

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



## Revisão Narrativa sobre a Terapêutica com Agentes Anti-Tumor Necrosis Factor $\alpha$ na Doença Inflamatória Intestinal Durante a Gravidez: Translocação Placentária de Imunoglobulinas e seu Impacto

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### ABSTRACT

**Introduction:** Inflammatory bowel disease activity is associated with adverse pregnancy outcomes. Anti-tumor necrosis factor  $\alpha$  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  $\alpha$  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  $\alpha$  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  $\alpha$  agents are safe for both the mother and the fetus.

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

### RESUMO

**Introdução:** O melhor preditor de complicações durante a gravidez, na doença inflamatória intestinal, é a atividade da doença. A terapêutica com agentes *anti-tumor necrosis factor  $\alpha$*  atravessa a barreira placentária o que levanta questões relativamente à sua segurança durante a gravidez.

**Material e Métodos:** Revisão bibliográfica suportada a partir de artigos indexados na PubMed (1958 a 01/2018) sobre a terapêutica *anti-tumor necrosis factor  $\alpha$*  durante a gravidez na doença inflamatória intestinal.

**Resultados e Discussão:** Os agentes *anti-tumor necrosis factor  $\alpha$*  são eficazes na doença inflamatória intestinal e podem garantir a remissão clínica durante a gravidez. Estes fármacos atravessam a barreira placentária, mas são seguros para a mãe e feto. Neste sentido, as orientações atuais defendem a manutenção terapêutica durante a gravidez para assegurar a remissão clínica. Paralelamente, as mesmas orientações consideram a suspensão terapêutica durante o terceiro trimestre para limitar a exposição fetal ao fármaco. No entanto, esta estratégia não só não previne totalmente a exposição fetal, como aumenta o risco de agudização da doença e da perda de resposta à terapêutica após o seu reinício. Esta exposição fetal não está associada a alterações do desenvolvimento in utero ou neonatal. Ainda assim, uma vez que é possível dosear fármaco no recém-nascido até aos sete meses de vida, recomenda-se adiar a administração de vacinas vivas em recém-nascidos expostos.

**Conclusão:** Não deve haver discordância na comunidade médica quanto à necessidade de garantir a remissão da doença inflamatória intestinal durante a gestação. Os agentes *anti-tumor necrosis factor  $\alpha$*  devem ser vistos como opções terapêuticas seguras para mãe e feto durante a gravidez.

**Palavras-chave:** Adalimumab; Doença Inflamatória Intestinal; Fator de Necrose Tumoral alfa; Gravidez; Infliximab

### INTRODUCTION

Biological therapies, namely anti-tumor necrosis factor-alpha (anti-TNF $\alpha$ ) 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,<sup>1</sup> making pregnancy an expected scenario at some point. For pregnant women, there is a recognized increased risk of

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adverse pregnancy outcomes in the setup of active IBD.<sup>2-6</sup> Therefore, current guidelines recommend that maintenance of disease remission is the most important factor for a successful pregnancy.<sup>7,8</sup>

Anti-TNF $\alpha$  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.<sup>9,10</sup> Indeed, infliximab and adalimumab concentrations may be up to fourfold higher in infant circulation compared to maternal peripheral blood<sup>9-14</sup> and can still be measurable up to 7 months after birth.<sup>15</sup>

Despite maternal-fetal drug transfer, anti-TNF $\alpha$  treatment during gestation has not been shown to result in adverse pregnancy outcomes.<sup>7,8</sup> Moreover, studies suggest that TNF $\alpha$  blockade does not appear to affect the development of the fetus either.<sup>16</sup> However, the long-term effect on the emerging immune system remains unknown. The theoretical influence of anti-TNF $\alpha$  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-TNF $\alpha$  agents are lacking, making quantitative data scarce. Therefore, we conducted a narrative review, aiming to assess the best evidence on anti-TNF $\alpha$  agent's safety during pregnancy in patients with IBD.

## MATERIAL AND METHODS

A search of literature was conducted to identify papers regarding anti-TNF $\alpha$  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-TNF $\alpha$  agents.

