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Review Article

Pregnancy and Inflammatory Bowel Disease: A Special Combination

Viviana Parra Izquierdo[1], Carolina Pavez Ovalle[2], Valeria Costa[3], Ana María Leguízamo[3], Juan Sebastián Frías Ordoñez[4*], Albis Hani[3]

[1]Gastroenterology and Rheumatology, Fundación Cardiovascular-Hospital Internacional de Colombia, Bucaramanga, Colombia
[2]Gastroenterology, Pontifica Universidad Católica de Chile, Santiago, Chile
[3]Gastroenterology, Universidad Javeriana, Hospital Universitario San Ignacio, Bogotá, Colombia
[4]Gastroenterology, National University of Colombia, Bogotá, Colombia

Abstract

Inflammatory bowel disease (IBD) comprises a spectrum of chronic immune-mediated diseases that affect the gastrointestinal tract. Onset typically occurs in early adulthood. The incidence of this disease has increased worldwide. Its prevalence has increased in Colombia and occurs predominantly in women. Considering that this disease is not curable, the main objective of management is to achieve remission. Many women are affected by IBD during different stages of their lives, including their reproductive life, pregnancy, and menopause. Because of this, the way the disease is managed in women of reproductive age can affect the course of IBD. Treatment and health maintenance strategies are very relevant; for patients with a desire to conceive, remission of the disease is very important at the time of conception and throughout the pregnancy to ensure adequate outcomes for both mother and fetus. Also, remission is necessary at least 3 months prior to conception. It is well known that active disease during conception and pregnancy is associated with adverse outcomes. In addition, active perianal disease is an indication of cesarean delivery, resulting in an increased risk of intestinal surgery and post-operative complications.

Keywords: Inflammatory bowel disease, Pregnancy, Colitis, Ulcerative, Crohn disease, Fertility, Women

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Introduction

Inflammatory bowel disease (IBD) comprises a spectrum of chronic immune-mediated diseases that affect the gastrointestinal tract, with a peak incidence between the second and fourth decades of life.[1] The incidence of this disease has increased worldwide. In North America, it affects 2 million people, and 3.2 million in Europe. Western countries began to report stabilization of incidence and even sporadic decreases in some regions. Perhaps elevations in incidence are still being reported, and overall, it is ranging from 5 to 15 per 100 000 person-years for both Crohn's disease (CD) and ulcerative colitis (UC). Furthermore, the limit on the incidence of IBD seems to be 40 and 50 per 100 000 person-years. Considering that the disease is not curable, the main objective of management is to achieve remission.[2] In Colombia, there are two prevalence studies. In 2017, a prevalence of UC of 58.1/100 000 inhabitants per year, and of 8.9/100 000 for CD were reported, and an incidence of UC of 6.3/100 000 inhabitants per year, and of 0.74/100 000 for CD.[3] In 2020, another article on prevalence in Colombia was published, and 42 647 individuals were documented with a diagnosis of IBD, with an estimated prevalence of 87 cases per 100 000 inhabitants, most frequently in women (58% of cases), with a female/male ratio of 1.39:1. The prevalence of CD was 17 per 100 000 inhabitants, and of UC was 113 per 100 000 inhabitants.[4] However, it is a population in which information about clinical and therapeutic phenotypes is still not well known, and data about women are even scarcer.[5]

Women are affected by IBD during different stages of their lives, including reproductive life, pregnancy, and menopause, so the way the disease is managed in women of reproductive age can affect its course.[6] At least 50% of patients with IBD are diagnosed at age 35, and the disease most often affects women during their peak reproductive years.[7] Treatment and health maintenance strategies are very relevant. IBD poses a particular challenge during pregnancy because the health of the mother and fetus must be considered. For this reason, it is of utmost importance that the gastroenterologist and patients with IBD are aware of the effect of IBD on pregnancy, the effect of pregnancy on IBD, and the effect of IBD medications on the fetus and on pregnancy outcomes.[8] Taking into account the importance of the subject in daily clinical practice, it was decided to conduct the following review

*Corresponding Author: Juan Sebastián Frías Ordoñez, Email: jsfriaso@unal.edu.co

to demonstrate different aspects from preconception to postpartum in women with IBD.

Inflammatory Bowel Disease and Women's Reproductive Health

What Is the Effect of Inflammatory Bowel Disease on Fertility?

