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Review

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Inflammatory Bowel Diseases (IBD) and Infertility. A narrative review.

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Abstract

The aim of our narrative review is to examine how the various factors associated with IBD affect more or less the fertility of female and male patients. We have reviewed the recent bibliography on the Medline. The infertility rates among patients of IBD and the general population do not differ, apart from some specific factors. The issue of infertility of IBD patients requires further epidemiological studies, as despite the latest efforts of the medical community there are still unclear areas of research in this field.

Keywords: Inflammatory Bowel Disease, infertility, drugs, surgery.

Introduction

Since the manifestation of Inflammatory Bowel Diseases (IBD) mainly concerns the population of reproductive age, childbearing is an issue that concerns both physicians and patients. The problem of infertility in patients with IBD is characterized by a number of aspects related both to the pathology of reproduction due to the inflammatory process, where it develops during the relap phase of IBD, and to the side-effects of surgical procedures that patients, women or men, can undergo in taking medication of all types of it, but also in the way of psychological management of the disease on the part of patients.

The fertility of patients with IBD is an element of particular concern to the scientific medical community, as the evolution in the study of diseases that constitute the phenomenon of IBD, the development of surgical techniques concerning these patients and the inclusion in the pharmaceutical arsenal of more and specialized drugs, have allowed patients to be given a better quality of life, so that having children is not today a different problem of everyday life in most cases compared to the general population.

IBD Characteristics

Under the general term Idiopathic Inflammatory Bowel Diseases (IBD) three disease entities are included. Crohn's Disease, Ulcerative Colitis and Unspecified Colitis. (1)

All three of these pathological conditions are distinguished by the appearance of inflammation in the intestinal lumen, which, depending on its location, their pathological picture and the clinical manifestations that accompany them, are classified respectively in each nosological form. Patients in about 50% also present a number of extraintestinal manifestations.

The causes of IBD are still unclear. A number of theories have been hypothesized, as well as a combination of them, i.e. a combination of genetic factors, environmental, dietary, immunological mechanisms, infectious causes and even psychosomatic condition.

IBD and female infertility

It is found that female patients with IBD who undergo only medication, do not have different infertility rates compared to the general population, as their rates are in the range of 4-15%.

It is considered that only active Crohn's disease plays a negative role in female fertility, as does surgical treatment of ulcerative colitis by creating enterocolic or enterorectal thelicity.

Focusing on female patients with Crohn's disease, an active incriminating element of infertility, *Inflammation* is recognized and especially in the pelvis as a specific immunological phenomenon.

Inflammation in Crohn's disease as a specific element is considered responsible for the appearance of inflammation in the oviducts, as well as for causing low oocyte reserve. Pelvic inflammation can cause inductive inflammation in the oviducts, which causes difficulty in moving the oocyte and in the final implantation after fertilization, or because due to the inflammation that will occur in the oviducts will cause their narrowing either because hydrosalpinxes can be caused, or even the proper functioning of the oviduct may be disrupted. (2)

The mechanism of reduction of oocytes reserves due to pelvic inflammation remains unclear. Several theories have been hypothesized about this. It has been speculated that pelvic inflammation may be associated with a decrease in anti-Müllerian hormone. A comparative study of 35 patients with Crohn's disease showed that they had a statistically significant decrease in this hormone (1.02 ± 0.72 ng/mL vs. 1.89 ± 1.80 ng/mL, p = 0.009). Also, among the patients, those with the lowest levels were those with active disease compared to those in remission. (3)

This has raised concerns about what characteristics patients who will experience a decrease in this hormone should have. Thus, it appeared that patients over 30 years of age had lower percentages of the hormone, as well as a smaller reserve of oocytes. (4) Another study, however, suggested that the age of patients with the decrease in the hormone should be reduced even further to 25 years, while another study suggested that the reduction of the hormone is not only associated with patients over 30 years of age,(5) but also with those who experienced the disease equal to or more than five years. (6)