## RESULTS AND DISCUSSION

### 1) Physiology

#### Anti-TNF $\alpha$ 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.<sup>17</sup> The introduction of biological therapies, in particular anti-TNF $\alpha$  agents, has dramatically changed the natural history of the disease. TNF $\alpha$  agents are primarily used to treat moderate-to-severe IBD in patients with inadequate response to standard medications.<sup>18</sup> By inhibiting TNF $\alpha$ , these agents can restrict the inflammatory pathway by inhibiting cellular proliferation, migration, adhesion, and cytokine response.<sup>19</sup>

Currently, four anti-TNF $\alpha$  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.<sup>20</sup> 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.<sup>21</sup> Certolizumab pegol is a recombinant antigen-binding fragment (fab') antibody against TNF $\alpha$ , which is conjugated with polyethylene glycol.

Table 1 - FDA-approved anti-TNF $\alpha$  agents for IBD

Name	Structure	Dosage form	Half-life	Approval
Infliximab (Remicade®)	IgG1	intravenous	9.5 days	1998
Adalimumab (Humira®)	IgG1	subcutaneous	10 - 20 days	2005
Golimumab (Simponi®)	IgG1	subcutaneous	7 - 20 days	2009
Certolizumab pegol (Cimzia®)	Fab**	subcutaneous	14 days	2008

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.<sup>22</sup> 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).<sup>23</sup> 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  $\mu\text{g/mL}$ .<sup>24</sup> As such, certolizumab data during pregnancy needs further clarification. Infliximab and adalimumab were the first anti-TNF $\alpha$  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.<sup>25,26</sup> 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.<sup>27</sup> However, once inflammation is controlled, the question of when to consider stopping anti-TNF $\alpha$  treatment frequently occurs. Reasons for stopping treatment most often include patients' concerns about adverse events, costs, or particular situations such as pregnancy.<sup>28</sup>

However, anti-TNF $\alpha$  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.<sup>29-36</sup> Anti-TNF $\alpha$  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.<sup>37</sup> But as appropriate placental perfusion studies and placental villi cultures developed, it has become apparent that the placenta allows maternal-fetal drug transfer.<sup>38</sup>

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 mother 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.<sup>39</sup>

### 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.<sup>40</sup>

### Placental immunoglobulin transport

Fetal immunity is acquired during pregnancy by transfer of IgG antibodies from the maternal to the fetal circulation.<sup>41</sup> 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.<sup>41</sup>

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.<sup>42</sup> As early as 1967, Hobbs *et al*,<sup>43</sup> 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*<sup>44</sup> 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.<sup>45</sup> In the third trimester, between gestational weeks 29 - 41, fetal IgG concentration is two times higher than between gestational weeks 17 - 28.<sup>42</sup> By gestational weeks 37 - 40, infant cord blood concentration of maternal IgG often exceeds that of maternal serum (130% of maternal concentration) by the delivery time point in full-term healthy pregnancies.<sup>43,45,46</sup> Similarly, other authors have demonstrated that the greatest rate of antibody transfer to the fetus is after gestational week 34.<sup>47</sup> There are no reports showing that IgG is transferred back to the mother's circulation once it has reached the fetus.<sup>48</sup>

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.<sup>49</sup> FcRn at the surface of the syncytiotrophoblast binds the Fc portion of IgG at acidic pH environment.<sup>50</sup> It is believed that maternal IgG in the