IBD occurs between 33.4 and 45 years of age, and it is vitally important to understand that infertility rates in women with non-active IBD are similar to those in the general population (8% to 10%).[9] Remission of the disease not only improves fertility rates but also, as most studies have shown, leads to more favorable pregnancy outcomes. Consequently, disease activity favors reduced fertility, probably in response to an inflammatory process and adhesions in the fallopian tubes or ovaries. Fear of infertility is common among patients with IBD and can negatively affect family planning decisions. Actually, women with inactive IBD and no previous pelvic surgery have similar infertility rates (5%–14%) to the general population. The active disease affects fertility, probably through multifactorial mechanisms, such as pelvic inflammation, malnutrition, decreased libido, dyspareunia, and depression. One small study showed decreased ovarian reserve in women with CD, especially those with active disease. Pelvic surgery significantly increases female infertility due to scars and adhesions.[10]

Surgery to control active IBD has a greater beneficial effect on fertility than uncontrolled disease. For the minority of women who require colectomy for UC and open ileal pouch, anal anastomosis surgery is associated with a two to three-fold increase in the rate of infertility. This is believed to be related to the pelvic adhesions; as described above, the open pouch surgery causes reduced motility and patency of the fallopian tubes. However, the new approach of laparoscopic pouch surgery is associated with lower infertility rates. Therefore, a minimally invasive approach to pouch surgery is preferable. In vitro fertilization success rates are similar for women after pouch surgery than for women without a history of IBD and surgery. Early referral to a fertility specialist should be considered for patients with ileal pouch-anal anastomosis surgery.[11-13]

It is clear that women who are affected by IBD and who are considering pregnancy often discontinue their treatment without informing their doctors. Studies in the Netherlands have shown that a systematic program of prior information with counseling prior to pregnancy improves the birth rate and reduces the risk of relapse of IBD during pregnancy.[12] Most medical treatments for IBD have no effect on the patient's ability to conceive. However, sulfasalazine is an exception, as it increases the risk of infertility in men by altering sperm counts, reducing sperm motility, and increasing the proportion of abnormal forms. A switch to 5-aminosalicylic acid (mesalazine) generally restores fertility and spermogram abnormalities. There is still some debate about the effects of thiopurines on fertility, but it is sometimes associated with impaired sperm motility.[14] Methotrexate may be responsible for oligospermia and is reversible when it is discontinued. This drug is contraindicated for both women and men because it is teratogenic. It appears that corticosteroids and cyclosporine have no effect on fertility. However, there is some debate about the effect of infliximab on fertility. In a small series of 10 patients with IBD, a trend toward decreased sperm motility with infliximab therapy was reported.[15] Data on the impact of adalimumab, vedolizumab, and ustekinumab on human fertility are insufficient.

The first step to treating infertility is to provide accurate counseling to positively impact preconception care. The optimization of nutritional status, vitamin supplementation (vitamin D and zinc), and the cessation of tobacco and alcohol are necessary. Overall, control of disease activity should be obtained and maintained. IBD couples facing infertility should be referred to specialized gynecology centers. However, the medical literature is scarce on infertility treatment in patients with IBD.[16,17]

What Is the Effect of Inflammatory Bowel Disease on Pregnancy?

Patients with active IBD, either CD or UC, have worse pregnancy outcomes compared with healthy women.[18] Studies have also shown that there is a greater chance of worse pregnancy outcomes in patients with CD than in patients with UC.

According to a review conducted by Subhani and Hamilton in 1998,[19] CD, especially when it is active, is associated with low birth weight (LBW), preterm birth, and cesarean section. Furthermore, it is evident that in patients with IBD, induction of labor (32% vs. 24%, $P=0.002$), chorioamnionitis (7% vs. 3%, $P=0.04$) and cesarean section (32% vs. 22%) are more frequent than in the general population. Neonatal complications include low birth weight, intrauterine growth restriction, low Apgar scores, and congenital anomalies, which are similarly found between populations with and without IBD.[20] There are no studies reporting a higher probability of fetal malformation in these patients. Although there may be multiple factors associated with fetal malformation, it should be noted that the product of the first gestation (fetal death) was related to the debut of inflammatory disease with the morphological alterations described. This invites us to reflect on this issue, and although there is no clear evidence in this regard, it does mean that prenatal follow-up of these patients should be much closer.