A specific issue that concerns all female patients is the effect of the disease during menstruation and menarche, when it concerns the onset of childhood – adolescence. IBD can act as an inhibition to the onset of menarche. This is determined by several factors. Either indirectly due to malnutrition and especially in Crohn's disease that can be caused as a result of IBD, so that the body gives priority to the development of the other systems of the body, resulting in not only delayed development of girls but also of boys, there is also a delay in the development

of the genital system, especially in severe cases. As a result, menarche is delayed or there is amenorrhea, as well as sometimes underdevelopment and under-functioning of the genital system. On the other hand, in IBD, the effect of inflammatory cytokines IL-1 and TNF-α negatively affect reproductive hormones, resulting in disruption of the menstrual cycle with secondary complications from this disorder.(7) IBD can worsen its symptoms during menstruation. This can be explained by the presence of intrauterine prostaglandins that worsen inflammation and intestinal motility, but also by the presence of estrogen receptors in the gastrointestinal tract associated with hypersensitivity and hyperactivity of the intestines.(8) Regarding menopause, studies are contradictory, but a newer series study concluded that there is no difference in the time of menopause of patients with IBD compared to the general population. (9)

Regarding genetic abnormalities and teratogenicity in children of IBD patients, there are no differences in their rates compared to the general population. The only confirmed cases of teratogenicity and birth defects are the intake of certain teratogenic drugs, which is no longer the case. (10)

Surgery for IBD and infertility in females

Surgical treatment is the second main pillar of treatment, in the management of patients with IBD. Given that surgical treatment is not a definitive solution to this pathological phenomenon, apart from total colectomy in ulcerative colitis, surgery will be resorted to either on an urgent or regular basis. Emergency surgery in a patient with IBD is intended to treat an acute abdominal problem that consists of treating ileus, perforation, twisting, toxic megacolon, peritonitis and rupture anywhere in the digestive tract with emphasis on the small and large intestine. On a regular basis, surgery aims to treat the appearance of strictures, abscesses, fistulas, and areas with persistent inflammation in the digestive tract that does not respond to conservative treatment. In many cases, especially in acute phases of relapse, surgery is performed in two times. That is, after an urgent problem is treated, a stoma, ileostomy or colostomy is created and in a second year the continuity of the gastrointestinal tract is restored. Sometimes it is chosen to excise part of the intestine and create a prophylactic ileostomy, which will give time to the anastomosis that will have been created to prevent any possible leakage. Bowel restoration in three times is also possible, but only in the special case, when initially a total colectomy and prophylactic ileostomy are performed, in the second round the creation of an entero-rectal pouch and in the third the reverse of the ileostomy. Sometimes the solution of the final ileostomy and the final colostomy may be chosen as permanent solutions in cases with multiple surgeries resulting in shortening of the intestine or difficulty in tissue preparation, so the solution of the stoma is preferable. As far as ulcerative colitis is concerned, its surgical treatment concerns the large intestine. On the contrary, in Crohn's disease, a surgical approach can be performed at any point of the digestive tract, although operations on the stomach, duodenum with the treatment of perforation, subtotal and total gastrectomy, creation of gastrointestinal anastomosis, but also partial or total esophagectomy for the treatment of perforation or esophagobronchial fistulas concern solitary cases. We should also keep in mind that the creation of anastomosis in the digestive tract follows a different technique than that performed for other surgical pathologies of the intestine, as the problem of recurrence of inflammation and narrowing of the anastomosis site lurks, so the technique of wide anastomosis is chosen, to prevent its possible future stenosis. Finally, the creation of an enterorectal

or enteroanal pouch after wide resections of the large intestine aims to avoid a final stoma and to maintain or create a sphincter, in order to facilitate the patient's daily life, but this technique mostly concerns patients with ulcerative colitis, as the creation of a fecal pouch in patients with Crohn's disease has the risk of inflammation that will lead to additional complications.

However, all these surgical approaches, both from the type of surgeries that will be selected for each patient, man or woman, as well as from the techniques that will be required, but also from the recovery period postoperatively, as well as the possible complications that may occur, affect patients to another extent in terms of fertility, sexual desire, sexual ability and the possibility of gestation. Secondarily, the malnutrition and cachexia that may arise has its own negative effect on childbearing.

