REVIEW ARTICLE

FERTILITY AND PREGNANCY IN INFLAMMATORY BOWEL DISEASE

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Abstract

Inflammatory bowel disease (IBD) is a chronic condition that includes Crohn's disease (CD) and ulcerative colitis (UC). Both conditions can impact patients' quality of life, particularly during their reproductive years. The influence of IBD on fertility and pregnancy has been widely studied, emphasizing the importance of proper management to minimize maternal-fetal risks and optimize reproductive outcomes.

The aim of this review is to understand the impact of IBD on fertility, pregnancy, and perinatal outcomes, as well as to explore recommended management strategies to ensure adequate clinical follow-up in accordance with clinical guidelines and the most up-to-date literature on these topics.

Fertility in women with IBD is comparable to that of the general population, although it may be reduced in cases of active disease, a history of abdominal surgery, or psychological factors. IBD activity during pregnancy is associated with increased obstetric complications, making preconception planning and continuous medical monitoring essential.

Most IBD treatments are considered safe during pregnancy and breastfeeding, except for certain medications such as methotrexate, JAK inhibitors, and sphingosine-1-phosphate inhibitors. Regarding delivery, cesarean section is recommended only in specific cases, such as active perianal disease or the presence of an ileoanal reservoir. Lastly, breastfeeding is encouraged whenever possible, and vaccination schedules for neonates exposed to immunosuppressants should be adjusted accordingly.

Keywords: fertility, pregnancy, Inflammatory Bowel Disease, breastfeeding.

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Introduction

IBD is a chronic pathology of autoimmune nature that affects the gastrointestinal tract, whose incidence is increasing like the rest of the immune-mediated diseases, and can occur in different periods of life of the patients. There is a peak at childbearing age, at 29 years of age in CD and at 39 years of age in UC. Since IBD affects patients in their reproductive stage, its impact on fertility, pregnancy and quality of life is a fundamental aspect to consider, and it is essential that patients are adequately informed about the disease and its treatments in order to optimize family planning, minimizing the risks for both mother and fetus[1].

Fertility in women with IBD is comparable to that of the general population; however, a lower birth rate is observed in this population. Fertility remains stable when the disease is inactive and in patients with no history of previous surgery, but disease activity can reduce fertility due to inflammation of the fallopian tubes, metabolic alterations and oxidative stress that negatively impacts hormone levels, which can decrease ovarian reserve due to a decrease in anti-Müllerian hormone and cause dyspareunia, making conception difficult. Active disease is associated with an increased risk of adverse effects during pregnancy, especially in the first trimester, underscoring the importance of close preconception and gestational surveillance. Other factors that may also play a role are toxic habits, the use of certain drugs, e.g. sulfasalazine which can cause reversible oligospermia and asthenozoospermia in males. Treatments with teratogenic risk should be suspended prior to conception in women, although they do not affect fertility in men, although it is recommended to evaluate fertility in men who plan to conceive and are on prolonged treatment[1,2].

Pregnancy in patients with IBD is associated with an increased risk of complications, such as gestational diabetes, fetal death, premature delivery, premature rupture of membranes, and low birth weight. Patients should be informed about the inherited risk, which is up to 8 times higher in CD and 4 times higher in UC, with a possible predisposition associated with female sex in the case of CD[3]. Patients with IBD have high rates of sexual dysfunction due to corticosteroid side effects, perianal disease and intimacy problems, affecting up to 40% of sexual intercourse.

Pelvic surgeries related to IBD may decrease fertility and conception rate in women, although the laparoscopic approach seems to reduce this risk. Rectal preservation in patients undergoing surgery has been described to be recommended to reduce the risk of sexual and ejaculatory dysfunction[4]. Because these surgeries may reduce the success rate in assisted reproductive treatments, sperm preservation is recommended in some cases before certain interventions[1].

Other factors that may reduce fertility include depression and nutritional deficiencies. In addition to voluntary factors such as the decision not to have children due to misinformation about the disease, treatments and the possibility of genetic inheritance, being more frequent in patients with Crohn's disease than with ulcerative colitis, with rates reported between 17% and 38%. Proper planning and close medical follow-up are essential to ensure the best possible reproductive health in these patients[2].

Pregestational phase

Pregnancy follow-up in patients with IBD begins with a preconception evaluation to ensure that the disease is in stable remission for at least 3 to 6 months before conception, thus reducing the risk of complications. Family planning and preconception counseling are essential, as they address questions about fertility, treatments, and possible complications. Factors such as misinformation, fear of intimacy, depression and surgical sequelae such as colectomy can affect reproductive capacity and quality of life, so it is crucial to provide adequate medical guidance to improve decision making and reduce anxiety.

