Review Article

Treating Inflammatory Bowel Disease in Pregnancy: The Issues We Face Today

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Abstract

Many women of childbearing age are living with inflammatory bowel disease [IBD], yet there are limited studies on the use of IBD medications in pregnancy. In this review, we provide a comprehensive update on the safety of these medications during pregnancy, particularly thiopurines and biologicals. Antibiotics, steroids, and aminosalicylates are relatively low risk for use in pregnancy, and growing evidence supports the safety of immunomodulators and anti-tumour necrosis factor agents as well. Available studies on infliximab, adalimumab, and certolizumab pegol show no increase in adverse events during pregnancy or perinatally. Similarly, studies on lactation demonstrate that concentrations of subcutaneous anti-tumour necrosis factor biologicals are undetectable, and levels of thiopurines and infliximab are negligible in breast milk. Less is known about anti-integrins in pregnancy [eg natalizumab and vedolizumab] but currently available data suggest they may be safe as well. Although more studies are needed to examine the long-term effects of these medications on offspring, the available data provide reassuring information for providers caring for women of childbearing age.

Keywords: Inflammatory bowel disease; pregnancy; Crohn's disease; breastfeeding; ulcerative colitis

1. Introduction

Inflammatory bowel disease [IBD] affects many women in their peak reproductive years. Women with IBD have a high rate of voluntary childlessness because of concern for medication side effects, advice given by their treating physicians, and overall low rates of counselling. Women with IBD when pregnant present unique challenges, most importantly maintaining remission in the mother while ensuring fetal health and viability. Although many medications are now available to treat IBD, ethical considerations involving studying pregnant patients have led to fewer studies examining adverse drug events in this population when compared with the wealth of studies on non-pregnant IBD patients. In this article, we review the latest data on the safety of IBD treatment in pregnancy and on drug delivery in breastfeeding.

Accumulating evidence suggests that many of the medications used to treat IBD are safe to use during pregnancy. There is less debate on the use of aminosalicylates, antibiotics, or steroids, because these medications have been available and in use for a longer time and there is more information on the effects of these drugs in pregnancy. For the most part, these medications tend to be relatively low risk and are less concerning when it comes to choosing to continue or to start them during pregnancy. At the same time, women only on aminosalicylates tend to have milder disease and are therefore generally of less concern to the gastroenterologist or obstetrician. The real debate is regarding patients with a history of severe disease that has been controlled with either thiopurines or anti-tumour necrosis factor drugs [anti-TNFs], which have broader side effect profiles. The dilemma over whether to continue or start these more efficacious medications in order to maintain or achieve remission during pregnancy has led to
many new studies in the past decade, many of which we will review in this article. In general, it appears that despite their known immuno-suppressant and theoretical teratogenic effects, these medications have an acceptable side effect profile for both mother and fetus.

The Food and Drug Administration [FDA] traditionally has categorised medications for use in pregnancy as A, B, C, D, or X. Category A medications are those for which controlled studies in animals and pregnant women show no risk in the first trimester and any possible harm to the fetus is rare. Category B drugs show no fetal risk in animals, but either there is no available information in humans or a risk seen in animal studies was not confirmed in controlled studies on pregnant humans in the first trimester. Category C drugs either show adverse events in animal studies with no available controlled studies in humans, or there are no studies in either humans or animals; these drugs should only be used when the benefits outweigh risks. Category D drugs have studies showing fetal risk; recommendations are to use these only if benefits strongly outweigh risks. Category X drugs are contraindicated in pregnancy because studies on animals or humans show teratogenic defects. Although we will refer to the FDA categorisation of IBD-related medications, these are suboptimal in the population of pregnant IBD patients given the absence of studies in this particular subgroup. In addition, most recently the FDA has announced that it will change labelling of drug categories in pregnancy by removing letter categories [A,B,C,D, or X] and replacing these with risk summary information on drugs, clinical considerations, and available data on use of medications in pregnancy.

Table 1 provides a summary of recommendations regarding administration of medications during pregnancy according to both FDA categories and the new recommended FDA medication categories.

