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Pharmacokinetics of Monoclonal Antibodies Used for Inflammatory Bowel Diseases in Pregnant Women

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Abstract

Inflammatory bowel disease (IBD) is a condition of chronic immune response and inflammation of the gastrointestinal tract. Most women with IBD are affected during their reproductive years, and untreated IBD can have detrimental maternal and fetal outcomes. In recent years, many biological therapies including anti-TNF agents (infliximab, adalimumab, and certolizumab) have been developed for the treatment of IBD. An increasing number of IBD patients are treated with these agents during pregnancy. Sporadic reports suggest an absence of negative pregnancy outcomes related to use of anti-TNF agents in women with IBD. However, it is unclear if the physiological changes occurring in pregnancy alter dose requirements for optimal maternal disease management and minimal fetal exposure to therapeutic antibodies. Based on current understanding of the pharmacokinetic profiles for anti-TNF agents in nonpregnant subjects, it appears very likely that physiological changes accompanying pregnancy can alter pharmacokinetics of anti-TNF agents. This review focuses on how such physiological changes may impact disposition of anti-TNF agents during pregnancy. Further improvement in pregnancy outcomes may be achieved in women with IBD by better understanding of pregnancy-mediated changes in the pharmacokinetics of anti-TNF agents.

Keywords Inflammatory bowel disease; Pregnancy; Monoclonal Antibodies

Abbreviations

ADCC: Antibody-Dependent Cellular Cytotoxicity; ADA: Antidrug Antibody, CDC: Complement-Dependent Cytotoxicity; CDR: Complementarity-Determining Region, CD: Crohn's Disease; ECCO: European Crohn's and Colitis Organization; IBD: Inflammatory Bowel Disease; mAb: Monoclonal Antibody; FcRn: Neonatal Fc Receptor, PEG: Polyethylene Glycol; RES: Reticulo-endothelial System; TNF: Tumor Necrosis Factor; UC: Ulcerative Colitis

Introduction

Inflammatory bowel disease (IBD) is a condition of chronic immune response and inflammation of the gastrointestinal tract. IBD is composed of Crohn's disease (CD) and ulcerative colitis (UC). Crohn's disease affects all layers of the intestinal wall, whereas UC affects only the intestinal mucosa. Inflammatory bowel disease can be painful and debilitating, and is estimated to affect approximately 1.4 million people in the United States, with about 30,000 new cases reported each year [1]. The peak age of onset is 15 to 30 years old, therefore the majority of women with IBD will be affected during their childbearing years [1].

Use of Monoclonal Antibodies for IBD during pregnancy

Pregnancies in women with IBD are typically uncomplicated if the patient is in remission or has only minor disease activity at the time of conception [2]. However, 20–30% of the women with quiescent disease at the time of conception will still suffer from relapse during their gestational period [3]. Furthermore, if the conception occurs during active disease, the prognoses of disease and pregnancy outcomes are less favorable [4]. IBD flares during pregnancy carry a high risk of adverse birth outcomes, including prematurity, low birth-weight, and congenital abnormalities [5,6]. Since the most important factor in the success of a pregnancy in women with IBD is considered to be the state of disease activity [7], stopping effective medications for IBD increases the risk of flares and deleterious neonatal outcomes. Thus, it is recommended that medical treatment for IBD (excluding methotrexate) should generally continue during pregnancy because the benefits outweigh the risk of medication-related adverse effects [8].

The goals of IBD treatment are to reduce the inflammation and maintain disease remission. Drug therapy is the mainstay in IBD treatment. The pharmacologic treatment options for IBDs are similar for both UC and CD [9,10], and include anti-inflammatory drugs (e.g., sulfasalazine, 5-aminosalicylic acid, and corticosteroids), immunosuppressants (e.g., azathioprine, 6-mercaptopurine, and methotrexate), and biologic agents. According to European Crohn's and Colitis Organization (ECCO) guidelines, therapy with biologic agents should be considered as an alternative for patients with objective evidence of active disease who have previously been corticosteroid-refractory, -dependent, or–intolerant [8]. In nonpregnant patients who relapse while on initial therapy, changing their maintenance therapy to methotrexate or a monoclonal antibody (mAb) should be considered. ECCO guidelines currently recommend 5-aminosalicylates, sulfasalazine, corticosteroids, azathioprine and 6-mercaptourine during pregnancy, and place the biologics under the "probably safe" category for IBD in pregnant women [11,12].