Another study of 461 pregnant patients with IBD showed that these patients were at increased risk of spontaneous abortion, eclampsia, pre-eclampsia, placenta previa, abruptio placentae, and premature rupture of membranes. In this study, disease activity was not associated with a worse outcome. However, a diagnosis of IBD, a history of intestinal surgery for IBD, and not being white were found to be independent predictors of worse

outcomes.[21]

These results support current treatment guidelines, which indicate that maintaining remission during pregnancy is vital. It is important to know that the risk in this type of patient could be similar to that of the general population if their disease is controlled at the beginning of pregnancy.

What Is the Effect of Pregnancy on Inflammatory Bowel Disease?

As stated earlier, many known chronic diseases can have active bouts during pregnancy. Moreover, about 30%-40% of women have active IBD during conception with an intense flare-up and adverse outcomes like spontaneous abortions, preterm and LBW (<2500 g regardless of gestational age), ischemic placental disease, stillbirth, and cesarean delivery. There is evidence that the disease activity is more detrimental to gestation and, consequently, to the fetus than medical therapy itself. Hence, as a first recommendation, the patient must be in disease remission at conception, favoring a pregnancy with lower risks of gestational adversities (Figure 1). Most of the conditions are associated with the maternal milieu and depressed nutrient delivery to the growing fetus.[22]

About 80% of women with IBD who become pregnant when the disease is in remission tend to be in remission in the intrapartum and postpartum periods.[23] It is reported that about 66% of patients who become pregnant when the disease is active continue to have disease activity or worsening of their symptoms.

Comparatively, it is described that in up to 45% of patients diagnosed with UC who conceive while their disease is active, the disease worsens during pregnancy, and in about 30% of patients with CD who conceive while their disease is active, the disease worsens during pregnancy.[22]

A prospective study found that the rates of disease exacerbation were similar in pregnant patients with CD while their disease was in remission and in non-pregnant patients with CD. On the other hand, relapse rates were higher in pregnant women with CD who conceived while their disease was active than in non-pregnant patients with CD (50% vs. 33%, respectively). Patients with UC who were pregnant had a higher risk of disease exacerbation in the intrapartum and postpartum period compared with controls, and exacerbations of disease were found to be more frequent in the first 6 months of pregnancy and in the first 3 months of the postpartum period.[24]

It should, therefore, be clear that disease activity at the time of conception helps to predict the course of the disease during pregnancy. Ideally, women should be in remission at the time of conception (Figure 1).

How Do the Drugs Used to Manage Inflammatory Bowel Disease Affect Fertility?

There are no data on the effect of drugs on female fertility. However, it is worth mentioning that the use of immunosuppressants such as methotrexate has a clear association with teratogenicity, and they are totally contraindicated in patients who wish to conceive.

The use of sulfasalazine has been described to cause a reversible reduction in sperm motility, an effect related to the dose of the drug.[25] Methotrexate promotes the presence of oligospermia, which may improve over time when the drug is discontinued.[26] Infliximab appears to affect semen quality by reducing sperm motility.[15] There