<table>
<thead>
<tr>
<th>Medications</th>
<th>Male and female fertility</th>
<th>Pregnancy [labour and delivery]</th>
<th>Placental transfer</th>
<th>Lactation</th>
<th>FDA label</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>5-ASAs</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mesalamine [oral]</td>
<td>Low risk</td>
<td>Low risk</td>
<td>Yes</td>
<td>Low risk</td>
<td>B</td>
</tr>
<tr>
<td>Asacol/ Asacol HD</td>
<td>Low risk</td>
<td>Low risk but contains DBP</td>
<td></td>
<td>Low risk</td>
<td>C</td>
</tr>
<tr>
<td>Sulfasalazine</td>
<td>Oligospermia ↓ motility in men</td>
<td>Low risk, ↑ folic acid</td>
<td>Yes</td>
<td>Low risk</td>
<td>B</td>
</tr>
<tr>
<td><strong>Immunomodulators</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cyclosporine</td>
<td>Limited data in transplant patients, may be low risk</td>
<td>Low risk</td>
<td>Yes</td>
<td>Contraindicated</td>
<td>C</td>
</tr>
<tr>
<td>Methotrexate</td>
<td>Stop optimally 3 months prior in men, stop ~6 months prior in females</td>
<td>Contraindicated</td>
<td>Yes</td>
<td>Contraindicated</td>
<td>X</td>
</tr>
<tr>
<td>Thiopurines</td>
<td>Low risk</td>
<td>Low risk</td>
<td>Yes</td>
<td>Low risk, breastfeeding after 4 h</td>
<td>D</td>
</tr>
<tr>
<td><strong>Oral steroids</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Prednisolone</td>
<td>Low risk</td>
<td>Low risk, risk of low birthweight and gestational diabetes</td>
<td>Yes</td>
<td>Low risk, breastfeeding after 4 h</td>
<td>C</td>
</tr>
<tr>
<td>Budesonide</td>
<td>Low risk</td>
<td>Likely compatible</td>
<td>Yes</td>
<td>Low risk</td>
<td>C</td>
</tr>
<tr>
<td><strong>Biologicals</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Adalimumab</td>
<td>Low risk</td>
<td>Most likely safe throughout but recommended to stop in 3rd trimester</td>
<td>Yes</td>
<td>Low risk</td>
<td>B</td>
</tr>
<tr>
<td>Certolizumab</td>
<td>Low risk</td>
<td>Low risk, can continue throughout pregnancy</td>
<td>Minimal</td>
<td>Low risk</td>
<td>B</td>
</tr>
<tr>
<td>Infliximab</td>
<td>Low risk</td>
<td>Most likely safe throughout but recommended to stop in 3rd trimester</td>
<td>Yes</td>
<td>Low risk</td>
<td>B</td>
</tr>
<tr>
<td>Golimumab</td>
<td>Low risk</td>
<td>Most likely safe throughout but recommended to stop in 3rd trimester</td>
<td>Yes</td>
<td>Low risk</td>
<td>B</td>
</tr>
<tr>
<td>Natalizumab</td>
<td>Limited human data</td>
<td>Limited human data</td>
<td>Possible</td>
<td>Limited human data</td>
<td>C</td>
</tr>
<tr>
<td>Vedolizumab</td>
<td>Limited human data</td>
<td>Limited human data, appears to be safe in animal studies</td>
<td>Possible</td>
<td>No human data, detected in milk of lactating monkeys</td>
<td>B</td>
</tr>
<tr>
<td><strong>Antibiotics</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Metronidazole</td>
<td>Avoid</td>
<td>Avoid 1st trimester</td>
<td>Yes</td>
<td>Avoid if possible, breastfeeding after 12–24 h</td>
<td>B</td>
</tr>
<tr>
<td>Ciprofloxacin</td>
<td>↓ in motility and viability in men</td>
<td>Avoid 1st trimester</td>
<td>Yes</td>
<td>Avoid, breastfeeding after 24 h</td>
<td>C</td>
</tr>
</tbody>
</table>

FDA, Food and Drug Administration; DBP: dibutyl phthalate; 5-ASA, 5-aminosalicylic acid.
2. Aminosalicylates

