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Review article

# Inflammatory bowel diseases and reproductive health

Agnieszka Kokoszko-Bilska [a,b,*], Slawomir Sobkiewicz [a], Jakub Fichna [b]

[a] "Salve Medica" Private Fertility Clinic, Łódź, Poland
[b] Department of Biochemistry, Faculty of Medicine, Medical University of Lodz, Łódź, Poland

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ABSTRACT

Inflammatory bowel diseases (IBD) constitute a group of chronic intestinal diseases, including Crohn's disease and ulcerative colitis, which typically involve patients of reproductive age and may influence several features of human reproduction. There are many concerns regarding the interactions between the course of IBD, applied treatment (pharmacological or surgical), and fertility, reproductive outcomes, and also neonatal outcomes.

To review the literature describing fertility in IBD patients (separately for female and male), and possible infertility treatment in this group of patients, a PubMed search for English only publications (articles and/or abstracts) was conducted. Initially, the titles of publications and their abstracts were screened, and the most appropriate articles were selected and reviewed.

Overall, in patients with quiescent IBD, fertility is almost identical to the general population, but particular subgroups of patients (with active disease, on pharmacological treatment, and after pelvic or abdominal surgery) may be affected by reduced fertility. Additionally, patients with IBD have fewer children than the general population, mainly as a result of voluntary childlessness. The main objectives for successful reproductive outcomes in IBD patients are proper guidance and also optimal treatment for achieving and maintaining disease remission. Recently, the European Evidence-Based Consensus on Reproduction and Pregnancy in IBD (the European Crohn's and Colitis Organization Guidelines) has been established to optimize preconceptional counseling and to promote an appropriate clinical management for patients planning to conceive. However, further studies are needed regarding the preservation of fertility in IBD patients and introduction of optimal infertility treatment in this group of patients.


**Contents**



## Introduction

Inflammatory bowel diseases (IBD) is a group of chronic bowel diseases, including Crohn's disease (CD), ulcerative colitis (UC) and indeterminate colitis (IBD unclassified), which typically affect patients of reproductive age and influence almost all aspects of a patient's life, including fertility.

The overall prevalence of IBD is 396/100,000 and the incidence rate of CD varies between 0.1 and 16/100,000, while that of UC varies greatly between 0.5 and 24.5/100,000 [1,2]. Based on the latest report of the European Crohn's and Colitis Organization-Epidemiological Committee (ECCO-EpiCom) the mean annual incidence rate of IBD is 11.3/100,000 in Eastern Europe and 14.0/100,000 in Western Europe [3]. Epidemiological studies have

* Corresponding author.
*E-mail address:* agnieszka_kokoszko@poczta.fm (A. Kokoszko-Bilska).

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shown that almost 50% of IBD patients have less than 35 years at the diagnosis and 25% of women with IBD become pregnant for the first time after the diagnosis [1,2,4].

The influence of IBD and its treatment on fertility (both female and male) and pregnancy is an important clinical problem. However, the management of IBD patients planning to conceive or being pregnant is contentious, because is mainly based on evidence obtained from expert opinion, retrospective studies and some case-control studies [5]. To date, there is still not enough prospective studies and randomized control trials (RCT) related to fertility and pregnancy in IBD patients [5]. Over the past few years, a number of reviews have been published, which referred to the IBD and human reproduction, pregnancy and lactation [1,5–11]. Unfortunately, only some of them take into account existing knowledge on the impact of IBD in the context of infertility, the use of assisted reproductive techniques (ART) and future reproductive potential in young patients [5,7–9].

Recently, the European Crohn's and Colitis Organization (ECCO) established the Second European Evidence-Based Consensus on Reproduction and Pregnancy in Inflammatory Bowel Disease to standardize and optimized preconceptional counseling and appropriate clinical management of pregnancy in patients with IBD [12]. This updated consensus paper stated that there is no evidence that inactive CD or UC affects fertility, however, active CD may reduce fertility (ECCO Statement 2A) [12].

## IBD and female fertility

In comparison to the general population, fertility is unchanged in women with quiescent IBD and who have received only pharmacological management (non-surgically treated IBD) [11]. Community-based and population-based studies suggest that infertility rate in this group of patients varies between 5% and 14%, which is similar to that of the general population [9,13]. There may be several reasons for the potentially reduced fertility in IBD women, among which surgery-related problems and psychological problems seem to be the most important [12].

Active CD may diminish fertility both directly, through pelvic inflammation (resulting in tubal infertility) and through reduced frequency of sexual intercourse (*e.g.* due to perianal localization of the disease causing dyspareunia), and secondarily, through surgical treatment and related tubal adhesions [12]. Fertility in women with UC is unchanged (as compared to the general population) until they undergo surgery [5–9,12]. Previous abdominal or pelvic surgery significantly reduces the possibility of pregnancy, probably due to the presence of post-operative adhesions, secondary obstruction of the fallopian tubes, higher rates of hydrosalpinx (a distally blocked fallopian tube filled with serous or clear fluid) or changing the normal function of the fallopian tubes [9,12,14].