Before pregnancy, it is recommended to evaluate disease activity by means of biomarkers such as CRP, hemoglobin and fecal calprotectin, the latter being the most specific during gestation, since the rest may vary due to the biological process of gestation itself. As for pre-pregnancy diagnostic tests, the same as in the general population can be used. The ideal scenario for management would be referral of all patients to tertiary centers with multidisciplinary teams including gynecologists, gastroenterologists, and IBD surgeons[1,4].

To optimize maternal health before conception, it is recommended to evaluate the nutritional status and correct vitamin deficiencies, to update the vaccination avoiding alive virus if there is immunosuppression and to encourage the abandonment of toxic habits such as tobacco, alcohol and recreational drugs. As for treatment, it will be evaluated below, but teratogenic drugs such as methotrexate, JAK inhibitors (JAKi) and ozanimod should be discontinued, the continuity of biologic therapy should be evaluated, and folic acid should be administered in patients with sulfasalazine. Reproductive counseling should also address possible disease transmission, contraceptive use and plan joint follow-up with gastroenterology and obstetrics. To achieve an uncomplicated pregnancy, it is essential to tailor treatment according to

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Pregestational phase	Recommendations
Preconception evaluation	Determine disease **activity** and look for clinical remission. Screen for **anemia, vitamin deficiencies and nutritional** status. Update vaccination, avoiding live virus vaccines if immunosuppression is present. Encourage cessation of tobacco, alcohol and recreational drugs.
Optimization of treatment	Suspend **teratogenic** drugs (methotrexate, JAK inhibitors, ozanimod). Evaluate the need to **continue biologic therapy**. Administer **folic acid** (2 mg/day in case of sulfasalazine use).
Reproductive counseling	Inform about possible disease **transmission**. Address fertility **concerns** and contraceptive use. Plan **multidisciplinary** follow-up with gastroenterology and obstetrics.

Table 1. ***Recommendations to be followed in the pregestational phase.***

need, optimize nutritional status, and ensure stable clinical remission[3].

Gestational stage

The main goal is to keep IBD in remission to minimize maternal and fetal risks. This requires close follow-up with gastroenterology and obstetrics, with periodic controls based on biomarkers such as fecal calprotectin, which has been shown to be an indicator of disease activity in pregnant women. In addition, evaluation with intestinal ultrasound is recommended to avoid invasive techniques. Monitoring should also include control of nutritional status and maternal weight to ensure adequate fetal development[1,3].

For the assessment of disease activity, fetal-safe imaging tools are recommended. Ultrasonography is the technique of choice, especially useful in the 20th week of gestation. MRI is a viable alternative as long as gadolinium is not used, due to the lack of conclusive studies on its fetal safety. Endoscopy is safe, but should be reserved for strictly necessary cases, given the risk of bronchoaspiration and impairment of maternal-fetal oxygenation; in these cases, it is recommended that sedation be administered by an obstetrical anesthesiologist. On the contrary, computed tomography, radiographs and any test with radiation are contraindicated, as well as capsule endoscopy, since there is insufficient data to support their safety during gestation[1].

Gestational stage	Recommendations
Evaluate withdrawal/ maintenance of treatment	Assess the need to **continue, adjust or discontinue** medications according to disease status and fetal safety.
Establish a delivery plan and route of delivery	Define whether delivery will be **vaginal or cesarean** based on disease activity and patient's clinical history.
Monitor adequate weight gain	Ensure adequate **weight** gain and monitor maternal **nutrition** to avoid fetal complications.
Monitor possible adverse effects on the fetus	Identify possible **adverse effects on fetal development** and adjust treatment if necessary.
Assess maintenance of treatment during breastfeeding	Review the compatibility of medications with **breastfeeding** and decide on continuation of **treatment**.
Safety of vaccines in the infant	Ensure that **vaccines** are safe for the **newborn** and avoid live virus vaccines in neonates exposed to immunosuppressants.
Management plan with the family physician and obstetrician	Maintain a **comprehensive follow-up** plan with specialist physicians to optimize disease management during pregnancy..

Table 2. ***Recommendations to follow in the gestational phase.***

Pharmacological treatment

The pharmacological management of IBD during pregnancy requires careful evaluation of the risks and benefits of each treatment. Most drugs used for IBD are safe during pregnancy, but some require special precautions. Maintaining disease remission has been shown to reduce maternal and fetal risks, so continued appropriate treatment is recommended. Among the most commonly used drugs are aminosalicylates, corticosteroids, tumor necrosis factor alpha inhibitors (anti-TNF) and immunomodulators such as thiopurines. Methotrexate, JAKi, ozanimod are recommended to be avoided due to their teratogenic effects and lack of data in humans[3].