Aminosalicylates (5-ASA), particularly sulfasalazine, are one of the earliest classes of medications used to treat IBD, and there are sufficient data on their effects in pregnancy and the fetus. There are many studies which have demonstrated the safety of these drugs [mesalamine, balsalazide, and sulfasalazine] in pregnancy, and they are considered category B for use in pregnancy.[5,6] A meta-analysis of seven studies, including 642 pregnant IBD patients receiving aminosalicylates and 1158 disease-matched controls, showed no difference in congenital anomalies (odds ratio [OR] 1.16, 95% confidence interval [CI] 0.76–1.77), stillbirth [OR 2.38, 95% CI 0.65–8.72], spontaneous abortion [OR 1.14, 95% CI 0.65–2.01], preterm delivery [OR 1.33, 95% CI 0.85–2.13], or low birthweight [OR 0.93, 95% CI 0.46–1.85] when compared with pregnant IBD patients without medications. Similarly, a recent UK study looking at IBD medication prescription in the first trimester of pregnancy found that the odds ratio for any major congenital anomaly in the 551 patients prescribed 5-ASA was only 0.82 [95% CI 0.42–1.61] after adjusting for maternal age, socioeconomic status, and smoking, indicating no increased risk for congenital malformations in patients prescribed aminosalicylates in the crucial first trimester. Similarly, sulfasalazine is known to cross the placenta but no teratogenicity has been observed; current recommendations are to increase folic acid intake to 2 mg/day to minimise the risk of neural tube defects. However, not all aminosalicylates are alike and olsalazine is considered category C because of teratogenic effects in mice and rat studies.[10] The FDA changed the drug rating of Asacol HD to category C because its coating component, dibutyl phthalate [DBP], showed an increase in urological defects in male offspring and external skeletal defects in animal studies—although the dosage given in these rats was more than 190 times higher than that prescribed to humans.[11,12] These teratogenic abnormalities have not been observed in human observational series. For instance, one study of 117 pregnant women taking Asacol compared fetal outcomes with 156 women taking other aminosalicylates and found no difference in congenital abnormalities [OR 0.65, 95% CI 0.25–1.65].[13] Taken all together, at this time there is no reason to change a pregnant woman to a different 5-ASA agent if she is in remission. However, women presenting for preconception consultation visits, who are already on Asacol, and those wanting to start this medication de novo during pregnancy, should be counselled regarding the small risk of teratogenicity seen in animal studies and be recommended a different 5-ASA agent. Because there are many available 5-ASA brands with similar efficacy, it is relatively easy to choose an agent without DBP in its coating.

3. Antibiotics

In general, the acceptable drugs of choice to treat infections during pregnancy are penicillins and cephalosporins, which are considered for the most part safe in pregnancy. For instance, in the treatment of pouchitis, Augmentin [amoxicillin/clavulanate, a category B drug] instead of ciprofloxacin is an adequate alternative.[1] Two prior studies using Augmentin showed no increase in teratogenicity.[12,13] However, as treating gastroenterologists, we must also understand the teratogenic effects of our more commonly used antibiotics [eg nitroimidazoles and fluoroquinolones], particularly when weighing their use in active gastrointestinal [GI] infections in the setting of patient allergies and bacterial-resistant strains. Metronidazole is considered a category B drug because despite crossing the placental barrier—studies using higher doses in rats have demonstrated no evidence of harm to the fetus.[14] Although in one study there was a mild but not statistically significant increase in cleft lip in children of pregnant patients exposed to metronidazole, recent meta-analyses and cohort studies have not demonstrated any birth defects with the use of metronidazole in pregnant patients.[6,12,15,16,17,18] In fact, metronidazole is currently recommended by the Center for Disease Control [CDC] for use in bacterial vaginosis at any stage in pregnancy.[19] On the other hand, fluoroquinolone use in pregnancy is restricted [category C] because of its historical effect on cartilage and bone formation in animal studies, which could potentially lead to arthropathies in children.[20,21] However, an expert review of published data on the use of ciprofloxacin in pregnancy by TERIS [Teratogen Information System] concluded that, at therapeutic doses, ciprofloxacin is unlikely to result in teratogenicity.[19] Two other studies composed of 200 and 57 pregnant patients exposed to fluoroquinolones, observed no increase in the development of congenital abnormalities.[20,21] Therefore, based on more recent studies, fluoroquinolones appear to be safe in pregnancy than historically considered, although the lack of uniform data leads us to believe that it may be safer to use alternative antibiotics if at all possible.[15,24] As with any drug use in pregnancy, it is important to carry out a detailed discussion with the patient of benefits versus risks.

