

# Inflammatory bowel disease in pregnancy

Delia Cudalba<sup>1</sup>, Anca Marina Ciobanu<sup>1,2</sup>, Corina Gica<sup>1</sup>, Mihaela Demetrian<sup>1</sup>,  
Brindusa Ana Cimpoaca-Raptis<sup>1,2</sup>, Gheorghe Peltecu<sup>1,2</sup>, Radu Botezatu<sup>1,2</sup>,  
Nicolae Gica<sup>1,2</sup>, Anca Maria Panaitescu<sup>1,2</sup>

<sup>1</sup> "Filantropia" Clinical Hospital, Bucharest, Romania

<sup>2</sup> "Carol Davila" University of Medicine and Pharmacy, Bucharest, Romania

## ABSTRACT

Inflammatory bowel disease (IBD), with its two main forms, Crohn's disease, and ulcerative colitis, are characterized by chronic inflammation of the gastrointestinal tract. It is frequently diagnosed during childbearing years and its overlapping with pregnancy adds more complexity to the management of the disease. This review article aims to summarize what is acknowledged so far regarding IBD in pregnancy, providing up-to-date information.

A systematic literature electronic search for journal articles and guidelines regarding IBD during pregnancy was undertaken.

The most favorable pregnancy outcomes for pregnant women with IBD occur when the disease is in remission both at the time of conception and during the pregnancy. Most of IBD medication is considered safe during pregnancy and continuing therapy in pregnancy is fundamental for achieving optimal outcomes. Proper management of active IBD in pregnancy requires multidisciplinary care to lower adverse outcomes. There is insufficient knowledge among patients regarding how their pregnancy outcomes could be optimized.

**Keywords:** inflammatory bowel disease, Crohn's disease, ulcerative colitis, pregnancy

## INTRODUCTION

Inflammatory bowel disease (IBD), including Crohn's disease and ulcerative colitis, is a polygenic disorder caused by a dysfunctional immune response to intestinal microflora. Both entities are lifelong conditions characterized by inflammation of the gastrointestinal tract and patients can experience periods of active disease or periods of remission. Ulcerative colitis affects colonic mucosa, and the extension of the lesions may vary from being limited to the rectum to the entire colon. In Crohn's disease any part of the gastrointestinal tract, from mouth to anus, can be affected.

IBD can occur at any age, but the peak incidence is observed between 15-40 years, which comprise the reproductive period. Therefore, reproduction and pregnancy are important issues to be considered. There is a lack of information among IBD pa-

tients regarding the interaction between their disease, fertility, and pregnancy.

Comprehensive patient counseling and proper management of the disease can lead to achieving optimal pregnancy outcomes.

This review article proposes to review current data regarding IBD and pregnancy.

## MATERIALS AND METHODS

A systematic literature electronic search for studies and guidelines was undertaken using major electronic databases. Search words were "inflammatory bowel disease", "Crohn's disease", "ulcerative colitis" combined with "pregnancy". Publications were selected based on accessibility to full paper article, quality evaluation, publication year. The publications used are mentioned in References section.

## FERTILITY IN IBD

Fertility rates for women with IBD in remission with no history of surgery are similar to those in the general population [1,2]. Active disease otherwise may decrease fertility rates after pelvic surgery on account of scarring and inflammation of the fallopian tubes or clinical symptoms which may have an unfavorable impact on libido and body image [3]. Sulfasalazine was proved to cause reversible oligospermia in males [4]. Concerning the rates of women who choose to be voluntarily childless, it is impressive compared to general population – 17% versus 6% and this may be attributed to disease burden and misinformation.

Regarding the genetic risk of IBD, the risk of developing Crohn's disease (CD) is 2.7%, while the risk for ulcerative colitis (UC) is 1.6%, with a risk of IBD up to 30% when the disease is carried by both parents [5,6].

There are a lot of concerns among IBD regarding the impact of their disease during pregnancy. Data suggests that 3/4 of women diagnosed with IBD worry about the transmission of the disease to the newborn, 1/2 question their fertility, 1/3 worry that their medical therapy could harm the fetus and 1/3 believe that enduring the symptoms is better than exposing the offspring to medication. There is insufficient knowledge among patients regarding how their pregnancy outcomes could be optimized in this situation [7,8].

## THE EFFECT OF IBD ON PREGNANCY

Studies estimate that 80% of pregnancies in women with IBD have a favorable course [9]. Adverse outcomes have been reported in active disease. There is a higher occurrence of preterm birth, small for gestational age and low birth weight in this cohort of pregnant women, but limited information concerning the risk of stillbirth and congenital malformations [10-12]. Other determinants are venous thromboembolism, with pulmonary embolism being a major cause of maternal death, active perineal disease which increases 10 times the risk of perineal damage and surgical interventions for IBD during pregnancy [13,14]. Though, it was reported that surgical intervention carries a lower risk than expectation management of severe disease [9]. Surgery is considered fairly safe no matter the gestational age, but there are a few studies which reported increased spontaneous miscarriage and preterm birth [15]. Considering that active IBD is a risk factor for venous thromboembolism, thromboprophylaxis should be considered if necessary. During pregnancy, the risk of pouch dysfunction in patients with ileal pouch-anal anastomosis increases to 20-30% and in most cases it resolves

postpartum [16]. There was reported a higher rate of C-sections in women with IBD [17].

