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Chronic inflammatory bowel diseases and pregnancy frequently asked questions

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Abstract
Many patients with inflammatory bowel disease (IBD), whether Crohn's disease or ulcerative colitis, are of reproductive age. The main concerns for young women with IBD are usually related to their fertility, IBD inheritance and IBD influence on pregnancy and fetus development. In addition, patients are concerned about the use of IBD medicines during pregnancy, fearing that they can negatively affect the fetus. For this reason, gastroenterologists and patients with IBD are of great importance to be aware of the effect of IBD on pregnancy and with a view to maintaining remission of the disease during conception and the effect of the medication administered throughout pregnancy, which is crucial for improving the results of both mother and fetus.

Keywords: chronic inflammatory bowel disease, Crohn's disease, Ulcerative colitis, pregnancy, complications and exit from pregnancy, immunomodulator therapy, antibiotics, biological therapy

Introduction
Inflammatory bowel diseases (IBD) are a group of diseases characterized by recurrent, destructive inflammation of the gastrointestinal tract. To this group belong Crohn's disease (CD) and ulcerative colitis (UC). There are also several rarer inflammatory bowel diseases such as collagenous, lymphocytic and indeterminate colitis. According to worldwide data, the incidence of inflammatory bowel disease is about 8.7-11.8/100,000 people, with most patients triggering the disease between their second and third decades, i.e. during their active childbearing years. This in turn leads to a number of questions being debated, such as whether fertility is impaired in IBD patients; what is the risk of disease relapses during pregnancy; what impact IBD has on pregnancy and fetal development, the incidence of inherited IBD, the teratogenicity of the medications administered, and what the long-term effects the medications may have on offspring.

Fertility in inflammatory bowel disease
It appears that fertility in IBD patients is influenced by: the localization of the disease (colonic involvement); history of surgical intervention; and disease activity [10].
According to the experts of the European Crohn's Colitis Organization (ECCO), there is no evidence that UC or BC in remission affects fertility [19] While during the active phase of Crohn's, it is possible that pregnancy may be more difficult, one possible cause being malabsorption, especially of vitamin D, as well as inflamatory changes. In women with UC who have not had surgical treatment, fertility is not affected. Conversely, those women who had a colectomy with ileo-anal anastomosis and a formed pouch (IPAA), fertility was significantly reduced [15, 16]. The most likely cause of reduced fertility was adhesions in the pelvic region at the creation of the pouch, as women who underwent a subtotal colectomy retained their childbearing capacity intact.
Another 2016 study revealed that women with inflammatory bowel disease (IBD) are more likely to be childless/about 17% of women with IBD/compared to healthy women/about 6%/of women in the population.One possible simpler explanation is simply that women with the disease more often prefer not to have children because of the risk of inheriting the disease in offspring, as well as for personal health reasons [17].

Impact of IBD on pregnancy and fetal development
Any pregnancy occurring in a patient with IBD should be considered a pregnancy at risk. Compared to healthy women, most studies have shown that women with IBD have a higher risk of delivery by cesarean section, both elective and as an emergency intervention; preterm delivery (before 37 weeks gestational age), low birth weight (<2,500 g), and low birth weight for gestational age [6].

IBD inheritance
The causes of Crohn's disease are complex. This condition results from a combination of genetic, environmental and lifestyle factors, many of which are unknown
Many of the major genes associated with Crohn's disease, including NOD2, ATG16L1, IL23R, and IRGM, are involved in the functioning of the immune system. The proteins produced by these genes help the immune system sense and respond appropriately to bacteria in the lining of the digestive tract. Many of the proteins play a role in autophagy, which is a process that cells use to bypass and destroy bacteria and viruses. Variations in these genes can disrupt autophagy or otherwise alter the immune system's response to bacteria in the digestive system. In combination with other genetic and environmental factors, these changes can lead to chronic inflammation and result in the digestive problems characteristic of Crohn's disease [33, 34, 35].
Researchers have identified at least 200 genetic variations that affect the risk of Crohn's disease. Most of these variations are thought to act by subtly altering the amount, timing and location of gene activity (expression). The

mechanism by which many of the variations affect disease risk is unknown, although they probably alter immune system function in some way. Considered together, the known genetic variations account for only a small percentage of the total risk of Crohn's disease that is attributable to genetic factors [33, 34, 35].