4. Corticosteroids

Corticosteroids are used in pregnancy to treat IBD flares, given growing evidence suggesting the lack of any major teratogenic effects.[4] They are considered relatively safe in pregnancy because, once the drug crosses the placenta, it is rapidly inactivated by the enzyme 11β-hydroxysteroid dehydrogenase type 2 [located in the syncytiotrophoblast of the human placenta] into its inactive metabolite, cortisone, thus preventing the pro-apoptotic effects of cortisone.[21] Prior studies, including case control studies and a meta-analysis, showed an association with cleft palate in women using steroids [mainly used to treat asthma].[21,26] In the meta-analysis, the reported odds ratio for cleft palate in those on steroids was 3.35 [95% CI 1.97–5.69]. Nevertheless, more recently, a retrospective study looking at 209 children born of women with IBD, who were prescribed corticosteroid therapy in their first trimester, demonstrated a similar risk for development of any major congenital anomaly [heart, limb, and genitourinary] when compared with children born of women with IBD but not exposed to corticosteroids [OR 0.48, 95% CI 0.15–1.50].[8] There is also no evidence of fetal adrenal insufficiency or abnormal T cell function in babies exposed to steroids in utero.[21] Similarly, ileal-release budesonide and budesonide MMX have not been associated with any teratogenic effects and may be good alternatives in mild to moderate flares in pregnancy.[21] Large-sample studies looking at the use of inhaled budesonide in asthma in pregnant patients have not identified an increase in postnatal adverse outcomes.[29] However, further studies are needed to confirm their safety in IBD pregnancy as current data are based mainly on small, retrospective studies.[29] Our most robust prospective data on steroid exposure and pregnancy are from the Pregnancy in Inflammatory bowel disease And Neonatal Outcomes [PIANO] study. This is an ongoing multicentre study at 30 US IBD centres, following patients through pregnancy and infants up to the first 4 years of life. Results presented at Digestive Disease Week in 2014 included information on 969 women who had steroid exposure [oral or intravenous] at one point in their pregnancy and who were followed at 4, 9, and 12 months post-partum. There was no relationship between maternal corticosteroid use and developmental delay or congenital anomalies. There was an increased risk of infection in the first 4 months of life [OR 1.5, 95% CI 0.9–2.7] but this relationship did not persist at 12 months after controlling for breastfeeding. However, it is important to note that whereas corticosteroids did not result in congenital anomalies, steroid use...
was associated with gestational diabetes [adjusted OR 2.8, 95% CI 1.36–0], low birthweight [adjusted OR 2.8, 95% CI 1.36–1], and a non-significant association with preterm birth [adjusted OR 1.8, 95% CI 1.03–1].

In light of the most recent studies, whereas corticosteroid use does not appear to result in major teratogenicity, it does increase the risk of gestational diabetes, low birthweight, and early infant infections, so it is important to emphasise to our patients that steroids are not a ‘safer’ alternative to their existing IBD maintenance drugs.

5. Immunomodulators

Immunomodulators are a class of IBD medications that encompass the most teratogenic IBD drugs, thalidomide and methotrexate, both of which are contraindicated in pregnancy [category X]. Azathioprine [AZA] and 6-mercaptopurine [6-MP], the most commonly used medications for IBD within this group, are considered category D drugs. However, this designation dates back to when thiopurines were given in high doses for leukaemia. At high doses, data in mice and rats confirmed teratogenicity. Although it is true that trans-placental passive transfer of 6-MP metabolites occurs, the oral bioavailability of AZA and 6-MP appears to be only 47% and 16%, respectively. Furthermore, drug exposure during the first trimester may be minimal given that the fetal liver does not have inosinate pyrophosphorylase, the enzyme that converts AZA to 6-MP.

Results from PIANO, examining a subgroup of pregnant IBD patients exposed to 6-MP or AZA monotherapy, demonstrate that thiopurine use is not associated with an increased rate of spontaneous abortions, congenital anomalies, preterm birth, intra-uterine growth retardation, caesarean section, or neonatal intensive care unit [NICU] stay after adjusting for disease type and disease activity. Similarly, recent interim analysis from PIANO, looking at developmental milestones in children exposed to immunomodulators, demonstrated no delay in children up to the age of 4 years. Developmental scores in children exposed to immunomodulators were actually slightly higher when compared with children unexposed to either immunomodulators or biologicals. Accumulating evidence from other cohort studies suggests similar findings, including no increased rate of infections in children or childhood neoplasia up to 3.8 years of age. There are a few smaller studies reporting adverse events associated with thiopurine use. These include one study by Norgard et al. on pregnant women with Crohn’s disease [CD] in which an increase in preterm births among women using steroids and 6-MP/AZA was reported; however, in this study they were unable to account for disease activity. Similarly, other reports exist of babies exposed to thiopurines resulting in complications of anaemia, pancytopenia and high alkaline phosphatase. In one cohort of 30 pregnant IBD patients on stable dose thiopurines, 16 babies [63%] had anaemia at birth [median haemoglobin 9.25 mmol/l], although these results have not been replicated in larger studies.