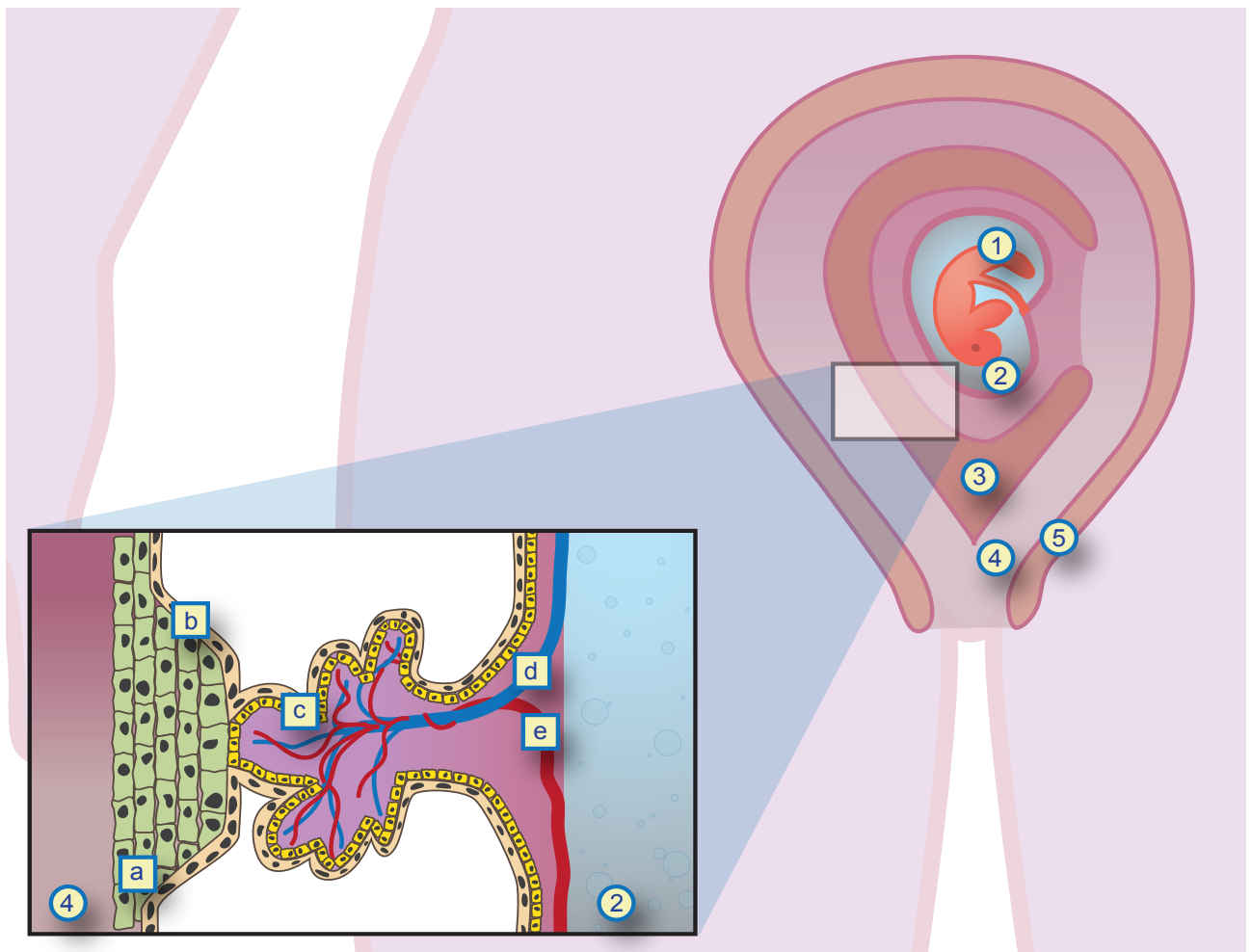


Figure 1 – Maternal-fetal interface

1: embryo; 2: amniotic cavity; 3: uterine cavity; 4: endometrium; 5: myometrium; a: cytotrophoblast; b: syncytiotrophoblast; c: villous trees; d: fetal vein; e: fetal artery. Original sketch by Roseira J, adapted from Huppertz, *et al* description, remade in vector format by Acta Med Port graphic department.

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.<sup>51</sup>

Placental transfer of anti-TNF $\alpha$  IgG such as infliximab and adalimumab follow the same pathway and timing, as FcRn is not able to discriminate beneficial from potentially harmful IgG.<sup>52</sup>

## 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.<sup>7,45</sup> However, as already stated, transfer of these agents across the placental barrier becomes significant in the second and third trimester,<sup>9,10,42,45,47</sup> which still raises concerns among parents, obstetricians and the pediatric community.

Although anti-TNF $\alpha$  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-TNF $\alpha$  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,<sup>53</sup> which is an insufficient dose to induce remission in active moderate-to-severe IBD. Higher doses increase the risk of infection and premature delivery.<sup>54</sup> Also, orofacial malformations are described in infants born to mothers exposed to corticosteroids in the first trimester.<sup>55</sup> Indirectly, the risk of maternal complications such as hypertension, diabetes, and preeclampsia are also increased,<sup>56,57</sup> 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-TNF $\alpha$  agents themselves do not increase the risk of adverse pregnancy outcomes.<sup>16,58-60</sup> Narula *et al*<sup>61</sup> published the first meta-analysis

reporting on the safety of infliximab, adalimumab and certolizumab treatment during pregnancy. Later, Shihab *et al*<sup>62</sup> issued a second meta-analysis that, again, found no increased risk of adverse pregnancy outcomes for patients on these anti-TNF $\alpha$  agents compared with matched controls. Optimizing disease control through anti-TNF $\alpha$  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.<sup>7,8</sup>