Accordingly, the use of mAb during pregnancy has become more prevalent over the past decade [13].

Moderate to severe IBD in nonpregnant subjects can be effectively managed with mAbs, specifically the anti-tumor necrosis factor (anti-TNF) α agents infliximab, adalimumab, certolizumab, golimumab, and the selective adhesion-molecule inhibitor natalizumab (Table 1).

Drug Name	Target	Source	Route of administration	FDA-approved indication	FDA pregnancy category	Bioavailability	Elimination half-life (days)	Volume of distribution	Dosage for IBD
Adalimumab [14]	TNFα	Human[a]	SC	IBD, RA[d], psoriasis, ankylosing spondylitis	B	64%	14	4.7-6 L	Day 1: 4x40 mg injections in one day or 2x40 mg injections per day for two consecutive days Day 15: 80 mg Day 29: a maintenance dose of 40 mg every other week.
Certolizumab pegol [15]	TNFα	Humanized[b]	SC	IBD	B	76-88%	14	6-8 L	400 mg at 0, 2, and 4 weeks. If response occurs, follow with 400 mg every four weeks
Golimumab [16]	TNFα	Human[a]	SC	UC, RA, psoriatic arthritis, ankylosing spondylitis	B	53%	14	58-126 ml/kg	200 mg at week 0, followed by 100 mg at week 2, then 100 mg every four weeks
Infliximab [17]	TNFα	Chimeric[c]	IV	IBD, RA, psoriasis, ankylosing spondylitis	B	-	7-12	3-6 L	5 mg/kg at 0, 2, and 6 weeks, then every 8 weeks
Natalizumab [18]	α4-integrin	Humanized[b]	IV	CD, multiple sclerosis	C	-	3-17	~5 L	300 mg IV infusion over 1hr every 4 weeks

Table 1: Biologics commonly used for IBD during pregnancy. [a]Entirely human amino acids; [b]Containing murine CDRs; [c]Composed of human constant and murine variable regions; [d]Rheumatoid arthritis.

TNFα is a potent pro-inflammatory cytokine that plays a key role in mediating the inflammatory process in IBD. TNFα is detected in serum in its soluble form and also on the cell membranes of activated macrophage, monocytes, and T cells. TNFα exerts pleiotropic effects on various cell types including enterocytes, and thus anti-TNF agents block the pro-inflammatory cascade, and reestablish the balance between pro- and anti-inflammatory signals in IBD [19].

In pregnant women, natalizumab and golimumab are not typically used due to adverse events observed in animal reproduction studies [18] and a paucity of available data to support the use in pregnancy, respectively. Infliximab is the first mAb used for the treatment of IBD and has the longest and most extensive history of published clinical trial data and clinical experience. Multiple studies evaluating the safety of infliximab during pregnancy describe that pregnancy outcomes with infliximab in IBD are similar to that of the general U.S. population of pregnant women with CD not exposed to infliximab [7,20]. The incidences of adverse pregnancy outcomes (complications such as spontaneous or elective abortions, congenital anomalies, preterm birth, intrauterine growth retardation, or cesarean delivery) were similar to those in pregnant women with IBD who did not receive the anti-TNF drugs [7]. Studies with other biologic agents (adalimumab and certolizumab pegol) suggest that they produce generally similar benefits [21]. However, the use of these anti-TNF agents is associated with an increased risk of infections in the newborn exposed in utero. Infliximab and adalimumab readily cross the placenta in the third trimester (see below for details) and stay in the infant for several months after delivery [22]. This potentially affects the normal development of immune systems and increases the risk of infections. Indeed, a case of disseminated Bacillus Calmette-Guéin (BCG) infection after BCG vaccination was reported in an infant born to a mother treated with infliximab throughout the pregnancy [23]. Live vaccine administration should be avoided or used with caution the first six months of life in neonates exposed to biologics during pregnancy [6]. Also, infants exposed to combination therapy with an immumodulator plus either adalimumab or infliximab had a significant increase in infection such as upper respiratory infections and otitis media (1.35; 95% confidence interval, 1.01–1.80) compared with infants exposed to monotherapy (with either immunomodulator or anti-TNF) [22]. Such increase in the risk of infection was not shown in the infants exposed to certolizumab-based combination therapy [22]. Since certolizumab pegol appears to have much less placental transfer during the third trimester when compared to adalimumab or infliximab (see below for details), it may be preferred for patients who require treatment during the third trimester [22,24,25]. The reports on the pregnancy outcomes from the use of different antibodies (including infliximab) have been recently summarized in excellent reviews [7,26]. Current ECCO guidelines recommend that women who are stable on infliximab should be continued during the preconception period and the first two trimesters of pregnancy (30-32 weeks gestational age) [8].