Aminosalicylates

Aminosalicylic acid derivatives reach very low levels in the fetal circulation due to their limited transplacental transfer and rapid renal elimination, making them safe drugs during pregnancy. Sulfasalazine, although it crosses the placenta and interferes with folic acid absorption, has not been associated with teratogenic or embryogenic effects. To minimize risks, its use accompanied by folic acid supplementation at high doses (2 g/day) is recommended during conception and gestation, in order to prevent neural tube defects[3,5].

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Corticosteroids

Corticosteroids are widely used drugs in the treatment of IBD, although they cross the placenta and may affect the fetus. Prednisolone, however, has a lower placental transfer capacity, so it is considered the first-line option if the use of corticosteroids is necessary during pregnancy. Despite their usefulness, they have limitations, as their administration in the first trimester has been associated with an increased risk of orofacial malformations, while their use in late pregnancy could lead to suppression of the neonatal adrenal axis, associated with an increased risk of hypertension, gestational diabetes and preeclampsia. Nevertheless, they are still considered relatively safe and their use is approved when the clinical situation requires it, always using the lowest possible dose and for the shortest time necessary to minimize risks[5].

Immunosuppressants

Regarding the use of immunosuppressants in pregnancy, thiopurines (azathioprine, 6-MP) have shown congenital anomalies in animal studies, but they have not been shown to increase the risk of malformations in humans, so they are considered safe throughout pregnancy, although their initiation in pregnancy is not recommended due to their late effect[1]. However, it is important to consider that, in patients with IBD who are not pregnant, discontinuation of thiopurine in combination therapy does not carry a significant risk of relapse in the following two years[6].

Cyclosporine has been used in cases of severe relapse, with no evidence of genetic malformations, although there is an increased risk of preterm delivery and low birth weight, which could be due to disease activity or to the drug itself. On the other hand, methotrexate is completely contraindicated in pregnancy due to its teratogenic effect, so it should not be administered to women who are planning to conceive or who are not using a safe contraceptive method. It is recommended to suspend it 3 to 6 months before conception and to administer folic acid in high doses to minimize risks. In case of accidental pregnancy under its use, it should be discontinued immediately and the patient should be referred to an obstetrician to evaluate the risk of teratogenicity[6,7].

Anti-TNF

Anti-TNF drugs, such as infliximab and adalimumab, cross the placenta in the third trimester, although, according to different series analyzed, exposure to these drugs is not associated with an increase in congenital malformations, spontaneous abortions, premature birth, low birth weight or infant infections, The results currently evaluated show that exposure to biologics, or a combination of thiopurines and biologics, does not increase the rate of perinatal complications or infections in the first year of life. Certolizumab is a Fab fragment of the monoclonal anti-TNF and not the complete IgG, its passage through the placenta being more limited, which could be an advantage over the use of infliximab and adalimumab; however, it has no indication in the technical file for IBD.

Its interruption may increase the risk of maternal relapse, and it has now been demonstrated that disease activity is a more relevant risk factor than exposure to these drugs for spontaneous abortion and premature delivery, also increasing the risk of postpartum disease activity. So, with the available evidence, anti-TNF therapy can be maintained throughout pregnancy in women with IBD to control the disease and reduce associated complications.[1,8].

JAK inhibitors

JAKi are small molecules that can cross the placenta and generate early exposure in pregnancy. Preclinical animal studies have revealed serious concerns about their teratogenicity. Tofacitinib has been shown to be feticidal and teratogenic in rabbits at doses six times the maximum dose in humans. Filgotinib, at doses equivalent to those used in humans, has been associated with fetal death and severe malformations in rats and rabbits. Upadacitinib has been shown to cause musculoskeletal and cardiovascular malformations at doses similar to those used in humans.

The limited exposure to these drugs in humans precludes drawing firm conclusions, so it is recommended that tofacitinib and upadacitinib be discontinued at least four weeks before planned conception, and filgotinib at least one week before. In specific and selected cases, where the clinical situation requires continuation of treatment, the patient should be fully informed of the risks in order to make a consensual decision.

Antisphingosine

S1P receptor modulators (anti-SP1), such as ozanimod and etrasimod commonly used for the treatment of multiple sclerosis, have been approved for the treatment of ulcerative colitis. These drugs have demonstrated teratogenic effects in animal studies, including fetal death and severe malformations at human-equivalent doses. Currently, there are no controlled clinical studies that determine the risk of fetal development in pregnant women exposed to these drugs. Prescribing information recommends the use of effective contraception to

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prevent unplanned pregnancies while taking these drugs and for up to three months after discontinuation[10,11].

Anti-interleukin and anti-integrins

Interleukin inhibitor drugs such as ustekinumab, which inhibits IL-12 and IL-23, and vedolizumab, anti-integrin alpha4-beta7, have a favorable safety profile during pregnancy, with no available studies reporting increased adverse effects in pregnant women. This has led to their consideration as safe options for use in this context. Although there are limited data on risankizumab and mirikizumab (IL-23 inhibitors), their mechanism of action and safety profile suggest that they may follow similar dynamics during gestation.[12,13].