The creation of a J-pouch-shaped enterorectal or ancrorectal pouch, i.e. with folding and lateral anastomosis of part of the small intestine to form a pouch in which feces will be collected and its anastomosis with the anus mainly and less with the remaining part of the rectum after total colectomy is the surgery of choice for ulcerative colitis(19) and not for Crohn's disease, as the newly formed pouch in this case may show evidence of inflammation with all the complications that may arise.(11)

It is judged that minimally invasive surgery in IBD has a beneficial effect on patients' fertility. (12)

Despite studies, analyses, and meta-analyses on the issue of surgical treatment of patients with IBD, it has not been possible to provide absolutely clear data on what exactly are the causes that lead part of patients after IBD operations to infertility.

The various analyses present the following data.

Fertility in groups of IBD patients who underwent some type of surgery compared to patients who never underwent surgery

The data collected from the retrospective studies were not clear. Infertility at 12 months of free intercourse did not appear to be associated with prior surgery (RR 5.45; 95% CI: 0.41 - 72.57). The patients studied had ulcerative colitis. One study looked at women with and without a J-pouch follicle and (13) another looked at them compared to and without ileorectal anastomosis construction.(14) Another study indicated infertility at 24 months of free intercourse with previous surgery involving mainly patients with ulcerative colitis (RR 3.59, 95% CI: 1.32 - 9.73), but not Crohn's disease (RR 2.03, 95% CI: 0.56 - 7.33), without giving further information on the type of surgery. (15)

A relationship of miscarriages was observed in patients who had undergone previous surgery regardless of the type of abortion in both women with Crohn's disease (OR 2.56, 95% CI: 1.19 - 5.51) and ulcerative colitis (OR 7.14, 95% CI: 1.02 - 50.18), while stillborn pregnancies were not associated with previous operations in ulcerative colitis (RR 1.91, 95% CI: 0.10 - 36.02), nor in Crohn's disease (RR 1.98, 95% CI: 0.32 - 12.16). (16)

The issue of prematurity could not be associated with prior surgery regardless of its type in IBD patients (RR 1.91, 95% CI: 0.67 - 5.48). The rates were catalytic for both Crohn's disease (RR 2.32, 95% CI: 0.75 - 7.21) and ulcerative colitis (RR 0.56, 95% CI: 0.03 - 9.73). Nor was there any association in the birth of underweight children of women with IBD who underwent surgery regardless of the type of surgery (RR 0.61; 95% CI: 0.08 - 4.83). (17)

Infertility before and after surgery in IBD patients

Most studies focused on patients with ulcerative colitis and those who had to undergo the creation of a J-pouch. On the contrary, for patients with Crohn's disease, the complexity of the surgeries that could potentially be undergone, the location of sur-

gical problems several times high in the large intestine and the final ileum, the more likely these patients to undergo enterectomies or enteroplasty in the small intestine, as well as the specialized cases that required operations on the upper digestive tract, led the researchers to turn their attention to patients with ulcerative colitis, especially those who had undergone the creation of the follicle. Both because the surgical fertility problems that could arise were placed anatomically low in the pelvis closer to the internal reproductive organs, and because it was possible to compare their conclusions with patients of Familial Polyposis Syndrome (FAP) who underwent a similar operation to create a pouch in the shape of a J-pouch, which were respectively.(18) The lack of studies on the infertility of IBD patients with a clear description of surgical procedures, as well as the existence or absence of a stoma, are data that require further study.