Taken together, anti-TNF agents are generally considered to be low-risk in pregnant women despite the concerns about increased risk of infection in the newborns. While anti-TNF agents appear not to increase the risk for adverse pregnancy outcomes, current clinical data are limited to determine whether the use of anti-TNF agents would ultimately improve the pregnancy outcomes, in part due to the difficulties in performing prospective, placebo-controlled clinical studies in pregnant women. Similarly, the information on pharmacokinetic changes of mAb during pregnancy, which can guide dose selection and clinical study design, is lacking. This paper reviews the pharmacokinetic considerations in the use of anti-TNF agents during pregnancy. The information is relevant in developing optimal dosage regimen for minimizing fetal exposure and maximizing maternal therapeutic outcomes.

Characteristics of monoclonal antibodies

Monoclonal antibodies have complex pharmacokinetic characteristics that are distinct from small-molecule drugs and affected by multiple factors including antigen properties, mAb structure and concurrent medications [27-29]. The mAb binds to its target, either circulating in the blood or located on cell membranes. For example, anti-TNFα agents bind to a soluble form of TNFα and transmembrane TNFα–bearing cells. The Binding of antibodies to their targets then triggers neutralization processes including antibody-dependent cellular toxicity (ADCC) and/or complement-dependent cytotoxicity (CDC) [28,30].

Humans have five isotypes of immunoglobulins: IgA, IgD, IgE, IgG, and IgM. Currently available therapeutic antibodies are all in IgG family [28,31]. The structure of IgG is composed of two identical heavy chains and two identical light chains linked through disulfide bonds at the hinge region (Figure 1).

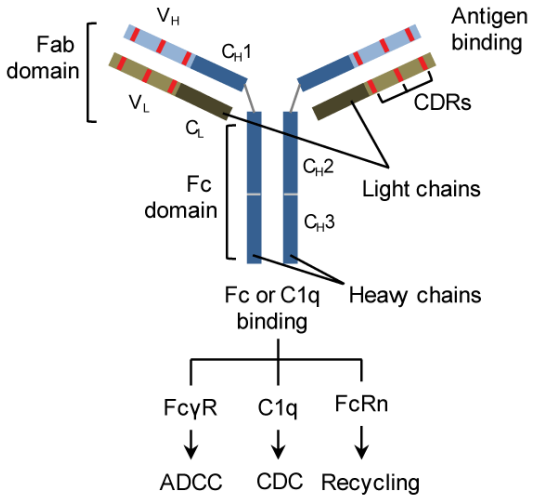

Figure 1: Structural features of monoclonal antibody for antigen binding and immune responses. C_H: Constant Region Heavy Chain; C_L: Constant Region Light Chain; FcRn: Neonatal Fc Receptor; V_H: Variable Region Heavy Chain; V_L: Variable Region Light Chain.

The antigen binding regions (called fragment antigen-binding or Fab regions) are composed of variable regions, which are formed by the intertwining of the light chain variable domain (V_L) and heavy chain variable domain (V_H). Complementarity-determining regions (CDRs) within the Fab region bind to specific target and cause antagonism or signaling. The constant regions of the antibody, on the other hand, are involved in initiating processes for cell lysis. The constant regions C_H2 and C_H3 from the heavy chain facilitate interaction with (1) C1q receptor which upon binding activates the complement cascade leading to cell lysis through CDC, (2) Fc_γ receptor to elicit ADCC by effector immune cells (e.g., natural killer cells), or (3) neonatal Fc receptor (FcRn) for recycling (and extended half-life) and placental transfer of antibodies (see below for details) [29]. While both adalimumab and infliximab have a molecular structure of full mAb, infliximab is a chimeric antibody that is composed of a murine variable region and a human constant region, and adalimumab is a fully human mAb (Table 1). Fully human or humanized antibodies carry a lower risk for inducing immune responses in humans than chimeric antibodies [32]. Certolizumab pegol, on the other hand, is a PEGylated Fab fragment of IgG [28]. PEGylation is a covalent attachment of polyethylene glycol (PEG) polymer chain to the peptide and delays the elimination of the peptide from the circulation by renal and immunogenicity-based clearance as well as proteolysis. Because certolizumab is lacking the Fc domain, it does not cause ADCC- or CDC-mediated cytotoxicity, or induce apoptosis of the activated immune cells. Although the molecular mechanisms underlying cell death caused by certolizumab pegol remain to be elucidated, certolizumab effectively antagonizes the TNFα-mediated inflammatory responses in IBD.