Drug	Recommendation
Aminosalicylates	Safe during pregnancy, with minimal transplacental transfer. **Folic acid** supplementation is recommended when using **sulfasalazine**.
Corticosteroids	**First trimester: risk of orofacial malformations.** Second and third trimester: risk of **hypertension, gestational diabetes and preeclampsia.**
Thiopurines and immunosuppressants	**Thiopurines are considered** safe, but their initiation in pregnancy is not recommended**.** **Cyclosporine:** risk of premature delivery and low birth weight. **Methotrexate** contraindicated.
Anti-TNF	**Infliximab and adalimumab** cross the placenta in the third trimester, so it is suggested to evaluate their suspension. The passage of **certolizumab** through the placenta is more limited, which could be an advantage over other anti-TNFs.
JAK inhibitors	Suspend during pregnancy. **Tofacitinib and upadacitinib**: discontinue four weeks before conception and **filgotinib** at least one week before.
Antisphingosine	**Ozanimod and etrasimod:** teratogenic.
Anti-interleukin and anti-integrin	**Ustekinumab and vedolizumab** have a good safety profile during pregnancy. It is recommended to maintain them in patients with active IBD in the periconceptional period or in those with particularly refractory disease. **Risankizumab, Mirikizumab:** there are few data to date.

Table 3. ***Use of drugs in pregnancy.***

Childbirth

A higher probability of cesarean delivery has been reported in patients with UC compared to patients with CD, the main factors influencing the decision for cesarean delivery in UC being smoking, pancolitis and the presence of an ileoanal reservoir, while in Crohn's disease, a history of previous surgery and active perianal disease are determinants. A higher incidence of preterm delivery has also been documented in women with uncontrolled IBD, underscoring the need for optimal disease management during pregnancy.

The route of delivery in women should be individualized according to each patient's condition. Cesarean section is recommended in cases of active perianal disease or in patients with ileoanal reservoir, as these conditions increase the risk of pelvic floor dysfunction and postpartum complications[13].

It has also been documented that preterm delivery is more frequent in women with uncontrolled IBD, highlighting the importance of proper disease management during pregnancy[1,3].

Breastfeeding

Breastfeeding is recommended in women with IBD, as a protective effect on the health of newborns has been demonstrated. Biologic drugs such as infliximab, adalimumab and certolizumab pegol show minimal transfer into breast milk, with concentrations of less than 1% of the maternal serum level, and are therefore safe during lactation. However, if corticosteroids are administered in high doses, it is recommended to wait at least 4 hours before breastfeeding to reduce infant exposure[3].

Most treatments, including aminosalicylates and biologic therapies, can be maintained during lactation. However, the use of small molecules and antisphingosine is not recommended due to lack of data on their safety. In these cases, the risk-benefit ratio should be carefully evaluated and safe alternatives should be considered[14].

Vaccination

It is advisable to follow the usual vaccination schedule in infants exposed to immunosuppressive drugs during gestation, with the exception of live attenuated virus and BCG vaccines. These vaccines should be postponed until 12 months of age to avoid the risk of reactivation of latent infections, especially in infants exposed to anti-TNF, where cases of severe disseminated infection have been documented. Rotavirus vaccination before 6 months of age is safe.

Recent studies have shown that the response to vaccines such as hepatitis B, Haemophilus influenzae type B, and pneumococcus is similar between children exposed and not exposed to biologic drugs, although some reports suggest a

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	Recommendation
Delivery	**Vaginal** delivery is the recommended option, unless there are obstetric contraindications. **Cesarean section** in UC with ileoanal anastomosis or CD with active perianal disease or ileoanal reservoir.
Breastfeeding	Breastfeeding is **safe and recommended**. Increase caloric and Omega-3 intake. Treatment with anti-TNF or other biologics should not be discontinued, except for small molecules and anti-SP1 which should be avoided.
Vaccination	Follow usual schedule except in children exposed to immunosuppressants, in this case postpone **live vaccines** for 12 months.

Table 4. ***Recommendations during labor, pregnancy and lactation.***

lower initial response, which normalizes after the booster dose at 12 months[3,15].

Conclusion

Pregnancy planning in patients with IBD should be performed with a multidisciplinary approach to ensure disease control and reduce maternal-fetal risks. Most treatments can be maintained during gestation and lactation, always prioritizing disease remission to avoid complications.

Adequate information to patients of childbearing age is key for informed decision making and optimization of perinatal outcomes. It is essential to coordinate with the obstetric team the delivery plan and breastfeeding, ensuring adequate follow-up for both mother and newborn.

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