Nevertheless, the overwhelming majority of studies support the safety of thiopurines in pregnancy. Results from a study by Cancers Et Surrise Assocé aux Maladies inflammatoires intestinales en France [CESAME] study, a cohort in which a total of 215 IBD pregnancies were recorded [86 exposed to thiopurines, 84 on other medications, and 45 on no medications] found that thiopurine use in pregnancy was again not associated with an increased risk of congenital abnormalities. Increased incidence of prematurity due to thiopurines was not significant and may instead correlate with having IBD. Another study looking at 149 children exposed to immunomodulators in the first trimester of pregnancy, found no increased risk in development of any major congenital anomaly when compared with children of IBD pregnant patients not exposed to AZA or 6-MP.

Studies looking at outcomes of pregnancies fathered by IBD patients exposed to thiopurines are scarce but overall support the continuation of thiopurines in male patients planning to conceive. A case control study of 46 conceptions exposed to either azathioprine or mercaptopurine and 84 controls [not exposed within 3 months of conception] found no difference between thiopurine-exposed and control groups in fecundity, congenital abnormalities, or perinatal outcomes. Similar findings are reported in cases of transplant patients who fathered thiopurines while on thiopurines.

Only one small study in 2000 showed an increased risk of congenital abnormalities and adverse pregnancy outcomes in pregnancies of fathers taking thiopurines at conception. However, the validity of this study has been criticised because of concerns regarding the study’s small sample size resulting in wide confidence intervals and unequal comparison groups, given the lack of adjustment for important confounders like disease activity and disease type (CD versus ulcerative colitis [UC]). Last, a recent meta-analysis inclusive of all available published studies showed no evidence for increased congenital anomalies in children exposed to thiopurines, and demonstrated that thiopurine use by fathers at time of conception was safe. Therefore, whereas it may be advisable not to start a thiopurine during pregnancy because of the possible maternal side effects including pancreatitis and leukaemia, evidence now suggests that thiopurine drugs as maintenance therapy in the preconception period and during pregnancy are relatively safe.

The two principal calcineurin inhibitors used in IBD are cyclosporine and tacrolimus. Prior studies suggest that cyclosporine is not teratogenic and can be used for steroid-refractory ulcerative colitis in pregnancy. A meta-analysis of 15 studies totalling 410 patients, including patients on cyclosporine post-transplant and for autoimmune diseases, demonstrated that the rate of congenital malformations is the same as in the general population. However, the overall prevalence of prematurity in the cyclosporine group was 56.3%, with an OR for prematurity of 1.52 [95% CI 1.00–2.32]; although these results were not statistically significant, it may suggest an increased risk of prematurity in cyclosporine-using pregnant patients. We can extrapolate from the dearth of data regarding adverse perinatal outcomes in transplant patients on tacrolimus that intake during pregnancy is not associated with increased pregnancy complications. Studies show tacrolimus crosses the placenta and is excreted in breast milk, but at very low measured concentrations [0.06 μg/kg/day].

6. Anti-TNF-α Agents

Currently there are about 472 described pregnancies exposed to anti-TNF published in the literature. Most published data available on the use of anti-TNFs during pregnancy are based on small studies, including case reports and case series, but interim reports of large registry data continue to provide us with important information regarding the safety of anti-TNFs in pregnancy. These ongoing studies in combination suggest that the risk of congenital malformations as a result of anti-TNF exposure during pregnancy is not increased. Infliximab [IFX], adalimumab [ADA], certolizumab pegol [CZP], and most recently golimumab [GOL], are all considered category B by the FDA.

Interim results from PIANO provide us with some of the most useful information on the safety of anti-TNFs in pregnancy. In this ongoing study, patients were divided into group A [6-MP/AZA],

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group B [IFX, ADA, CZP] and group AB [both thiopurines and anti-TNF], and compared with patients unexposed to either immunomodulators or biologicals during pregnancy. Interim results looking at pregnancy adverse events were last analysed in 1052 women of whom 797 had completed pregnancy [unexposed=337; Group A=265; Group B=102; Group AB=59]. Neither thiopurine nor anti-TNF agent use was associated with an increase of spontaneous abortions, congenital anomalies, preterm birth, intra-uterine growth retardation, caesarean section, or NICU stay, after adjusting for disease type [UC or CD] and disease activity; there was a 4.1% rate of spontaneous abortions and a 4.6% rate of congenital anomalies in the exposed groups. There was however, a significant increase in infant infections at 12 months of age in the combination therapy group compared with the unexposed group, risk ratio [RR] 1.50 [1.08–2.09]. Similarly, in an analysis of 1097 women providing safety reports to the FDA adverse event reporting system on the use of TNF-alpha inhibitor during pregnancy, there was no reported increase in maternal and/or fetal adverse events in patients using thiopurine monotherapy, anti-TNF monotherapy, or combination therapy. Therefore, it appears that the use of anti-TNF agents is relatively safe in pregnancy, albeit with a possible increased infection risk for the baby if combination therapy is used.