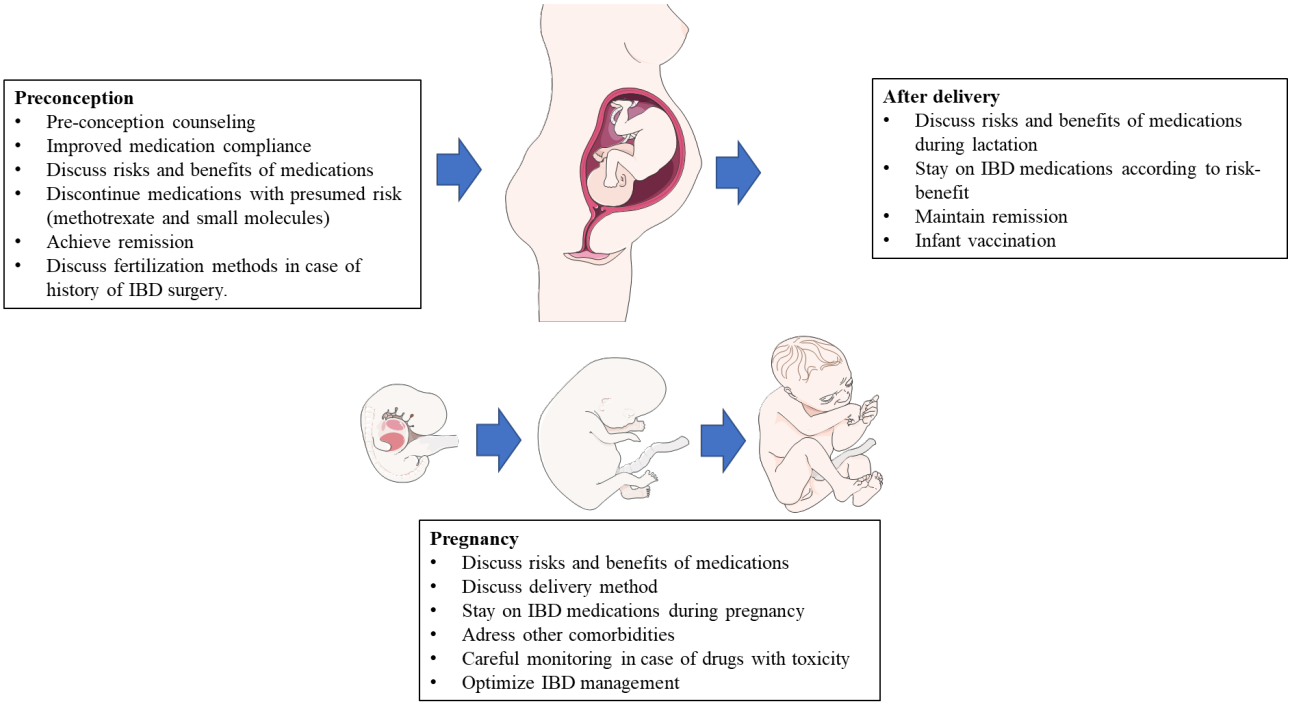

Figure 1. Preconception counseling and care during the different stages of gestation in women with inflammatory bowel disease. Source: Scheme made using images from Servier Medical Art, under their own conditions of use

are no conclusive results with regard to the possible effects of thiopurines on sperm quality.[14,27]

IBD is often diagnosed in the reproductive years and is most often diagnosed before the first pregnancy. Relapse of IBD during conception and pregnancy has been associated with a negative pregnancy outcome. Therefore, intensive preconception and pregnancy care is of utmost importance (Figure 1), and current guidelines advise maintaining medications such as tumor necrosis factor-alpha (anti-TNFα) to prevent relapses (Table 1). Most IBD medications are considered to be low risk during pregnancy, as no increase in congenital malformations has been reported (Table 1). However, the effects on the developing immune system, especially of drugs transferred through the placenta, are unknown, as most published cohorts are small and retrospective.[28]

Preconception counseling has been associated with improved medication compliance and reduced relapses during pregnancy, and it is important in optimizing disease management. The authors of this article recommend that all gastroenterologists discuss with their patients of reproductive age the risks and benefits of medications before conception, during pregnancy, and during lactation (Figure 1). The goal of treatment in patients with IBD is remission. If clinical remission is achieved during pregnancy, it is likely to be maintained throughout the rest of the pregnancy, thus reducing risks to the fetus.[29]

According to the recommendations of the management guidelines for IBD and pregnancy, women who need drug treatment to maintain remission should continue treatment during pregnancy, considering that methotrexate should be discontinued before conception and during pregnancy (Table 1). Also, if during the pregnancy, there is an exacerbation of the disease, the treatment must be aggressive. Regarding the drugs to be used, we will describe the following:

Aminosalicylates and sulfasalazine. They are generally considered safe. A cohort study conducted in Denmark found an increased risk of premature birth and fetal death in women who received aminosalicylates during pregnancy. However, that study did not distinguish between the effects of disease activity and the use of aminosalicylates.[30] In other studies, no significant association was found between aminosalicylates and adverse effects during pregnancy.[31] Sulfasalazine is known to inhibit folate synthesis, so women using this drug should be supplemented with folic acid to reduce adverse effects on the neural tube.[32]

In summary, aminosalicylates and sulfasalazine can be used without limitation during pregnancy. They are not associated with significant adverse outcomes during pregnancy.