Pharmacokinetic properties of monoclonal antibodies used during pregnancy

Pregnancy is accompanied by multiple physiological changes that may impact the pharmacokinetics of biologic agents. However, whether and how these changes indeed impact the pharmacokinetics of mAbs are largely unknown, mainly due to limited clinical data obtained from pregnant women. The following is a summary of our current understanding on how pregnancy may impact the pharmacokinetics of anti-TNF agents used for IBD's in pregnant women (Figure 2).

Absorption: Most mAbs, including infliximab, are administered parenterally due to their large molecular size (~150 kD), poor lipophilicity, and gastrointestinal degradation. A smaller percentage of these agents are administered subcutaneously, (including adalimumab and certolizumab), or intra-muscularly for systemic absorption through the lymphatic system [29,33]. Bioavailability of adalimumab or certolizumab administered subcutaneously tends to vary and ranges from 50 to 100%. The incomplete bioavailability is attributed in part to degradation at the injection site, a process dependent on the rates of extracellular degradation by proteolysis. The extent of this proteolysis can be affected by disease states such as hypertension, diabetes, and infection [34]. Whether pregnancy is associated with changes in different protease expressions and activities and thus alters bioavailability of adalimumab or certolizumab remains unknown. Adalimumab or certolizumab administered subcutaneously are slowly transported into the lymphatic system and then to the systemic circulation, reaching peak plasma concentration between 2-7 days after administration [29,33,35]. This rate of antibody uptake to the systemic circulation is potentially affected by administration site and blood flow to the injection site. Considering that pregnancy is accompanied by an overall increase in blood flow, it appears possible

that the rate of absorption from subcutaneous dosing of adalimumab or certolizumab may increase during pregnancy. How these potential changes in antibody absorption may impact drug therapy for IBD in pregnant women, however, remains to be investigated.

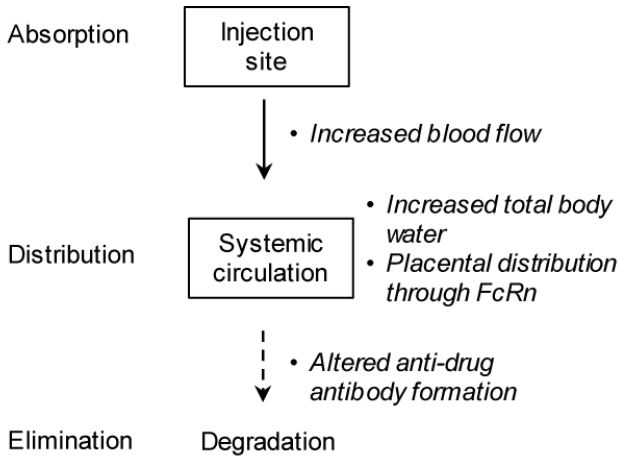

Figure 2: Schematic of pregnancy-mediated changes (shown in italics) that can potentially impact pharmacokinetics of mAbs.

Distribution: Monoclonal antibodies have a relatively small volume of distribution due to their high molecular weight and hydrophilic profile. These characteristics lead to limited tissue distribution, and yield a small volume of distribution [28]. The volume of distribution of these agents approximate the size of blood and extracellular spaces and are in the range of 3-8 L [14,15].