Evidence suggest that the incidence of subfertility (failure to conceive within a year) is increased amongst women with IBD who have undergone ileal pouch anal anastomosis (IPAA), which is the operation of choice in UC [5–9,12]. This type of surgical approach avoids a permanent stoma and is associated with an improved quality of life when compared with proctocolectomy and end ileostomy [15–17]. Several studies found that IPAA conferred a 2–3 fold increased risk of infertility compared with pharmacological management [12]. In a systematic review, Cornish et al. demonstrated that the infertility rate in women with UC was 12% prior to IPAA and increased to 26% after IPAA [15]. In turn, Waljee et al. in a systematic review and meta-analysis showed that IPAA increases the risk of infertility in women with UC by approximately threefold (the relative risk of infertility after IPAA was 3.17) [16]. In 2011, Rajaratnam et al. conducted another systematic review and meta-analysis to determine the effect of IPAA on female fertility in UC, its mechanisms, and also strategies for prevention and management of infertility post-IPAA [17]. Weighted average infertility rates were 20% before IPAA and 63% 12 months post-IPAA, while the relative risk of infertility after IPAA was 3.91 [17]. Post-operative tubal dysfunction (secondary to adhesions) was recognized as the main mechanism leading to this increased risk of infertility [17].

In turn, Lepistö et al. used a different approach to evaluate fertility in the IPAA group by measuring time to first pregnancy and selecting two end-points to complete the study – pregnancy or starting infertility treatment [18]. The authors revealed that after 2 years the probability of conceiving was reduced to 47%, but after 6 years, the cumulative incidence for all (natural and assisted) pregnancies was 80% [9,17,18]. Thus, they concluded that in women after IPAA, mostly a reduction in the probability of conception rather than complete infertility is recognized [18].

Various intra-operative methods, such as oophoropexy, interposition of an omental pedicled graft, or anti-adhesion products have been suggested to reduce the incidence of pelvic adhesions, but none of them was able to have any effect on the prevention of infertility [17]. There is now some evidence from retrospective and cross-sectional studies that only a laparoscopic approach to IPAA may decrease infertility rate compared with an open surgical approach, which may result from reducing the formation of adhesions [12,19,20]. These data allowed to consider a laparoscopic approach to IPAA as the method of choice in young women (ECCO Statement 2D) [12]. Additionally in 2015, Harnoy et al. conducted a retrospective study to assess the impact of the IPAA technique (hand sewn *vs.* stapled IPAA) on fertility in female patients with UC [21]. The IPAA technique did not influence the fertility outcomes of UC patients, but there was a trend for better female fertility after hand sewn IPAA ($p = 0.07$) [21]. Another way to preserve fertility in IBD patients (mainly UC patients) is to use a two-stage surgical approach, which comprises subtotal colectomy with end ileostomy (rectal preservation) as a first stage procedure and IPAA postponed until the patient's family is complete as a second stage procedure [9,17]. Unfortunately, this type of surgery would be not acceptable to most women [9,17]. Moreover, preoperative embryo cryopreservation is also possible in patients about to undergo IPAA surgery [9,17]. This procedure involves controlled ovarian hiperstimulation, then retrieval of oocytes, *in vitro* fertilization (IVF) and finally embryo cryopreservation [17]. Subsequent cryopreserved embryo transfer would be available postoperatively [17]. Despite the above mentioned possibilities of prevention and management of infertility post-IPAA, up to now no guidelines for the preservation of fertility in IBD women undergoing surgery have been approved [9,17]. Palomba et al. indicated that an effective strategy in these patients should be based on the proper qualification for surgery with choosing a minimally destructive surgical technique and additionally on the appropriate assessment of ovarian reserve indicators [*i.e.* age, serum anti-Müllerian hormone (AMH) concentration and antral follicular count] [9].

In this connection, there are recent data suggested a reduction in ovarian reserve status in IBD women, as estimated by serum AMH concentration, which is one of the best predictors of ovarian reserve [12]. In 2012, Freour et al. revealed that women with CD in remission did not have significantly reduced ovarian reserve when compared to a control population (*i.e.* age-matched women with normal ovarian reserve) [22]. However, serum AMH levels remained comparable between CD and control women less than 30 years of age, but they were significantly lower in CD woman $\geq$30 years [22]. Furthermore, it was found that the negative correlation between age and AMH level tended to be more pronounced in CD than in control women [22]. Additionally, the serum AMH concentration was influenced by the location of CD, with a colonic location of the disease being independently