Another ongoing prospective study, reported by the Organization for Teratology Information Specialists [OTIS], involves ADA. Interim analysis in 2012 demonstrated that 167 women with CD using ADA had similar rates of spontaneous abortions, stillbirth, preterm deliveries, and congenital malformations compared with disease-matched controls and the general population; similar results were seen in a 2015 OTIS analysis presented at Digestive Disease Week in 2015, looking at 74 ADA-exposed pregnant women with rheumatoid arthritis in their first trimester. These results mirror previous findings from the TREAT Registry [Crohn’s Therapy Resource, Evaluation and Assessment Tool] and the Infliximab Safety Database. Lastly, a recent meta-analysis of five cohort studies looked at a total of 1216 participants [349 receiving anti-TNF therapy and 747 matched controls] and found no significant difference in the rates of total unfavourable pregnancy outcomes [including rates of abortion, preterm birth, or congenital malformations] between pregnant women with IBD who were on anti-TNF-alpha therapy [IFX, ADA, or CZP] and controls [OR 1.00, 95% CI 0.72–1.41]. One limitation of this meta-analysis, however, is the fact that included studies provided inconsistent reports on the timing and administration of anti-TNF during pregnancy. Therefore, whereas the previous studies help to diminish concerns over the safety of anti-TNF administration during pregnancy, they do not address an existing concern over the safety of anti-TNF therapy in the third trimester. This concern is based on a direct correlation observed between the level of measured drug in infants and the timing of delivery of the last dose, the impact of which is still uncertain.

Previous studies show that most anti-TNFs have increased placental transfer during the third trimester and that drug levels can be present in the baby at the time of delivery and up to 6 months after use, see Figure 1. This is because most anti-TNFs are immunoglobulin G1 [IgG1] antibodies [IFX, ADA, and GOL] and, in humans, transmission of IgG1 occurs mainly in the third trimester. CZP, an IgG4-binding pegylated Fab’ fragment of an anti-TNF antibody, has less placental transfer compared with IgG1 antibodies because it crosses the placenta by passive diffusion as opposed to the active transfer seen in IgG1 antibodies; see Figure 2. Therefore, CZP levels measured in infants at birth appear to be very small [<2 ug/ml] irrespective of timing of dose in the mother. To date, the effects of high infant anti-TNF levels at birth, especially in those not using CZP, are still questioned, particularly as they relate to a possible increased risk of infant infections.

The results from PIANO are edifying regarding this debate. In their latest update in 2014, 422 women were exposed to a biological in the third trimester (214 IFX, 117 ADA, 89 CZP, 9 natalizumab [NTZ]) and compared with 597 either unexposed to anti-TNF or exposed in the first or second but not third trimester [a total of 70]. After controlling for maternal age, preterm birth, and type of biological, it appeared that the risks of infant infections and preterm birth were not based on timing of the biological. This is an important

![Figure 1](https://example.com/figure1.png) Anti-TNF drug levels in cord blood were measured in pregnant patients exposed to medications in utero. Certolizumab levels were minimal in all cord blood samples measured. Figure created based on study findings from Mahadevan U et al.
maternal blood, TNF cord blood levels as compared with the mother’s peripheral weeks of gestation in a stable mother, given concerns of unknown guidelines advocate the discontinuation of anti-TNF therapy at 24 a dose within the last month before delivery. In addition, European pregnancy is not common practice. Since ADA and IFX will cross the placenta, for patients in remission clinicians could consider avoiding TNF in the third trimester of pregnancy was largely described only in case reports and case series. Therefore, it is reasonable to conclude that if an IBD patient is at risk for having a flare in the third trimester, it is safe and possibly better for infant outcomes to continue the biological throughout pregnancy or to even consider induction if the patient is biological-naive.