Maternal-fetal transport of IgG starts at the beginning of the second trimester, and is maximal during the third trimester, around gestational week 37 to 41.<sup>45</sup> Studies addressing drug levels in the cord serum and blood of the newborn at the time of birth found that concentrations of infliximab and adalimumab were higher in infants than in the mothers – 160% and 153% of maternal concentrations respectively. Furthermore, the drugs could be detected for as long as 6 months after birth.<sup>63</sup> Julsgaard *et al*<sup>64</sup> further investigated infliximab and adalimumab washout timings and showed that the mean time for drug disappearance in infants was 4 months for adalimumab 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-TNF $\alpha$  and avoid live virus vaccines for the first 6 - 9 months in children who were exposed to anti-TNF $\alpha$  treatment during pregnancy.<sup>7,8</sup> To limit the fetus exposure to anti-TNF $\alpha$  treatment, the therapy can be stopped around gestational week 24 - 26 or as early as possible in the third trimester<sup>7,8</sup> as infant drug levels negatively correlate with the timing of the last dose during pregnancy.<sup>64</sup> However, Mahadevan *et al*<sup>63</sup> published data suggesting that interrupting anti-TNF $\alpha$  therapies during the third trimester, namely infliximab and adalimumab, does not completely prevent placental drug transfer and high infant drug levels at birth. The recommendation to stop treatment with anti-TNF $\alpha$  agents only applies to very specific cases, as the benefit of maintaining remission by treatment continuation exceeds the risks of fetal exposure. However, even for the specific cases, disease flares during pregnancy and early post-partum after anti-TNF $\alpha$  discontinuation have been reported.<sup>60,65</sup> Furthermore, the consequences of treatment interruption may lead to lack of response later.<sup>66</sup>

For newborns exposed to anti-TNF $\alpha$  agents, the theoretical infection risk and the recommended vaccination policy 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.<sup>67</sup> Subsequently, minor reports of skin infections and neutropenia in neonates that had been exposed to infliximab followed.<sup>68</sup> No cases like these were ever reported again. Currently, there is no data that meets the theoretical risk for neona-

tal 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.<sup>11,69-71</sup> 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-TNF $\alpha$  exposure.<sup>72</sup> Preliminary data published earlier, reported an increased risk of infection for newborns exposed to a combination of thiopurines and anti-TNF $\alpha$ , but not for anti-TNF $\alpha$  alone.<sup>73</sup> Finally, two meta-analysis found that there is no data that demonstrates a risk of increased infection or neonate immune system disorder due to anti-TNF $\alpha$  exposure.<sup>61,62</sup>

Current guidelines recommend avoiding live vaccines, such as BCG and rotavirus, during the first 6 - 9 months for infants exposed to anti-TNF $\alpha$  treatment in utero. Other vaccination strategies follow the recommendations from national guidelines, as the infants can adequately respond to non-live vaccines.<sup>11</sup> 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-TNF $\alpha$  during pregnancy. This would easily make parents, physicians, and public health authorities aware of this recommendation.

Novel findings have demonstrated that anti-TNF $\alpha$  pharmacokinetics may be altered during pregnancy, and current guidelines do not address how to handle this.<sup>64,74, 75</sup> Julsgaard *et al*<sup>64</sup> found that infliximab half-life was longer than adalimumab in exposed infants. In addition, Seow *et al*<sup>74</sup> reported that maternal levels of infliximab increased during pregnancy even when keeping the non-pregnant weight adjustment, while adalimumab levels remained stable. In line with this, Seow *et al*<sup>74</sup> showed that there is no need to adjust anti-TNF $\alpha$  dosages in response to pregnancy 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*<sup>75</sup> 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 advantage of one agent over the other, and it is too early to provide recommendations on the choice of anti-TNF $\alpha$  agent based on these reports alone.

Future studies should determine ways to ensure therapeutic levels for the mother and limited exposure for the fetus. Prospective data from the Pregnancy IBD and Neonatal 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-TNF $\alpha$  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-TNF $\alpha$  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-TNF $\alpha$  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-TNF $\alpha$  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-TNF $\alpha$  therapy during pregnancy in IBD and demystified the risk of adverse pregnancy outcomes, teratogenicity, neonatal infections susceptibility, and newborn immune system disruption.

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## PROTECTION OF HUMANS AND ANIMALS

The authors declare that the procedures were followed according to the regulations established by the Clinical Research and Ethics Committee and to the Helsinki Declaration of the World Medical Association.

## DATA CONFIDENTIALITY

The authors declare having followed the protocols in use at their working center regarding patients' data publication.

## CONFLICTS OF INTEREST

All authors report no conflict of interest.

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