

## REVIEWS

# Inflammatory bowel disease and infertility: analysis of literature and future perspectives

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**Abstract.** *Background:* inflammatory bowel diseases (IBD) are chronic disorders that affect the gastrointestinal tract but which also present extraintestinal manifestations. One of the problems related to IBD is the presence of both female and male infertility. *Aim:* determine the correlation between IBD and male and female infertility by analyzing the literature. *Material and methods:* Studies carried out in the last twenty years have been selected through the pubmed search engine. Only studies were selected that in their conclusions showed a real correlation between IBD and infertility. *Results:* the first cause of infertility in both sexes is related to the surgical interventions that patients have to face during the course of the disease, but there are also psychological causes or causes related to the use of drugs used for therapy. *Conclusions:* further studies are needed to understand what are the real mechanisms underlying infertility in subjects suffering from IBD.

**Keywords:** IBD, infertility, pregnancy, Chron's disease, ulcerative colitis, male infertility, female infertility

## Introduction

Inflammatory bowel diseases (IBD) represent a set of chronic bowel disorders on an inflammatory basis. IBDs include Chron's disease (CD), ulcerative colitis (UC), and indeterminate colitis. CD and UC differ from each other in localization. In fact, CD affects the entire gastrointestinal tract, from the mouth to the anus, while UC is mainly localized in the last section of the intestine, i.e. the colon and rectum. The lesions of the CD also have a typical segmental trend, i.e. we find tracts of healthy mucosa that alternate with tracts of pathological mucosa, while the UC has a linear trend, i.e. all the mucosa affected by the disease is pathological (1-5).

The pathogenesis of IBD is multifactorial and includes three main causes that contribute to the onset of diseases: genetic susceptibility, environmental fac-

tors and immunopathogenic factors. All three causes cause a condition known as dysbiosis, which is a change in the intestinal flora which determines, with a chain mechanism, an alteration in the permeability of the gastrointestinal barrier with consequent alteration of the immunoregulatory mechanisms. Dysbiosis determines the growth of microorganisms that produce metabolic components with toxic action, able to activate the local immune system (GALT) and therefore to trigger an inflammatory reaction in the mucous membranes themselves (1).

In addition to the typical gastrointestinal manifestations, IBDs also present extraintestinal symptoms that can involve numerous organs and systems. An example is the one that links the presence of IBD with both male and female infertility.

Infertility is a pathological condition of the reproductive system defined as the inability to conceive after

12 months or more of regular, unprotected sex. Notably, most pregnancies occur in the first six cycles with sexual intercourse in the fertile phase. If this is not the case, subfertility in one in two couples should be assumed. After 12 months there is talk of infertility and after 48 months 5% of couples are definitively infertile with an almost zero probability of spontaneously becoming pregnant in the future (6). Fertility rates are influenced by multiple factors such as age, acute or chronic conditions, environmental toxins, occupational exposures, general lifestyle problems, infectious diseases, genetic conditions and specific reproductive disorders that can affect both men and women. try to conceive (7).

Infertility linked to female causes could be linked to peritoneal factors, obstruction of the tubes, abnormalities of the uterus and / or cervix or ovulatory dysfunctions. Infertility linked to male factors, on the other hand, includes alterations in the spermatozoa. These alterations can be linked to pathologies such as cryptorchidism and varicocele, or to structural and functional alterations of the spermatozoa such as reduced mobility and insufficient sperm count. Sometimes infertility has no apparent cause. Infertility has a negative impact on the psychological health of the couple and causes a loop in which there is an increase in stress which corresponds to a lower ability to conceive (6,7).

In this review we will talk about what are the correlations between male and female infertility and IBD and what prospects there are for the future to improve these conditions.

## Materials and Methods

The research of the studies was carried out using the Pubmed search engine. The study selection criteria were as follows:

- studies carried out in the last twenty years were taken into consideration to have a broad vision and a high number of cases.
- findings and conclusions. We have only included articles that show a true correlation between IBD and infertility.

We divided the research into three sections, female infertility, pregnancy, and male infertility, taking into

consideration among all 5 articles regarding female infertility, 5 articles regarding pregnancy, 6 articles regarding male infertility, for a total of 16 articles.

## Results

### *Female infertility*

The infertility rate in large population-based studies of patients with IBD is similar to that in the general population and ranges from 5 to 14% (8). However, women with IBD can have fertility problems essentially for two reasons: psychological problems and mechanical problems related to repeated surgery.

Psychological problems mainly concern the perception of risk, which influences reproductive behaviour. In particular, women show concern about the potential teratogenicity of drugs, the risk of abortions and / or malformations, the inheritance of IBD and the possibility of ectopic pregnancies (9,10).

One study investigated the general attitudes of women with IBD about fertility, drug use, childbirth and pregnancy. The results of the study showed that 36% of patients believed that all drugs used for IBD are harmful to the foetus, 46% worried about possible infertility, 75% were worried about the genetic transmission of the disease. Additionally, nearly all participants were concerned about the effects of IBD on pregnancy and the effects of pregnancy on IBD symptoms (8,11).

These problems require both medical and psychological support to deal with the situation. In fact, most of the drugs used for the treatment of IBD such as corticosteroids, mesalazine, azathioprine, anti-TNF agents and cyclosporine, do not show evident signs of teratogenicity (9).