A positive family history is an important predictor of the risk of inheriting IBD. About 5.5-22.5% of patients have another family member who is also affected by the disease. Overall, the risk for children with one parent who has IBD is 2-3 times higher than for the general population. For children where both parents have IBD, the lifetime risk of the disease is over 30%. The relative risk for a sibling of a patient with CD to develop the disease is 13-36% higher than this risk for the general population, whereas the relative risk for siblings of a patient with UC is 7-17% higher compared to the general population. Given the overall incidence of IBD in Europe and North America, it can be assumed that 10 new cases per 100,000 will develop for JC and 5-6 newly diagnosed cases per 100,000 for CD. This gives a risk of 2-3% for a sibling of a patient with BC and 0.5-1% for a sibling of a patient with UC. The risk increases significantly if the parent who has BC is the mother and the child is a girl. Transmission of BC from an affected mother to a daughter implies a specific female pattern of inheritance, which has not been demonstrated for JC or when a father and his future male child are involved. Patients with a family history of IBD show a tendency to manifest the disease at an earlier age and in the same form of the disease (BC or UC) and most likely with the same localization [19].

Acuity of the disease during pregnancy

Most women who become pregnant during a remission of the disease can have a normal pregnancy. According to the Crohn's & Colitis Foundation of America, the most favorable time to become pregnant in Crohn's patients is during a remission period of 3-6 months. Data show that a large number of women who become pregnant during the disease's relapse, it remains active until the end of pregnancy. During the active phase of Crohn's, there is a higher risk of miscarriage, preterm birth, underweight newborn and other complications during the delivery itself. According to a 2017 study, becoming pregnant during remission does not increase the risk of relapse. What's more, some data suggests that the risk of relapse even decreases, as does the incidence of needing surgery in 1/3 of patients. [33].

Teratogenicity of administered drugs

It is currently accepted that drug treatment associated with IBD should generally be continued during pregnancy, as the benefits to mother and fetus of maintaining remission far outweigh the risks of treatment.

Table 1

Safe	Relatively Safe	Contraindicated
Oral 5-aminosalicylates	Infliximab	*Methotrexate*
Topical 5-aminosalicylates	Adalimumab	*Thalidomide*
Sulfasalazine/mesalazine	Certolizumab	$6-thioguanine$
Azathioprine	Cyclosporine	
6 -Mercaptopurine	Tacrolimus	
	Budenoside	
	Metronidazol	
	Ciprofloxacin	

Glucocorticoids (FDA, Category C)

Prednisone (Cortancyl®) and prednisolone (Hydrocortancyl®, Solupred®) can be used without special restriction to treat IBD in pregnant women. They are not currently considered to increase the risk of deformities. Placental 11-beta-hydroxygenase metabolizes prednisone and prednisolone, so the fetus is exposed to only about 10% of the maternal dose when treated with either of these two steroids.

They should be preferred over long-acting forms such as betamethasone and dexamethasone. No side effects have been reported with respect to gut and colon-releasing budesonide (Entocort®, Rafton®).

Sulfasalazine and 5-aminosalicylic acid (5-ASA)

Sulfasalazine (Salazopirine®) and 5-ASA (Pentasa®, Rowasa® and Fivasa®) administered at doses of 2 g/d have no specific adverse effects during pregnancy.

Sulfasalazine does not cause fetal malformations. It increases the risk of folic acid deficiency and given the increased folic acid requirements during pregnancy and the risk of neural tube defect, folic acid supplementation (2 to 5 mg/d) is necessary in women taking sulfasalazine who wish to have a baby and during pregnancy.

Therefore, the use of maximum doses of 2 g/d is recommended. If this dose is insufficient, then it is necessary either to resort to a therapeutic alternative or to monitor the fetal kidneys more regularly by ultrasound.

Antibiotics (FDA, Category B - C)

Ampicillin, Erythromycin, cephalosporins are considered safe.

Fluoroquinolones (Ciprofloxacin, Levofloxacin, Norfloxacin) - Have high affinity for bone tissue and cartilage.May cause changes in fetal cartilage, arthropathies in children.

Tetracyclines and sulfonamides cause retardation of fetal skeletal development.

Metronidazole is allowed after the first trimester of pregnancy (in II- III month of pregnancy - labium leporinum or palatum fisum is more commonly seen. It is not taken during breastfeeding.

Immunomodulators - Azathioprine and 6-mercaptopurine

For azathioprine (Imurel®) and 6-mercaptopurine (Purinethol®), a prospective long-term multicenter study found no long-term adverse effect on immune development in children exposed intrauterine. Azathioprine is widely used in pregnant women with IBD [23, 24].

Methotrexate and Thalidomide (Thalidomide ®)

These two immunosuppressive drugs are teratogenic, category X, and should not be used during pregnancy and lactation.

Methotrexate is responsible for chromosomal abnormalities and miscarriages. Severe malformations have been reported in neonates exposed during the 1st trimester of pregnancy. Methotrexate should be discontinued in women for at least three months (and more conservatively, 6 months) before attempting pregnancy.

Thalidomide is well known for causing limb defects and major organ complications.

Cyclosporine (Neoral®, Sandimmun®)

Cyclosporine is not teratogenic, but exposes the risk of tubular nephropathy in the fetus as in the mother. In a meta-analysis of fifteen studies with a total of 410 patients, the overall prevalence of major malformations (4.1%) was not significantly different from that reported in the general population.