Existing studies suggest that the creation of a J-pouch in patients with ulcerative colitis is the procedure that potentially carries greater risks of infertility. These risks focus on injury to the oviducts during fibrosis surgery and the appearance of adhesions in them, (19) while operations farther from the pelvis clearly involve fewer potential injuries to these organs. In fact, the creation of the pouch in three stages compared to the two-stage operation was associated with higher rates of adhesions and inductive infertility,(20) while the technique of anastomosis with the use of an incisor again indicated higher adhesion rates compared to this construction with the surgeon's hand. (21)

Artificial insemination and IBD

Apart from natural childbearing, IBD patients have also undergone artificial insemination methods with positive results. The most recent studies on the subject examine various aspects of the rules, conditions and elements that would favor the successful outcome of an artificial conception in this category of patients. (22)

A 2015 comparative study of healthy control patients undergoing artificial insemination showed similar results in these two populations, as examining 49 patients with Crohn's disease, 71 with ulcerative colitis, 1 with unspecified colitis compared to 470 healthy controls, 53% live births were achieved in controls, 69% in patients with ulcerative colitis and 57% in patients with Crohn's disease. In all three populations, pregnancy success in the first cycle of artificial insemination was around 41% and around 30% of live birth from the first cycle. This study enrolled both patients who underwent pelvic surgery without also distinguishing patients based on their medication. (22)

However, the largest series study on artificial insemination in IBD patients to date is based on Danish national data by examining a database of 432 patients with ulcerative colitis, 182 with Crohn's disease and 52489 IBD-free women who all underwent assisted reproduction over 20 years.(23) The study showed that patients with ulcerative colitis had a lower live birth rate than controls (OR=0.79) taking into account the couple's ages, time of year, type of assisted treatment, cause of infertility, body mass index and tobacco and alcohol use, but not taking into account the severity of IBD, as in Denmark only patients with a disease in remission are allowed to undergo artificially assisted reproduction, while children had an increased risk of prematurity (OR=5.29). For patients with Crohn's disease, this study showed that if they had undergone any surgery prior to assisted reproduction, there was a reduced probability of live birth for each embryo transfer compared to controls (OR=0.51). The same researchers found in a later study that for patients with Crohn's disease, the failure of assisted reproduction within 18 months of the first cycle was increased for those who

had undergone surgery, especially if it occurred less than two years before assisted reproduction (OR=0.29), while no corresponding difference was observed for patients with ulcerative colitis regardless of the type of surgery. (24)

Because the studies so far are few, more should be published that will take into account as large a sample of patients as possible and examine in particular the relationship of the types of surgeries that women who will resort to artificial insemination may have undergone, as this data has not been thoroughly studied.

Infertility in male IBD patients

A more specific approach is needed to examine male infertility in patients with IBD. The global focus of studies was on female patients, which is easily understood, as gestation and childbirth are fundamental elements in reproduction, so that the additional difficulties that may arise from IBD pathology during these periods attract maximum interest.

However, although fewer in number, there have also been studies on the effect of IBD on male infertility dealing now with elements that could negatively affect the functioning of the male reproductive system and could be the result of the manifestation, medication, surgical treatment and mental effect of IBD on patients.(25)

Comparing the infertility of men with IBD compared to that of the general population, increased rates are found (26) 24% for ulcerative colitis and 27% for Crohn's disease. (27) However, the parameters that affect male infertility in IBD acquire special characteristics.

Male patients show increased rates of serum antisperm antibodies (28) compared to healthy controls, where approximately 16% of samples were positive. (29) This fact has not been clarified. Only hypotheses have been put forward with the strongest being the one because of the immune disorder observed in IBD patients in general, so that the development of antisperm antibodies is also a result. Of course, it is considered that the Male infertility in unoperated males with IBD has no statistically significant difference from the general population during the remission phase. (30)

The medication that has been shown to negatively affect the quantity and quality of sperm in the form of azoospermia, oligospermia and sperm motility, is treatment with Sulfazalazine because of its synthetic, Sulfapyridine, which causes all the side effects of treatment. That is why it is recommended as a guideline for childbearing to discontinue and replace Sulfazalazine, as after a three-month break there is a reversal in the effect of sperm.