Thiopurines (azathioprine): This drug has been shown to reach fetal serum levels as high as 5% of the maternal drug level. The results of human studies on the safety of using azathioprine during pregnancy have been discordant. However, it is recommended to continue this medication in order to keep the disease in remission during pregnancy. Recent studies have shown that the use of azathioprine does not increase the risk to the fetus, and in turn, it is safe to continue the medication during pregnancy.[33] It is considered that the activity of the disease in exchange for the use of the medicine may favor greater effects on the fetus. Therefore, in view of the current information, its continuation is safe; also, it

Table 1. Recommendations on medications to be used during pregnancy and lactation

Medication	Recommendation in pregnancy	Recommendation in lactation
Corticosteroids	Potentially toxic Use with caution throughout pregnancy. Increased risk of preterm birth, low birth weight, and neonatal intensive care unit admission.	Potentially toxic Use with caution throughout lactation. Pass into breast milk.
Aminosalicylates	Low risk Safe to continue Increase folate supplementation with sulfasalazine use.	Mesalazine is preferred Avoid sulfasalazine
Antibiotics		
Metronidazole	Low risk Not recommended during the first trimester	Low risk Low levels are detected in breast milk.
Ciprofloxacin	Potentially toxic Crosses the placenta	Low risk Low levels are detected in breast milk.
Penicillins	Low risk First line therapy	Low risk First line therapy
Immunomodulators		
Cyclosporine	Potentially toxic Consider risk-benefit Crosses de the placenta Use with caution	Avoid during lactation Present in breast milk.
Methotrexate	High risk Contraindicated Discontinue 3-6 months before attempting pregnancy.	High risk Avoid during lactation
Thiopurines	Low risk Safe to continue Avoid new starts	Low risk Safe to continue
Biologics		
Adalimumab	Low risk Safe to continue	Low risk Safe to continue
Certolizumab	Low risk Safe to continue	Low risk Safe to continue
Golimumab	Low risk Safe to continue	Low risk Safe to continue
Infliximab	Low risk Safe to continue	Low risk Safe to continue
Natalizumab	Low risk Safe to continue	Low risk Safe to continue
Ustekinumab	Low risk Safe to continue	Low risk Safe to continue
Vedolizumab	Low risk Safe to continue	Low risk Safe to continue
Small molecules		
Tofacitinib	Presumably crosses the placental barrier. Discontinue 1 month before attempting pregnancy.	Avoid (limited data)

is recommended to avoid starting this medication during pregnancy.

Methotrexate: It is well known that methotrexate is teratogenic and abortive, so it is contraindicated during conception and pregnancy. The use of methotrexate between weeks 6-8 of pregnancy may lead to congenital anomalies, and its use in the second and third trimesters may lead to abortions. In addition, it is considered that methotrexate should be discontinued 3-6 months before attempting pregnancy since the drug remains active for some time in the tissues.[32]

Corticosteroids: Glucocorticoids are known to cross the placenta and may reach the fetus, but it should be noted that placental enzymes convert corticosteroids to fewer active metabolites. This type of medication is often used to treat episodes of IBD activity, and conflicting results have been found in pregnancy. Recently, in a prospective registry, a statistically significant association was found for increased risk of preterm birth (< 37 weeks) (OR: 1.79, 95% CI: 1.18-2.73), LBW (OR: 1.76, 95% CI: 1.07-2.88) and neonatal intensive care unit admission (OR: 1.54, 95% CI: 1.03-2.30).[34] Also, there is an increase in reports of association between orofacial cleft in newborns and the use of these drugs in the first trimester of pregnancy.[35]

There is little data on the exact dose of corticosteroids that induce toxicity to the mother and fetus. Therefore, these should be administered with caution, following the criteria of the treating physician. Extrapolated studies on other autoimmune diseases have documented that the use of corticosteroids can promote preterm birth and LBW.

Antibiotics: Metronidazole and ciprofloxacin are used with some frequency in IBD to treat abscesses and fistulas. Low levels of both drugs are detected in breast milk. A study of women with IBD who required the use of metronidazole during pregnancy found that it was safe in all trimesters. However, it is recommended not to use it during the first trimester.[36] As for ciprofloxacin, studies have not reported a significant increase in major congenital anomalies, including musculoskeletal problems, but, in view of the risk of congenital arthropathy, it is recommended not to use it during pregnancy.[37] As for penicillins, they have not been shown to cause fetal malformations or adverse pregnancy outcomes, and are considered the first line therapy in pregnancy.