Physiological changes accompanying pregnancy will likely impact the distribution of mAbs. During pregnancy, plasma volume increases by 40% [36]. As the distribution of biologics is limited to plasma and extracellular fluid, changes in total body water during pregnancy may potentially impact pharmacokinetics and thus pharmacodynamics of biologics drugs. Interestingly, however, previous studies indicate that the changes in total body water do not significantly alter pharmacokinetics of most mAbs. For example, the antibodies in Table 1 (except infliximab) are dosed at set amounts regardless of the differences in body weight or the size of total body water. Thus, for adalimumab and certolizumab, an increase in total body water during pregnancy may not significantly impact their pharmacokinetics during pregnancy. Of note, the dosing of infliximab is based on body weight, likely because the volume of central compartment of infliximab increases proportionally to body weight [37]. The increased plasma volume during pregnancy may require higher doses of infliximab in pregnant women although such possibility has yet to be examined clinically.

FcRn is a receptor for the Fc region of mAbs, widely expressed in endothelial and epithelial cells of skin, muscle, kidney, liver, and placenta. FcRn protects IgG from intracellular catabolism; IgG enters endothelial cells by nonspecific endocytosis and binds to FcRn in acidic environment (pH 6.0). While unbound IgG inside the cells is subject to proteolysis in lysosomes, the FcRn-bound IgG is recycled to the cell surface where it is released at the physiological pH of 7.4 [38]. This process is responsible for distribution of mAbs to the tissues (where drug targets may be located). The similar FcRn-mediated transport of mAbs is also at placental membranes, which is responsible for transport of antibodies to the fetal circulation [7,38]. This is considered as a protective mechanism for the developing fetus by conferring immunity after birth. IgG concentrations in fetal blood increase steadily from early in the second trimester until delivery, with antibodies being transferred most significantly during the third trimester [25]. Because FcRn recognizes the Fc portion of mAb, antibodies with Fc are readily transported across placenta, most significantly during the third trimester. On the other hand, antibodies lacking the Fc portion would theoretically show minimal transfer across the placenta. Indeed, a recent study in over 20 pregnant women with IBD reported that median concentrations of infliximab and adalimumab (i.e., Fc-containing antibodies) in umbilical cord blood are 160% and 153% higher than the maternal blood level, respectively [22], and should be held after 30 weeks gestational age in women with quiescent IBD [6]. On the contrary, certolizumab pegol (Fc-free antibody) exhibited minimal penetration across the placenta; in a study of 10 pregnant women with IBD, the median concentration of certolizumab pegol in the cord blood was only 3.9% of that of the mother [22]. Considering that the transfer of therapeutic mAbs across the placenta can potentially lead to short-term side effects (e.g., infection) as well as as-yet-unknown long-term consequences in developing fetus, the use of Fc-free antibodies has been proposed as a better option for pregnant women especially during the third trimester [22,24,25].

Elimination: Unlike small molecule drugs, renal excretion and hepatic metabolism are not primarily involved in elimination of mAbs and thus renal and hepatic impairment does not significantly affect clearance of mAbs [29]. The large size of mAbs prevents excretion into the urine; instead they are catabolized into peptides and amino acids (via proteases) that can be re-used for de novo protein synthesis [28]. While elimination of mAbs is not clearly understood, there appear to be two unique pathways: FcRn- and target-mediated pathways. The first mechanism requires binding of the Fc region of the antibody to FcRn. IgG antibodies are then taken up into the endothelial cells via endocytosis, and the binding to FcRn protects the antibody from lysosomal degradation. While the binding of mAbs to FcRn at the endothelial cells temporarily "clears" the antibody from systemic circulation, this process in fact serves as a salvage pathway for IgG because the antibodies taken up by the cells are released back to the systemic circulation intact. Thus, FcRn plays a critical role in extending the retention time of IgG antibodies in the body. Indeed, differences in binding affinities of IgGs to FcRn result in differences in the elimination half-life of the antibodies. As human FcRn does not recognize the murine Fc region, the half-life of IgG-based mAbs in humans generally increases with the degree of "humanization"; fully rodent<chimeric<humanized<fully human. On the other hand, the mAbs that share the same human Fc exhibit similar serum half-life (Table 1). The FcRn-mediated recycling of IgG's is functional for both therapeutic and endogenous IgG antibodies. Since therapeutic mAbs compose only a small part of endogenous IgG, this route is not likely to become saturated, and the elimination produces linear, nonspecific clearance [27,28].