The more difficult question is what to do with patients who are in remission; currently there is a suggestion that IFX, ADA, and GOL should be stopped in this cohort at 30–32 weeks of gestation, given placental transfer at the end of pregnancy. However, given the most recent evidence accumulating regarding safety of anti-TNFs in pregnancy—even when administered beyond the second trimester—it is increasingly difficult to discontinue anti-TNFs, knowing the possibility that patients could flare in the third trimester without therapy and that this could result in worse adverse patient and infant outcomes. The decision to maintain CZP throughout pregnancy is easier, given its overall low, steady placental transfer, but the decision to continue other anti-TNF agents in stable patients throughout their pregnancy is not common practice. Since ADA and IFX will cross the placenta, for patients in remission clinicians could consider avoiding a dose within the last month before delivery. In addition, European guidelines advocate the discontinuation of anti-TNF therapy at 24 weeks of gestation in a stable mother, given concerns of unknown long-term fetal outcomes as well as data reporting higher anti-TNF cord blood levels as compared with the mother’s peripheral blood. Although discontinuation of the anti-TNFs during longer stretches of time is not recommended, a recent study from Baert et al. demonstrated that discontinuation of IFX in patients in remission, often during pregnancy, did not result in immunogenicity when the biological was re-initiated.79

One major long-term concern is whether children with high levels of anti-TNF at birth, given their presumed immunosuppression, will have an appropriate response to vaccinations administered within the first year of life. A recent case series examined 25 children exposed to anti-TNFs in utero and found that all children vaccinated had a detectable serological response to vaccinations.74 Similarly, ongoing studies by Mahadevan et al. have shown that despite exposure in utero to IFX, infants have appropriate response to vaccines.75 A case study by Vasiliaszukas et al. reported a child with high levels of IFX at birth and an appropriate response to vaccinations.76 Further, there are no adverse events reported of vaccinations in offspring with elevated biological levels at birth except one report of a fetal outcome due to disseminated BCG infection in a fetus exposed to IFX throughout pregnancy.77 Therefore, given the relatively unknown effects on immunity of the baby with high levels of a biological post-partum, current recommendations are that live vaccines recommended during the first 6 months of life should be avoided until the levels of the biological are undetectable; this includes the vaccine against rotavirus which is normally given at 2, 4 and 6 months and intranasal influenza vaccine. The oral polio vaccine and the BCG vaccine, which are normally administered in developing countries, should also be withheld in the first 6 months of life.78,79,80

7. Anti-integrins

To date, there is no published experience with VDZ in pregnant women. Since VDZ came on the market, the use of NTZ in IBD has fallen out of favour because of its rare association with the development of progressive multifocal leukoencephalopathy. The safety of NTZ and VDZ in pregnancy and lactation is relatively unknown and they are labelled categories C and B, respectively. Natalizumab is an IgG4 antibody which should therefore cross the placenta preferentially in the second and third trimester, although not as much as does IgG1.81 Consequently, NTZ administration is recommended up to week 36 of pregnancy; given a similar mechanism of action in VDZ [an IgG1], we believe the same should be true for this medication.

Our current data on the safety of NTZ largely come from cases of multiple sclerosis [MS] patients exposed to this medication. We can perhaps extrapolate from these data that results are similar in patients with VDZ. One study, looking at 164 pregnant women to NTZ [in IBD and MS patients], found no increased incidence of birth defects.41 Another study looking at 35 women with MS who were exposed to NTZ during pregnancy found no significant differences in adverse outcomes when compared with the MS group not exposed.42 Preliminary data from the Tysabri Pregnancy Exposure Registry in 2011 suggest that the rate of spontaneous abortions and fetal abnormalities are similar to that expected in general US population, and are not associated with drug-related patterns.43 In addition, PIANO included six patients on NTZ and noted no increase in congenital abnormalities or abnormal infant development.44 There are no controlled studies of VDZ in pregnant women.45 Similarly to IFX and ADA, it is hypothesised that any adverse effect from VDZ would likely be greater during the second and third trimester of pregnancy, given the mechanism of transfer of IgG1 antibodies across the placenta.46 At the 2015 European Crohn’s and Colitis Organisation [ECCO] meeting, the first descriptive data from the VDZ clinical development programme were reported. Pregnancy outcome data were available on both VDZ-exposed IBD mothers