Cyclosporine: This drug crosses the placenta, but no teratogenicity has been found in animal models. Studies with this drug have been conducted in connection with kidney transplantation, and a relationship with LBW and preterm delivery is suggested. Similarly, cyclosporine has been used in severe relapses of UC during pregnancy, with favorable responses. It has reduced the need for colectomy and has had no significant adverse effects. The most frequently reported side effect is hypertrichosis in the mother. Other adverse effects, such as nephrotoxicity and hepatotoxicity, have also been described.[38] Therefore, the use of cyclosporine may be considered in patients with fulminant UC during pregnancy.

Biological agents and small molecules: These drugs include anti-TNFs such as infliximab, adalimumab, certolizumab, golimumab, anti-integrin such as vedolizumab, anti-IL-12/23 such as ustekinumab, and small molecules such as tofacitinib.[39] These are used for the management of moderate to severe IBD and fistulizing-stenosing CD.[40] TNF levels increase during pregnancy as it is produced mainly by the placenta. It is important in the early stages of pregnancy and also for the development of the fetal immune system.

Observational studies and systematic reviews have demonstrated its safety during pregnancy.[41] In relation to infliximab and adalimumab it should be noted that they are monoclonal IgG1 antibodies and cross the placenta, while certolizumab is a Fab fragment of IgG1 that has no transplacental transport.[42] Because of this, it has been recommended not to use infliximab and adalimumab from the second trimester of pregnancy. Other groups recommend continuing biological therapy throughout pregnancy, especially in high-risk patients and patients with disease activity, and only recommend stopping it if the mother wishes to do so.[43] In case of considering suspending biological therapy to decrease fetal exposure, it is recommended to suspend administration between the 22nd and 26th week of gestation.

No increase in the rates of spontaneous abortion, fetal death, congenital malformations, or preterm delivery has been observed among pregnant women exposed to adalimumab or golimumab.[44] In turn, anti-TNFs do not increase the risk of complications during pregnancy compared to thiopurines and the non-use of medications.

Infliximab and adalimumab levels have been detected in infants up to 12 months postpartum.[45] Infections and allergic reactions have not increased, nor has the response to vaccinations decreased, but an increase in infections has been observed among infants between 9 and 12 months of age exposed to the combination of immunomodulators and biological agents.[46]

Anti-integrin: The first one to be used was a humanized monoclonal IgG4 antibody that acts against the adhesion molecule α4-integrin, but there is little data on the use of this drug during pregnancy. The review of natalizumab's overall safety database showed no increase in birth defects in children whose mothers were exposed to natalizumab during pregnancy. In its extrapolation to other diseases, multiple sclerosis is described in the pregnancy outcomes of 35 patients who accidentally became pregnant while being treated with natalizumab. Of these patients, 29 had viable pregnancies, 28 had children without alterations, and one child was born with hexadactyly. Of the remaining six patients, one decided to have an abortion, and the other 5 had early abortions.[46]

Vedolizumab (VDZ) is an IgG1 monoclonal antibody approved for the treatment of UC and CD. VDZ acts on α4β7 integrin, which is selective in blocking intestinal lymphocyte transport and thus avoids many undesirable systemic effects. Mahadevan and colleagues analyzed

data from six initial VDZ clinical trials involving 27 pregnancies with exposure during pregnancy, showing no adverse effect on pregnancy outcomes.[47] In a more recent retrospective observational study, Moens and others identified 23 pregnancies in patients exposed to VDZ, including three patients who continued on VDZ throughout the pregnancy. This study described 18 live births, including two congenital abnormalities, as well as one case of intrauterine growth retardation and two cases of premature rupture of membranes and five pregnancies still in progress at the time of the study.[48] Given the number of congenital abnormalities and complications among the small number of identified pregnancies, further research is needed to determine the safety of VDZ during pregnancy and for the strict monitoring of any pregnant woman receiving VDZ. The conclusion of the study by Moen and colleagues shows that this is the largest cohort study reporting on pregnancy outcomes in patients treated with VDZ.[48] Although the number of pregnancies remains low and no guidelines are available, these results support the fact that VDZ should only be used in pregnancy if the benefits to the mother outweigh the potential risks to the mother and fetus. Meanwhile, strict surveillance and monitoring of pregnant patients with IBD treated with VDZ are guaranteed. Prospective studies are needed, not only on the outcomes of pregnancy with VDZ, but also on the minimum levels of VDZ in the mother and the newborn. Therefore, although there is less evidence on the use of anti-integrins in pregnancy, it can be suggested that they may be safe.[6]