Regarding the hereditary transmission of IBD, current data suggest the genetic component is partial, and that the chances that the child will not develop the disease are very high: 91% if only one parent is affected and 60% if both parents are affected. It is therefore important to emphasize to patients that a family history is neither necessary nor sufficient for the onset of IBD in children and that the absolute risk remains very low (1.6% for UC and 5.2% for CD) (10).

As regards the problems relating to surgical interventions, these mostly concern the formation of adhesions caused by the disease itself and/or by repeated surgical interventions. For example, in the case of UC treated with ileal pouch anal anastomosis (IPAA), the possibility of pregnancy is significantly reduced due to pelvic adhesions, tubal obstruction or alteration of the tubal-ovarian relationship. For example, some studies have shown that in women undergoing surgery with the creation of ostomies or anastomosis, in 50% of cases complete unilateral or bilateral obstruction of the fallopian tubes was observed (9). An increase in infertility rate from 12% before proctocolectomy to 26% was also shown (8,12).

### *Pregnancy*

Pregnancy appears to have a beneficial effect on IBD symptoms, especially when it occurs during disease remission. A large prospective European study, showing that 74% of patients with CD and 67% of patients with UC with active disease at the time of conception achieved remission during pregnancy (9,13). However, some patients observe an increase in IBD-related symptoms in the first trimester of pregnancy, presumably related to the discontinuation of maintenance drugs, and in other patients the presence of active disease at the time of conception increases the risk of miscarriage, reduced birth weight and pre-term birth (9).

The presence or absence of disease during pregnancy also appears to be related to the state of the disease at the time of conception. Patients with active disease at the time of conception often continue to have symptoms during pregnancy, while a normal course of pregnancy can be expected in patients who conceive during a period of remission. In a cohort study it was observed that if conception occurred during remission, the risk of an exacerbation was comparable to that of non-pregnant patients with IBD. In contrast, when conception occurred during a period of active disease, 2/3 of the patients had a relapse during pregnancy and more than 60% of these patients experienced further worsening (14).

The long-term effect of pregnancy on the symptoms and relapses of IBD is also interesting. Numerous

studies have been carried out in this regard, the results of which have shown a reduction in the recurrence rate of IBD after 4 years from pregnancy, a reduction in annual exacerbation rates (from 0.34 to 0.18 for UC and from 0.76 to 0.12 per CD), and a reduction in the rate of stenosis and resection (9,15). The mechanisms potentially involved could be related to the hormone relaxin, the effect of pregnancy on the immune response, as well as the foetus-maternal HLA disparity (9,16).

### *Male infertility*

In the general population, drugs are responsible for erectile dysfunction in up to 25% of cases. In particular, the drugs related to this problem are not those for the treatment of IBD but those for the treatment of anxiety and depression associated with IBD. The only drug that has been shown to cause male infertility is sulfasalazine (8). This drug causes reversible and non-dose related sperm abnormalities (oligospermia, abnormal morphology and decreased sperm mobility). It also causes an infertility rate of up to 60%, presumably due to impaired sperm maturation and oxidative stress due to the sulfapyridine constituent of the drug. Male fertility is restored two months after stopping sulfasalazine or switching to other mesalamine preparations (9,17,18).

There are also surgical complications in men that can compromise fertility. For example, proctocolectomy with IPAA appears to be associated with sexual dysfunction (such as erectile dysfunction, retrograde ejaculation and anejaculation) linked to parasympathetic and sympathetic nerve damage during surgery, but sometimes due to anatomical changes, fibrosis or post psychological factors. intervention (19). The incidence of erectile dysfunction or retrograde ejaculation in patients with IBD is 25.7%, and in particular it has been observed that in men undergoing IPAA the prevalence of retrograde ejaculation is 8.2% after surgery (19,20).

### **Conclusions**

The presence of IBD has a major impact on both female and male fertility, and also affects pregnancy.

IBDs affect female infertility through mechanical problems related to repeated abdominal surgery and psychological causes. In particular, repeated surgical interventions can lead to the appearance of abdominal adhesions that compromise the patency of the fallopian tubes with a consequent reduction in the possibility of conception. In this case, the use of in vitro fertilization could partially solve the problem. Furthermore, psychological problems, linked to the fear of using certain drugs and the fear of a possible genetic transmission of the disease, greatly influence a woman's decisions about becoming pregnant (8-12). On pregnancy there are studies that show how pregnancy can lead to a reduction in the flare-up of pathologies even in the long term, and studies that indicate that in pregnancy the remission of symptoms is linked to the moment of conception. Some women in fact showed an almost total remission during pregnancy, others instead found an increase in symptoms. Furthermore, in women with active disease, there was an increase in the rate of spontaneous abortions, pre-term pregnancy and low birth weight. Considering therefore that the risks related to pregnancy are closely related to the presence of active disease and that most of the drugs used for IBD show a low risk of fetal abnormalities, it would be desirable to continue the therapies during pregnancy in order to induce remission as long as complete as possible (9,13-16).

In men with IBD, the main cause of infertility is linked to the drug sulfasalazine, but the problems related to surgery also greatly affect, in particular erectile dysfunctions occur in men undergoing IPAA (8,9,17-20).

Further studies are needed to understand what are the real mechanisms underlying infertility in subjects suffering from IBD and to plan therapeutic strategies aimed at overcoming this problem.

**Conflict of interest:** Each author declares that he or she has no commercial associations (e.g. consultancies, stock ownership, equity interest, patent/licensing arrangement etc.) that might pose a conflict of interest in connection with the submitted article

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Received: 9 December 2020

Accepted: 8 February 2021

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