Biological therapy (anti - TNF)

Infliximab (Remicade®); adalimumab (Humira®) and Golimunad (Simponi®)

The newest class of drugs used to treat IBD are biologics or anti-TNF drugs such as infliximab, adalimumab and certolizumab. TNF-alpha is an important component in fetal development and there are concerns that TNF blocker may affect the growth of the fetal immune system. These drugs have a much shorter duration of use in IBD and their safety during pregnancy is still being determined. These immunoglobulins cross the placental barrier from the 13th gestational week until reaching a maximum in the third trimester. Subsequently, infliximab and adalimumab levels are detectable up to 6 or even 12 months of life without further administration [21, 33].

For these three molecules, it is advisable, to be stopped in pregnant women with IBD before the 30th gestational week.

Anti-TNF alpha inhibitors are excreted in breast milk and their use appears safe during lactation [30, 32].

Certolizumab (Cimzia®) is a pegylated fragment of a humanized monoclonal antibody, so it can only cross the placenta by passive diffusion. Therefore, its use could theoretically continue throughout pregnancy [29].

Vedolizumab (Entyvio®)

The lack of available data so far should lead to the utmost caution in their use during pregnancy.

Ustekinumab (Stelara®)

There are currently few data available. No clear recommendation can be established to date.

Conclusion

Pregnancy and childbearing in patients with IBD is a clinically relevant topic. Every woman with IBD and childbearing potential should be questioned about her reproductive plans and provided with appropriate information. The majority of pregnancies in IBD patients end in good outcomes. However, success can be achieved only after careful preparation before conception, assessment of risk factors, and constant monitoring of both the disease and the health of the fetus. Women with IBD in remission should not be discouraged from becoming pregnant, but should be counseled and carefully monitored during pregnancy and the early postpartum period by a team of specialists.

References

1. Agret F, Cosnes J, Hassani Z, *et al*. Impact of pregnancy on the clinical activity of Crohn's disease. Alimentary Pharmacology and Therapeutics,2005:21:509-13.
2. Beaulieu DB, Kane S. Inflammatory bowel disease in pregnancy. Gastroenterology Clinics of North America,2011:40:399-413.
3. Bortoli A, Pedersen N, Duricova D, *et al*. Pregnancy outcome in inflammatory bowel disease: prospective European case–control ECCO-EpiCom study, 2003-2006. Alimentary Pharmacology and Therapeutics,2011:34:724-34.
4. Cappell MS, Fox SR, Gorrepati N. Safety and efficacy of colonoscopy during pregnancy: an analysis of pregnancy outcome in 20 patients. Journal of Reproductive Medicine,2010:55:115-23.
5. Caprilli R. European evidence based consensus on the diagnosis and management of Crohn's disease: special situations. Gut,2006:55:i36-58.
6. Cornish J, Tan E, Teare J, *et al*. A meta-analysis on the influence of inflammatory bowel disease on pregnancy. Gut,2007:56:830-7.
7. Dotan I, Alper A, Rachmilewitz D, *et al*. Maternal inflammatory bowel disease has short and long-term effects on the health of their offspring: a multicenter study in Israel. Journal of Crohn's and Colitis, 2012. http://dx.doi.org/10.1016/j.crohns.2012.08.012.].
8. Fayez JA, Clark RR. Operative laparoscopy for the treatment of localized chronic pelvic-abdominal pain caused by postoperative adhesions. Journal of Gynecologic Surgery,1994:10:79–83.
9. Hahnloser D, Pemberton JH, Wolff BG, *et al*. Pregnancy and delivery before and after ileal pouch-anal anastomosis for inflammatory bowel disease: immediate and long-term consequences and outcomes. Diseases of the Colon and Rectum,2004:47:1127-35.
10. Hudson M, Flett G, Sinclair TS, Brunt PW, Templeton A, Mowat NA. Fertility and pregnancy in inflammatory bowel disease. International Journal of Gynaecology and Obstetrics,1997:58:229-37.
11. Kane S, Kisiel J, Shih L, Hanauer S. HLA disparity determines disease activity through pregnancy in women with inflammatory bowel disease. American Journal of Gastroenterology,2004:99:1523-6.
12. Lakatos PL, Golovics PA, David G, *et al*. Has there been a change in the natural history of Crohn's disease? Surgical rates and medical management in a population-based inception cohort from Western Hungary between 1977-2009. American Journal of Gastroenterology,2012:107:579-88.
13. Mayberry JF, Weterman IT. European survey of fertility and pregnancy in women with Crohn's disease:

a case control study by European collaborative group. Gut,1986:27:821-5.
14. Naganuma M, Kunisaki R, Yoshimura N, *et al*. Conception and pregnancy outcome in women with inflammatory bowel disease: a multicentre study from Japan. Journal of Crohn's and Colitis,2011:5:317–23.
15. Olsen K, Juul S, Berndtsson I, Oresland T, Laurberg S. Ulcerative colitis: female fecundity before diagnosis, during disease, and after surgery compared with a population sample. Gastroenterology,2002:122:15-9.
16. Olsen KO, Joelsson M, Laurberg S, Oresland T. Fertility after ileal pouchanal anastomosis in women with ulcerative colitis. British Journal of Surgery,1999:86:493-5.
17. Rajaratnam SG, Eglinton TW, Hider P, Fearnhead NS. Impact of ileal pouchanal anastomosis on female fertility: meta-analysis and systematic review. International Journal of Colorectal Disease,2011:26:1365-74.
18. Stephansson O, Larsson H, Pedersen L, *et al*. Congenital abnormalities and other birth outcomes in children born to women with ulcerative colitis in Denmark and Sweden. Inflammatory Bowel Diseases,2011:17:795-801.
19. van der Woude CJ, Ardizzone S, Bengtson MB, Fiorino G, Fraser G, Katsanos K, Kolacek S, Juillerat P, Mulders AG, Pedersen N, Selinger C, Sebastian S, Sturm A, Zelinkova Z, Magro F; European Crohn's and Colitis Organization. J Crohns Colitis,2015:9(2):107-24. The second European evidenced-based consensus on reproduction and pregnancy in inflammatory bowel disease.
20. Waljee A, Waljee J, Morris AM, Higgins PDR. Threefold increased risk of infertility: a meta-analysis of infertility after ileal pouch anal anastomosis in ulcerative colitis. Gut,2006:55:1575-80.
21. Casanova MJ, Chaparro M, Domènech E, *et al*. Safety of thiopurines and anti-TNF-α drugs during pregnancy in patients with inflammatory bowel disease. Am J Gastroenterol,2013:108(3):433-440.
22. Hutson JR, Matlow JN, Moretti ME, Koren G. The fetal safety of thiopurines for the treatment of inflammatory bowel disease in pregnancy. J Obstet Gynaecol,2013:33(1):1-8.
23. Akbari M, Shah S, Velayos FS, Mahadevan U, Cheifetz AS. Systematic review and meta-analysis on the effects of thiopurines on birth outcomes from female and male patients with inflammatory bowel disease. Inflamm Bowel Dis,2013:19(1):15-22.
24. Nørgård B, Pedersen L, Fonager K, Rasmussen SN, Sørensen HT. Azathioprine, mercaptopurine and birth outcome: a population-based cohort study. Aliment Pharmacol Ther,2003:17(6):827-834.
25. Mahadevan U, Kane S. American gastroenterological association institute technical review on the use of gastrointestinal medications in pregnancy. Gastroenterology,2006:131(1):283-31133.
26. Matalon ST, Ornoy A, Lishner M. Review of the potential effects of three commonly used antineoplastic and immunosuppressive drugs (cyclophosphamide, azathioprine, doxorubicin on the embryo and placenta) Reprod Toxicol,2004:18(2):219-230.
27. Polifka JE, Friedman JM. Teratogen update: azathioprine and 6-mercaptopurine. Teratology,2002:65(5):240-261.
28. Cleary BJ, Källén B. Early pregnancy azathioprine use and pregnancy outcomes. Birth Defects Res A Clin Mol Teratol,2009;85(7):647-654.
29. Martin PL, Oneda S, Treacy G. Effects of an anti-TNF-alpha monoclonal antibody, administered throughout pregnancy and lactation, on the development of the macaque immune system Am J Reprod Immunol,2007:58(2):138
30. Nørgård B, Hundborg HH, Jacobsen BA, Nielsen GL, Fonager K. Disease activity in pregnant women with Crohn's disease and birth outcomes: a regional Danish cohort study. Am J Gastroenterol,2007:102(9):1947-1954.
31. Jürgens M, Brand S, Filik L, *et al*. Safety of adalimumab in Crohn's disease during pregnancy: case report and review of the literature. Inflamm Bowel Dis,2010:16(10):1634-1636.
32. Martin PL, Oneda S, Treacy G. Effects of an anti-TNF-alpha monoclonal antibody, administered throughout pregnancy and lactation, on the development of the macaque immune system. Am J Reprod Immunol,2007:58(2):138-149
33. Boyapati R, Satsangi J, Ho GT. Pathogenesis of Crohn's disease;
34. Ellinghaus D, Bethune J, Petersen BS, Franke A. The genetics of Crohn's disease and ulcerative colitis--status quo and beyond. Scand J Gastroenterol;
35. Achkar JP, Duerr R. The expanding universe of inflammatory bowel disease genetics