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**Figure 2** The neonatal Fc receptor of IgG [FcRn] is well characterised for the passive placental transfer of humoral immunity from mother to fetus. FcRn binds to the Fc portion of IgG. Infliximab [IFX], adalimumab [ADA] and golimumab [GOL] are anti-TNF IgG1 monoclonal antibodies which contain an Fc portion. Certolizumab is structurally different. It is a pegylated, univalent IgG4 and lacks an Fc portion, resulting in minimal placental transfer. Image adapted by permission from Macmillan Publishers Ltd: Roopenian DC, Akilesh S. FcRn: the neonatal Fc receptor comes of age. Nature Reviews Immunology 2007;7:715–25. Copyright (2007).
and VDZ-exposed partner pregnancies. A total of 47 pregnancies were observed from six clinical studies where either placebo or VDZ was administered. Of the 24 VDZ-exposed pregnancies, 11 resulted in live births of which 1 was premature. A congenital anomaly was seen in one out of the two healthy volunteers exposed to one dose of VDZ pre-conception [although it is reported that this patient had previous spontaneous abortions]. There were 16 VDZ-exposed partner pregnancies and of these there were 9 live births, 2 spontaneous abortions, 2 elective terminations, and 3 undocumentd outcomes.66 This is the first report of VDZ-exposed pregnancies documented in humans, but we are very limited in our ability to draw conclusions given that it is an observational study of multiple clinical trials in which patient groups may have varied in disease type, severity, frequency, and/or dosage of VDZ. We know from previous studies done on rabbits and monkeys exposed to VDZ doses 20 times that of preliminary observational data on humans suggest that perhaps VDZ exposure in pregnancy results in no increased risk of complications, further studies to confirm this are needed.

8. Drug Delivery in Breast Milk
In general, breastfeeding is recommended in all women, including those with IBD.48 Review of previous studies suggesting an increase in disease activity during breastfeeding showed that once medication use was accounted for, the results were not significant.57 Medications safe for use in breastfeeding include sulfasalazine, mesalamines, and steroids, although a few reports of diarrhea in infants exposed to aminosalicylates in utero exist.58,59,60 In general, thelalidomide, methotrexate, and cyclosporine are contraindicated in the lactation period because most are known teratogens and all show high drug concentrations when measured in breast milk.61 Even though a few studies have found that breastfeeding while on tacrolimus is safe, data are limited.53,62,63 In patients taking metronidazole, it is recommended to breastfeed 12-24 h after use of the medication.59,64 Information on thiopurines and lactation appears to be favourable, since several studies have observed undetectable levels of these medications in the breast milk.59,65,66 In addition, one study measuring levels of azathioprine in breast milk found that the highest levels are seen in the first 4 h after medication administration; therefore, it is reasonable to recommend to patients to breastfeed at least 4 h after medication is taken; see Table 1.54

Studies with anti-TNFs suggest similar favourable results. Physiologically it makes sense that anti-TNF levels in breast milk should be minimal since IgA is the primary immunoglobulin excreted in milk, not IgG [Figures 1 and 2].67 In addition, IFX is not absorbed after oral ingestion, and CZP studies appear to suggest the same. Studies quantifying levels of anti-TNF in breast milk demonstrate that drug levels are miniscule, especially if last administration dose is around week 30.54,61,62,68,69,70 Not surprisingly, preliminary results of PIANO presented in Digestive Disease Week in 2015 demonstrate that breastfed infants of mothers on biologics have similar rates of NEC, and/or dosage of VDZ. We know from previous studies done on rabbits and monkeys exposed to VDZ doses 20 times that of preliminary observational data on humans suggest that perhaps VDZ exposure in pregnancy results in no increased risk of complications, further studies to confirm this are needed.

9. Conclusions
The health of the mother is the most important factor in ensuring the best perinatal outcome for the infant; it is important to convey this when sharing the decision with the patient to discontinue medications.99,100,101 Many studies now suggest that the drugs used for IBD are low risk for use during pregnancy and even lactation. Studies of developmental outcomes up to 4 years of life are encouraging. It is unlikely that these medications will continue to have long-lived effects once cleared from the infant. Nevertheless, we await long-term immunological functional studies on infants born from mothers on anti-TNFs and thiopurines. The treatment provider must consider all the available evidence and, together with the obstetrician and the patient, decide the best treatment approach on an individual basis. These are discussions best had in advance of a pregnancy—not once a patient is pregnant.

Conflict of Interest
None to declare.

Author Contributions
OMD: concept and design of the study, acquisition of background literature, interpretation of data, drafting the article, tables and figures, and final approval of the version to be submitted. ARD: concept of the study, interpretation of data, revision of the article for critically important intellectual content, and final approval of the version to be submitted. DJA: acquisition of background literature, interpretation of data, drafting the article, and final approval of the version to be submitted. MTA: revision of the article, figures, and tables for critically important intellectual content, and final approval of the version to be submitted.

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