In recent years there has been a study with a limited number of patients, which indicated that Mesalazine can also cause alterations in the quality and quantity of sperm that only part of motility returned after a three-month break, while another study(31) indicated as a causative factor for this phenomenon with Mesalazine the presence in excipients of Dibutyl Phthalate (Dbp), which has an effect on the urinary system. However, a recent review did not ultimately indicate an association of Mesalazine with a negative effect on sperm. (32) Regarding corticosteroids, the possible effect on the axis Hypothalamus – Pituitary – Gonads through the effect on the synthesis of hormones GnRH, LH and FSH, indicates as a general guideline its use for a limited period during periods of childbearing. (33)

A study that focused only on male patients with ulcerative colitis who underwent pouch formation showed that 12% of these patients had an ejaculation problem. (34) A meta-analysis 20 years ago of patients who underwent pouch formation concluded that 25.7% of these patients had erection and ejaculation problems after surgery. (35) Another study of 122 patients who underwent similar surgery showed that the problem of retrograde

ejaculation increased from 1.6% preoperatively to 8.2% postoperatively, while there was no change in erectile dysfunction (36) rates before and after surgery. A study of a higher percentage of patients (762) with similar surgery concluded that one year after surgery, sexual dysfunction problems of all types amounted to 1% and after two years to 2%. (37) Also, a newer prospective study in patients with ulcerative colitis who also underwent pouch formation did not reveal substantial rates of erectile dysfunction according to the international control system, International Index of Erectile Function (IIEF-5), six months after surgery (22.0 vs 23.0, p=0.152).(38) Regarding the problem of erectile dysfunction, this was treated in about 79% with the administration of Sindelafyl. (39)

An important element for the sexual dysfunction of men with IBD becomes the chronicity and especially the acuity of the symptoms. In periods of relapse and long-term presence of intense symptoms, it is inevitable that sexual desire and function recede and take second place in the lives of these men, as priority is shifted to the treatment of the disease, so that inductively it affects reproduction.

In addition, psych stressful phenomena with the manifestation and management in the pharmaceutical, surgical and social dimensions of IBD can lead to the presentation of depressive behavior with subsequent administration of psychotherapeutic medication. Already the increase in anxiety and possible depressive syndrome can lead to a decrease in the production of Testosterone and LH and the consequent alteration of sperm quality, in order to inductively create sexual dysfunction that will in turn lead to infertility.(40) To this should be added the side effects on desire and erectile dysfunction that can be caused by antidepressant treatment, so that finally the depressive manifestations of IBD patients are recognized as an incriminating factor of infertility, as indicated (41) in the comparison with the general population.(42) Moreover, stopping the use of alcohol and tobacco helps equally to improve the sexual function of patients with IBD, as does improving nutrition to avoid malnutrition that again leads to problems in sexual desire and function.(43) To all these factors should be added the conscious abstinence from childbearing of patients with IBD and especially those with Crohn's disease, under the impression that it will be passed on to their offspring, although the genetic background of IBD does not seem to obey the rules of Madelene Inheritance, this is why patients need information and psychological support.

Surgeries, where pelvic manipulations must be performed and especially total colectomies with the creation of a J-pouch, can cause clear problems of erectile dysfunction and inability to ejaculate due to possible injury to the sympathetic and parasympathetic nerve plexuses. However, if the surgical manipulations are done diligently and if the complications of IBD have not altered the nerve tissues or adjacent tissues, to allow their protection, then the outcome of the operation may be free of complications for sexual activity. However, more studies, prospects, retrospectives, and analyses are needed to examine the effect of IBD on the sexual health of male patients, as the multitude of studies have focused on female patients.

Results

The international medical community studied the issue of reproduction and the specific aspects concerning IBD patients in the field of conception, pregnancy, childbirth and lactation. And through the European Crohn's and Colitis Organization (ECCO), after thoroughly analyzing the issue, it came up with some commonly accepted general principles(44).

The fertility of patients with IBD is an element of

particular concern to the scientific medical community, as the evolution in the study of diseases that constitute the phenomenon of IBD, the development of surgical techniques concerning these patients and the inclusion in the pharmaceutical arsenal of more and specialized preparations, but also the deeper knowledge of treating physicians today in valid diagnosis, management and treatment of patients, have allowed patients to be given a better quality of life, so that having children is not today a different problem of everyday life in most cases compared to the general population.

The term infertility means the non-achievement of conception in a couple who for a period of one year has sex without the use of contraception, but pregnancy is not achieved. This general rule will also be used as a reference for IBD patients.