Anti-IL12/23 (Ustekinumab): An all-human type IgG1 monoclonal antibody. It binds to the IL-12 and IL-23 via the p40 subunit in both cytokines, thus blocking the inflammatory cascade these cytokines trigger. It is used for the treatment of CD and UC. The safety of continuous ustekinumab (UST) treatment in patients with IBD during pregnancy is unclear. No reports of meta-analyses of UST exposure during pregnancy is available. One study described a case report of a pregnant patient with CD who was successfully treated with UST maintenance therapy throughout pregnancy and delivered a baby without congenital malformations, neurological abnormalities, or birth defects and with the maintenance of clinical, biological, and endoscopic remission of CD during and after pregnancy.[49] Mahadevan and colleagues suggest that in pregnant patients with IBD it is recommended to adjust the dose weeks before pregnancy according to the estimated date of delivery.[50] However, it is important to note that IL-12 is an important cytokine in uterine angiogenesis and vascular remodeling. IL-12 depletion has a potential role in implantation failure after in vitro fertilization.[3] There is even a report of an abortion using this molecule.[51,52] The literature on rheumatology reports the use of ustekinumab during pregnancy in a total of 176 patients, mainly in psoriasis and psoriatic arthritis.[53] However, more studies are needed to assess the safety and vulnerability of the fetus during pregnancy and lactation.

Small molecules (Tofacitinib): This is an oral Janus kinase inhibitor used for the treatment of UC. Since it is a small molecule, tofacitinib is likely to cross the placental barrier. However, information on the effects of tofacitinib on pregnancy outcomes is limited. There is a study that reported pregnancy and newborn outcomes among patients in UC clinical trials with prenatal (maternal/paternal) exposure to tofacitinib. Of 1157 patients enrolled in the UC interventional studies, 301 were women of childbearing age. Eleven cases of maternal exposure and 14 cases of paternal exposure to tofacitinib (doses of 5 mg or 10 mg twice daily) before/at the time of conception or during pregnancy were identified. Outcomes included 15 healthy newborns, no fetal deaths, no neonatal deaths, no congenital malformations, two spontaneous abortions, and two medical terminations. Outcomes across other tofacitinib studies and post-marketing cases were consistent, with a healthy newborn being the most common outcome and no fetal deaths. However, the results are limited, and more studies are needed to evaluate the safety of this molecule during pregnancy and lactation.[54]

What Should Be the Type of delivery in Pregnant Women with Inflammatory Bowel Disease?

In the context of pregnancy and IBD, it should be borne in mind that delivery should be managed in a multidisciplinary manner by the obstetrician, the gastroenterologist, and the coloproctologist.

In the presence of active perianal disease, rectovaginal involvement, or surgical history of ileoanal reservoir or ileorectal anastomosis secondary to IBD, cesarean delivery is indicated. It has been shown that vaginal delivery with episiotomy may be associated with increased risk of perianal involvement.[55] Another point to be highlighted is that patients with IBD without perianal involvement have vaginal delivery indicated, with all the benefits it brings to the newborn. Studies report and suggest that cesarean delivery is a risk factor for the development and exacerbation of IBD. Multidisciplinary management is essential for the comprehensive management of this difficult pathology.[56]

What Should Be Considered During Lactation?

Lactation may be associated with increased inflammation, as prolactin is associated with increased TNF production. However, one study found no increase in the rate of disease relapse in the first year postpartum among women who breastfed (26%) and those who did not (29.4%).[57] Some studies have found that infants breastfed by mothers on biological drugs, immunomodulators, or combination therapies have similar risks of infection compared to non-breastfed infants or those not exposed to these drugs.[58]

Regarding the use of medication during breastfeeding (Table 1), it should be noted that:

1. Aminosalicylates and sulfasalazine can be continued during lactation, bearing in mind that

aminosalicylates can cause osmotic diarrhea and that sulfasalazine can cause jaundice. However, drug concentrations in breast milk are low.
2. Azathioprine can be continued during lactation. Low concentrations of azathioprine have been detected in breast milk; higher concentrations of the drug have been found during the first 4 hours after taking it, so it is recommended to discard the milk obtained in that period of time.
3. Given its teratogenic potential, methotrexate is contraindicated during lactation.
4. Corticosteroids are found in low concentrations in breast milk, with moderately high levels found in the first 4 hours after taking the drug. Because of this, it is recommended that milk obtained during this time interval be discarded to reduce the risk of transfer to the infant.
5. Biological agents can be continued during pregnancy. Minimal concentrations of infliximab and adalimumab have been found in breast milk, and no significant adverse events have been reported in infants. Detectable levels in the newborn after birth are considered to be related to placental transfer during pregnancy. Furthermore, no association has been found between breastfeeding and the risk of infection in newborns exposed to biological agents.[45]

How Should Babies Be Vaccinated?

