

Authors' answers to editors and reviewers

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Manuscript Title: Sexual health and fertility for individuals with inflammatory bowel disease
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Again, the authors thank the Reviewers for giving of their time to review this study and for their questions and comments.

Answers to the reviewer 1 comments

"The paper merits the publication."

The authors really appreciate this comment and thank the reviewer.

Answers to the reviewer 2 comments

"This review is relevant because the incidence and prevalence of IBD is not reduced, and the sexual health and fertility of IBD patients can be seriously impaired. The review is structured, includes informative tables and a figure, and contains enough recent references. However, the manuscript has a number of inaccuracies and incomplete scientific data."

1. *Consideration of fertility outside the context of the influence of common factors, especially medications, on the course and outcomes of pregnancy (with few exceptions) is an important omission. This can be misleading, for example, when the drug affects both fertility and pregnancy/fetus.*

The authors thank the reviewer and agree with this important comment. Some drugs can affect both fertility and pregnancy outcomes, that's why the example of MTX has been mentioned in the manuscript. However, this review tried to focus more on sexuality and fertility aspects in IBD patients rather than pregnancy to avoid confusion for readers.

That's why major papers about IBD and pregnancy have been cited in the reference :

- Selinger CP, Eaden J, Selby W, Jones DB, Katelaris P, Chapman G, McDonald C, McLaughlin J, Leong RWL, Lal S. Inflammatory bowel disease and pregnancy: lack of knowledge is associated with negative views. *J Crohns Colitis*
- Nguyen GC, Seow CH, Maxwell C, Huang V, Leung Y, Jones J, Leontiadis GI, Tse F, Mahadevan U, van der Woude CJ, IBD in Pregnancy Consensus Group, Canadian Association of Gastroenterology. The Toronto Consensus Statements for the Management of Inflammatory Bowel Disease in Pregnancy. *Gastroenterology* 2016
- Cornish J, Tan E, Teare J, Teoh TG, Rai R, Clark SK, Tekkis PP. A meta-analysis on the influence of inflammatory bowel disease on pregnancy. *Gut* 2007

2. *The description of medications that affect sexual health and fertility is incomplete. Reported that "the use of immunosuppressants or biological therapies is not associated with sexual dysfunction changes", but the reference is missing. The authors cite that in women "corticosteroids were independently associated with sexual dysfunction", but do*

not report a reduction of serum testosterone during prolonged corticosteroid treatment in men. There are also no data on sexual/erectile dysfunction with mesalazine or MTX (described in the literature and specified in the SPCs). Mesalazine-induced infertility described earlier is not mentioned. References are missing when describing that "MTX can be responsible for oligospermia and is reversible after stopping usage; this drug is contraindicated for both women and men because it is embryotoxic." Authors report that "infliximab therapy seems to decrease sperm motility." while only "a trend toward decreased sperm motility" ($P = N.S.$) was identified in the study. The possible associations between vitamin D deficiency (in women) and zinc deficiency (in men) and infertility are not reported.

The authors thank the reviewer for this comment. However, this manuscript didn't intend to list the entire list of medications responsible for fertility/sexual disorders as these informations are available in most reviews on this topic and papers cited in our manuscript.

- Review article: the safety of therapeutic drugs in male inflammatory bowel disease patients wishing to conceive. *Aliment Pharmacol Ther* 2015

- Fertility and Contraception in Women With Inflammatory Bowel Disease. *Gastroenterol Hepatol* 2016

However, the authors made a few modifications according to these comments.

Concerning MTX inducing erectile dysfunction, we added the very recent review talking about this topic by Allocca M et al.

Concerning, vitamin D and zinc, a sentence has been added in the section "how to treat infertility".

3. *The section "Male fertility" may be excluded because it does not claim to be complete, and many aspects are already included in other sections. In general, the manuscript may be published after the revision."*

The authors think this section should be kept and will let this decision to the editor's choice.

Answers to the reviewer 3 comments

Dear authors, I appreciated reviewing your paper. It is globally clear and well structured and considers completely various aspects of the topic, which is more and more actual. I only have some suggestions: - as it is a review, you could add a brief "methods" paragraph to explain your literature search methods, if systematic or not and to express if literature is scarce or rich about this topic, what themes are well known and what is still unclear - it could be useful to add a table on drugs effects on fertility for both men and women, which could be immediate and useful for clinical practice - for what concerns the "surgery influence", it could be useful to expand on all the most common types of surgery IBD patients often undergo (e.g. ileo-cecal resection, ileal resections etc) to make clear eventual differences of the different types of surgical interventions on fertility problems or miscarriage. - finally, it could be useful to add strength to authors' proposals for ameliorating sexual health and fertility issues in IBD patients and explain what should be practically added to the usual clinical practice.

We thank the reviewer for this interesting comment. The authors added a brief methods paragraph to explain the literature search. Moreover, the authors voluntarily did not add a table on drugs effects as this has already been reported many times in past medical literature and cited in this review.

- Review article: the safety of therapeutic drugs in male inflammatory bowel disease patients wishing to conceive. *Aliment Pharmacol Ther* 2015

- Fertility and Contraception in Women With Inflammatory Bowel Disease. *Gastroenterol Hepatol* 2016

Data Sources and Searches (ADDED IN THE TEXT)

An electronic search of the literature was conducted using MEDLINE (PubMed). The search was restricted to English language. The search strategy used the following MeSH and text words: “Sexual dysfunction”, “Inflammatory Bowel disease”, “Fertility”, “Psychological”, “Crohn’s Disease” and “Ulcerative colitis”.

Regarding the type of surgery IBD patients often undergo, literature on fertility aspects is scarce about other techniques than IPAA. No data are available on the fertility after ileo-cecal resections or ileal resections in IBD patients. However, the authors adapted the paragraph on this topic to make it more understandable.

Answers to the reviewer 4 comments

“I really enjoyed the opportunity to review the manuscript by Dr. Leenhardt and colleagues from Paris, France. The review topic by the authors is really interesting and very important. It is a review paper about sexual health and fertility for individuals suffering from inflammatory bowel disease. As herewith reported, sexual health is multidimensional with five dimensions: physical, emotional, social, mental, and spiritual as well as is associated with anxiety, depression, impaired quality of life, and fatigue. Along with body image, it is an important aspect of psychosocial functioning and has a significant impact on overall quality of life. In younger couples challenged with IBD are faced with failure to achieve pregnancy after 12 months of unprotected intercourse (infertility) is quite common and painstaking. In fact, as the authors have indicated that even pouch surgery, restorative proctocolectomy (RPC) with ileal pouch anal-anastomosis (IPAA), which in fact is supposedly intended to cure the patient increases the risk of infertility in women and men with UC by approximately threefold. The mechanisms likely responsible for this important increase of the subfertility rate have been related to postsurgical abdominal adhesions, tubal obstructions and damage to pudendal nerve, the main nerve of the perineum. The paper is well summerized and contains valuable information regarding chllenges and advances about sexual health in IBD patient.”

The authors really appreciate this comment and thank the reviewer.

End of revisions

Thank you again for your thorough reviewing of our study