## THE EFFECT OF PREGNANCY ON IBD

A major predictor of activity or flares during pregnancy and postpartum period is peri-conceptual active disease [18,19]. It has been proved that near one-third of patients which conceive during remission will relapse during pregnancy. Oppositely, about two-thirds of patients which conceive during active disease will continue to have active disease and furthermore, two-thirds of these will additionally have worse disease outcomes [20]. If it is to compare UC with CD, the first was reported to have higher rates of relapse [21]. Those being mentioned, the preconception counseling plays a considerable role, disease evaluation before conception being able to improve adherence to treatment.

Studies reported that pregnancy increases the quality of life and lowers the risk of flares for up to 10 years after birth in IBD patients. Studies that tried to assess whether pregnancy modulates IBD and its course after birth concluded that the disease phenotype or resection rates were not influenced, but pregnancy seemed to reduce the number of flares postpartum. Whether this effect is generated by the positive effect on the immune system of pregnancy, or the medical efforts put into maintaining the patient in remission still remains unclear [22,23].

## MANAGEMENT OF IBD IN PREGNANCY

### IBD medication in pregnancy

Medical therapy in IBD includes 5-aminosalicylic acid (sulfasalazine, olsalazine, balsalazide), immunomodulating drugs (azathioprine, 6-mercaptopurine, methotrexate), biologic agents (infliximab, certolizumab, adalimumab, golimumab, vedolizumab, natalizumab, tofacitinib), antibiotics and probiotics.

Guidelines recommend that 5-aminosalicylic acid should be continued in pregnancy, supplementing with folic acid prior to conception and for the first 12 weeks of pregnancy because of the antifolate actions of sulfasalazine [9,24].

Corticosteroids are also continued during pregnancy if needed. Corticosteroid use was associated with elevated risk of urinary tract infections, maternal hypertension, gestational diabetes mellitus and preterm birth. Some studies suggest that the use of steroids in the first trimester could increase the risk of cleft lip and palate. There should be an enhanced fetal growth monitoring in the third trimester in case of administration of corticosteroids [25].

Regarding immunomodulating drugs, azathioprine is considered to be low risk during pregnancy,

but methotrexate is known to be teratogenic, and it carries elevated risk of miscarriage. Methotrexate should not be administered 3 months before the conception. If miscarriage does not occur, the risk for significant congenital malformations is more than double (growth deficiency, facial dysmorphic features, limb defects, microcephaly) [26-28].

There is no evidence that biologic agents are teratogenic, but in the third trimester they should be avoided. Studies show that newborns exposed to anti-tumor necrosis factors (anti-TNF) have greater risk of adverse reactions to live vaccines [29]. Maternal exposure to biological agents (excepting certolizumab) during the third trimester postpones neonatal administration of live vaccines (Calmette-Guerin bacille, measles, mumps, rubella, rotavirus, oral polio, varicella vaccine) [24]. Data concerning third trimester cessation has been continuously updating. In 2015 guidelines recommended discontinuation of anti-TNF to lower neonatal exposure for patients in remission [9]. In 2016, studies showed that continuing biological treatment would improve subsequent IBD course and cessation would be possible in pregnant women with reduced risk of relapse [24]. In 2019 the American Gastroenterology Association recommended the continuation of anti-TNF therapy in the third trimester, with an adjustment of the last dose timings [30].

Tofacitinib showed teratogenicity in animal models and guidelines recommend contraception while using it and up to 6 weeks after exposure [31].

Mycophenolate mofetil may be a favorable option for maintaining remission in patients with IBD which do not tolerate thiopurines, but as it is teratogenic, its use is not recommended [32].

In patients with IBD certain vitamin deficiencies may occur. Vitamin D, B12 deficiency, low levels of iron and folate and other nutritional deficiencies caused by protein and lipid malabsorption should be assessed and improved prior or during pregnancy.

### IBD investigations in pregnancy

Endoscopy is considered to be safe in pregnancy and it should be performed, if possible, in the second trimester of pregnancy. Unsedated endoscopy is preferred, but if needed, midazolam is the seda-

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tive of choice. Exposure to radiation should be avoided, but it can be performed if benefits outweigh the risks. Ultrasound and MRI may be a safer option, but the practical application may be limited [24,33].

### Birth

The mode of birth for most of pregnant women with IBD will be discussed in matter of obstetric indications. Candidates for C-sections could be patients with active perianal disease at the time of delivery and women who had recently IPAA surgery [24].

### CONCLUSIONS

The most favorable pregnancy outcomes for pregnant women affected by IBD occur when the disease is in remission both at the time of conception and during the pregnancy. Therefore, in order to enhance pregnancy outcomes, maintaining the disease inactive and continuing IBD medication are fundamental in the management of IBD in pregnancy.

Patients with IBD should be counseled that fertility rates are similar to general population if the disease is inactive. Preconceptional patient evaluation should take in account a proper disease control. Most of IBD medication are considered safe during pregnancy, excepting methotrexate and mycophenolate mofetil.

Mode of delivery is determined by obstetric indication, giving consideration to a possible history of surgical interventions and active perianal Crohn's disease.

The necessity of a multidisciplinary approach for the management of IBD in pregnancy is indisputable. The collaboration between gastroenterologists, obstetricians, neonatologists, colorectal surgeons, radiologists, rheumatologists, and psychologists, combined with extensive patient education could maintain the disease at its most favorable course could decrease adverse pregnancy outcomes. It is crucial that patients affected by IBD benefit from comprehensive counseling in order to understand the benefits of preventing, treating and proper managing of the disease during pregnancy.

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