Vaccination with non-living virus vaccines in newborns exposed to anti-TNF in utero is not different from vaccination in unexposed infants, and they have an adequate response to vaccination. Regarding live virus vaccines, such as rotavirus, oral polio, and BCG, they should be given when anti-TNF levels are not detectable. For this reason, newborns should not receive live vaccines during the first 6 months of life, so it is recommended that anti-TNF be discontinued at the 33rd week of pregnancy; in this way it is possible to reach the time of delivery with undetectable levels of anti-TNF, which allows the newborn's vaccination schedule not to be affected.

And What About the Infants of Women Who Use Non-anti-TNF Biologicals or Small Molecule Agents?

The vaccination in infants of women with the use of non-anti-TNF biologicals or small molecule agents is still a matter of uncertainty. In this specific setting, the evidence is much scarcer. However, the dearth of reported adverse events in exposed infants does not mean that there is no risk of harm, and each case must be individualized depending on the characteristics of the drug exposure, concomitant maternal immunosuppressive therapy, and potential postnatal exposures to infectious diseases. So, it is recommended that vaccination with non-living virus vaccines does not differ from unexposed infants, while live vaccines should not be given until they reach the age of 6 months.

Conclusion

The medical team involved in the follow-up of patients with IBD must know how to deal with and be clear about the preconceptual, conceptual, and postpartum management of these patients since multiple factors must be considered, such as the control of the disease during the fertile period, in order to achieve a successful pregnancy. They must also be clear about the use of the medications during the different stages of childbearing age, which will create peace of mind for both the treating physician and the patient. Therefore, such awareness of appropriate education increases the likelihood that physicians will follow best practice guidelines in the management of pregnant patients with IBD.

Authors' Contribution

Conceptualization: Viviana Parra Izquierdo, Carolina Pavez Ovalle, Valeria Costa, Ana María Leguízamo, Albis Hani.
Data curation: Viviana Parra Izquierdo, Carolina Pavez Ovalle, Valeria Costa, Ana María Leguízamo, Albis Hani
Formal analysis: Viviana Parra Izquierdo, Carolina Pavez Ovalle, Valeria Costa, Ana María Leguízamo, Albis Hani.
Funding acquisition: Viviana Parra Izquierdo, Carolina Pavez Ovalle, Valeria Costa, Ana María Leguízamo, Albis Hani.
Investigation: Viviana Parra Izquierdo, Carolina Pavez Ovalle, Valeria Costa, Ana María Leguízamo, Albis Hani, Juan Sebastián Frías Ordoñez.
Methodology: Viviana Parra Izquierdo, Carolina Pavez Ovalle, Valeria Costa, Ana María Leguízamo, Albis Hani.
Project administration: Viviana Parra Izquierdo.
Resources: Viviana Parra Izquierdo, Carolina Pavez Ovalle, Valeria Costa, Ana María Leguízamo, Albis Hani.
Software: Viviana Parra Izquierdo, Carolina Pavez Ovalle, Valeria Costa, Ana María Leguízamo, Albis Hani.
Validation: Viviana Parra Izquierdo, Carolina Pavez Ovalle, Valeria Costa, Ana María Leguízamo, Albis Hani, Juan Sebastián Frías Ordoñez.
Visualization: Juan Sebastián Frías Ordoñez.
Writing–original draft: Viviana Parra Izquierdo, Carolina Pavez Ovalle, Valeria Costa, Ana María Leguízamo, Albis Hani, Juan Sebastián Frías Ordoñez.
Writing–review & editing: Viviana Parra Izquierdo, Carolina Pavez Ovalle, Valeria Costa, Ana María Leguízamo, Albis Hani, Juan Sebastián Frías Ordoñez.

Competing Interests

The authors declare no conflict of interest related to this work.

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The data and material available for publication are in the manuscript, and no information is omitted.

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