It should be emphasized that female IBD patients who undergo only medication do not have different infertility rates compared to the general population, as their rates are in the range of 4-15%.

It is considered that only active Crohn's disease plays a negative role in female fertility, as does surgical treatment of ulcerative colitis by creating enterocolic or enterorectal thelicity.

Focusing on female patients with Crohn's disease, an active incriminating element of infertility, *Inflammation* is recognized and especially in the pelvis as a specific immunological phenomenon.

Inflammation in Crohn's disease as a specific element is thought to be responsible for the appearance of inflammation in the oviducts, as well as for causing a low reserve of oocytes. Pelvic inflammation can cause inductive inflammation in the oviducts, which causes difficulty in moving the oocyte and in the final implantation after fertilization, either because the inflammation that will occur in the oviducts will cause them to narrow, or because hydrosalpinges may be caused, or even the proper functioning of the oviduct may be disrupted.

The mechanism of reduction of oocytes reserves due to pelvic inflammation remains unclear. Several theories have been hypothesized about this. It has been speculated that pelvic inflammation may be associated with a decrease in anti-Müllerian hormone.

Regarding genetic abnormalities and teratogenicity in children of IBD patients, there are no differences in their rates compared to the general population. The only confirmed cases of teratogenicity and genetic abnormalities are the intake of certain teratogenic drugs, which no longer occurs, which is why studies do not show different rates for IBD patients compared to the general population.

IBD are considered as thrombophilic diseases and especially in the nosological entity of deep vein thrombosis. Therefore, the use of oral contraceptives increases the risk of embolism in IBD patients.

Surgical treatment is the second main pillar of treatment in the form of intervention, in the management of patients with IBD. Given that surgical treatment is not a definitive solution to this pathological phenomenon, with the exception of total colectomy in ulcerative colitis, recourse to surgery will either be urgent or on a regular basis. Emergency surgery in a patient with IBD is intended to treat an acute abdominal problem that consists of treating ileus, perforation, twisting, toxic megacolon, peritonitis and rupture anywhere in the digestive tract with emphasis on the small and large intestine. On a regular basis, surgery aims to treat the appearance of strictures, abscesses, fistulas and areas in the digestive tract with persistent inflammation that does not respond to conservative treatment. In many cases, especially in acute phases of relapse, surgery is performed in two times.

However, all these surgical approaches, both from the type of surgeries that will be selected for each patient, man or woman, as well as from the techniques that will be required, but also from the recovery period postoperatively, as well as the pos-

sible complications that may occur, affect patients to another extent in terms of fertility, sexual desire, sexual ability and the possibility of gestation. Secondarily, the malnutrition and cachexia that may arise has its own negative effect on childbearing.

A more specific approach is needed to examine male infertility in patients with IBD. Male patients have increased rates of serum antisperm antibodies compared to healthy controls, where approximately 16% of samples were positive. The medication that has been shown to negatively affect the quantity and quality of sperm in the form of azoospermia, oligospermia and sperm motility, is treatment with Sulfazalazine because of its synthetic, Sulfapyridine, which causes all the side effects of treatment. That is why it is recommended as a guideline for childbearing to discontinue and replace Sulfazalazine, as after a three-month break there is a reversal in the effect of sperm.

Conclusion

The issue of infertility of IBD patients requires further epidemiological studies, as despite the latest efforts of the medical community there are still unclear areas of research in this field. It is considered that only active Crohn's disease plays a negative role in female fertility, as does surgical treatment of ulcerative colitis by creating enterocolic or enterorectal thelicity. Men suffering from IBD face the problem of rectal dysfunction after specific types of surgery, while the use of specific drugs have negative impact in men's fertility. In recent years, the interaction between the immune system, the normal gut flora and the colon epithelium has been supported as the cause of IBD, although there is still no clear evidence. Greater emphasis is placed on the search for gene variants, as seen mainly in patients with Crohn's disease. The immune system of the intestinal mucosa is thought to be involved in the pathophysiological mechanism of IBD. Therefore the research should focus on DNA structure of the patients and their immune's system response regarding their influence on infertility.

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