The target-mediated elimination pathway involves interaction between a mAb and its pharmacological target, and represents the primary route of antibody clearance. Once the therapeutic IgG binds to the target (via Fab region), the antigen-bound IgG binds to Fcγ receptors on the effector cells (via Fc region). The resulting immune complexes are then cleared from the body through reticulo-endothelial system (RES). For targets expressed on cell membranes, the binding of mAb on the targets on cell surfaces may trigger internalization of the

complex into the cells followed by subsequent lysomal degradation of the complex. Unlike the FcRn-mediated pathway, the target-mediated elimination is saturable because of the finite amounts of target antigen, which may lead to non-linear elimination. Typically, clearance of mAb's that bind to membrane antigens is faster at low doses as the unbound targets will "sop up" the antibodies, serving as a sink (this phenomenon is referred to as the "antigen sink") [28,39]. Also, changes in the number of targets as a result of desired effect of mAbs alters the clearance of therapeutic antibodies through target-mediated elimination pathway.

Other factors which may significantly influence the clearance of biologics include antidrug antibodies (ADAs) [29]. Any biologics, whether entirely of human origin, chimeric, or humanized, can exhibit immunogenicity in humans, leading to the formation of ADAs. The agents used for IBD all note the presence of ADAs. For example, the incidence of immunogenicity with adalimumab (a fully human IgG) can be as high as 87% [40]. The presence of ADA is implicated in the failure of anti-TNF drugs in chronic IBD that occur in at least one third of the patients [41]. The lack of clinical response in patients with ADA can be explained by neutralization of the functional part of anti-TNF agents by ADA, thus preventing the binding of anti-TNF agents to its targets. Also, the immune complexes formed between ADAs and anti-TNF agents are cleared by RES, thus increasing the elimination of anti-TNF agents and lowering serum drug levels. Indeed, clinical studies have reported that clearance of mAbs (including infliximab, adalimumab, and certolizumab pegol) is greater in patients with ADAs [41,42]. For example, the presence of ADA against adalimumab has been associated with low or undetectable serum trough levels of adalimumab [41].

The development of ADA's may depend on the doses or frequencies of administered mAbs. Low serum TNF inhibitor concentrations are associated with the presence of ADAs. Although this may reflect the increased clearance of mAbs by forming immune complexes with ADA, an alternative explanation can be that the low serum concentrations of anti-TNF agents permit ADA development [41]. While the relationship between the dose of mAbs and the formation of ADAs remains to be further defined, changing the dose (e.g., increasing the dosage or decreasing the frequency) of anti-TNF agents may prove to be an effective strategy to improve the response to mAbs. Similarly, the altered serum levels of mAbs during pregnancy (e.g., due to changes in distribution) may also impact the extent of ADA development and thus elimination rate of anti-TNF agents in pregnant women. Other factors such as patient's immune status can also influence ADA development [41]. For example, immunomodulators such as methotrexate and azathiopurine are known to decrease the incidence of ADA development [14,15]. Of note, pregnancy is accompanied by complex changes in the immune system; the first trimester is manifested by a strong inflammatory response for implantation and placentation while during the second trimester an anti-inflammatory state is induced for rapid fetal growth and development [43]. Whether this leads to altered levels of ADA formation against biologic drugs and thus altered pharmacokinetics of biologics during pregnancy remains unknown.

Conclusion

Most women with IBD are affected during their reproductive years, and untreated IBD can have detrimental outcomes in both mothers and fetus. In recent years, many biological therapies including anti-TNF agents have been developed for the treatment of IBD. An increasing number of IBD patients are treated with these agents during pregnancy. Results from sporadic reports suggest a lack of additional negative pregnancy outcomes from the use of anti-TNF agents in women with IBD. What remains unknown is whether the physiological changes accompanying pregnancy require different doses of mAbs for optimal disease management in the mother and minimal fetal exposure to therapeutic antibodies. Based on current understanding about mAb disposition in nonpregnant subjects, it appears very likely that pregnancy can alter pharmacokinetics of anti-TNF agents, and this may impact the safety and efficacy of anti-TNF agents in pregnant women. Despite the possibility and its clinical implication, clinical data are sparse on how pregnancy alters the pharmacokinetics of mAbs and whether dosage adjustment is required during pregnancy. Additional studies are needed to determine if dosing or administration of anti-TNF agents should be altered to adequately address pregnancy-associated pharmacokinetic changes. A better understanding of such pregnancy-mediated changes in the pharmacokinetics of anti-TNF agents may potentially allow further improvement in pregnancy outcomes in women with IBD.

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