that there is no
need to adjust anti-TNFα dosages in response to pregnan
cy weight gain. Additionally, it is suggested that targeting
the lower end of the therapeutic level range by therapeutic
drug monitoring during pregnancy could possibly control
high therapeutic infliximab levels and limit placental drug
transfer. Recently, Kanis et al.75 stated that adalimumab may
be continued for a longer period during pregnancy, because
transfer to the placenta is certainly lower than for infliximab.

In summary, there is still no evidence of a definitive ad
vantage of one agent over the other, and it is too early to
provide recommendations on the choice of anti-TNFα agent
based on these reports alone.

Future studies should determine ways to ensure therapeu
tic levels for the mother and limited exposure for the
fetus. Prospective data from the Pregnancy IBD and Ne
onatal Outcomes study (available in abstract form) on all
medications used for IBD is also awaited. In the meantime,
meta-analyses and reviews may provide reassurance to
expectant parents and may guide clinician decisions.
CONCLUSION

Anti-TNFα agents are efficient treatments for patients with moderate-to-severe IBD requiring lifelong maintenance therapy to avoid flares and a disabling disease course. Concerning pregnancy in IBD patients treated with anti-TNFα agents, it is widely accepted that disease activity is the best predictor of pregnancy outcomes, and there should be little disagreement as to the need to maintain therapy aiming to control the disease during gestation. Anti-TNFα agents cross the placenta and are found in high levels in the newborn at birth. This can be distressing for parents and medical doctors. Therefore, physicians handling these patients should be aware of the evidence regarding the safety of anti-TNFα agents during pregnancy for both mothers and fetus. In this review, we have made a critical revision of the most relevant data focusing on anti-TNFα therapy during pregnancy in IBD and demystified the risk of adverse pregnancy outcomes, teratogenicity, neonatal infections susceptibility, and newborn immune system disruption.

REFERENCES


