Answer to reviewers

Dear reviewers, we are very grateful for your valuable comments, which have allowed us to significantly improve the manuscript. Below is how we have corrected the manuscript according to your comments.

Reviewer #1:

Title: A bit "broad". It is stated that the manuscript deals with "gynecological manifestations" but mainly disturbances in menstrual cycle and ovarian capacity are described.
ANSWER: We changed the title to “Menstrual cycle abnormalities in inflammatory bowel disease patients and the effects of anti-TNF alpha drugs on gynecological pathology: a literature review”;

Introduction: I think a short description of fertility problems in women with IBD with major references of interest is necessary to frame why it is of interest to dig deeper into gynecological manifestations is needed.
ANSWER: We added information on fertility in IBD patients;

Besides there is a lack of references to underline the major statements in the two first sections of the introduction.
ANSWER: We added references;

It is mentioned that several studies have provided new information regarding benefit of biological therapy but these studies are animal studies which should be noted.
ANSWER: We noted that the studies mentioned are animal studies;

Methods: There is a lot of focus on adalimumab in the manuscript. This could reflect that data are lacking on other treatments but I would suggest that the search is including other therapies as well (TNFalpha blocking agents as a group; Vedolizumab, Ustekinumab, 5-ASAs, steroids, immunomodulators, small molecules). Should no data on some of these drugs not be available this should be noted.
ANSWER: We focus our review of the literature on biologics. Today, the information is very limited and we could not find additional information on gynecological pathology or menstrual abnormalities, VEDO, UST or small molecules. As you suggested, we note that data on these drugs are not available to this day.

Table 2 and 3: No need to use space on providing tables describing few animal studies and case reports. The tables should be omitted IBD and menstrual cycle: A study regarding 662 female patients with IBD undergoing surgery is cited. However it is not discussed whether the results presented is related to IBD or to the surgery. This is of importance since the study by Saha et al produced contradictory results. The reason for
that might well be that the populations described in the two papers differs in many aspects.

Adalimumab and gynecologic manifestations: Adalimumab is a TNFalpha blocking agent and the section should be named "TNFalpha blocking agents and gynecological manifestations".
ANSWER: We changed the name of the segment to “TNF alpha blocking agents and gynecological manifestations” and corrected accordingly.

If data is not available regarding effects of other therapies than TNFalpha blockers this should be mentioned in the manuscript.
ANSWER: We mentioned in the introduction that data on VEDO, UST and small molecules are not available to this day.

Lymphoma is listed as a primary side effects of adalimumab. This is no true. It is debated as to whether TNFalpha blockers seldomly can lead to development of lymphomas but anyhow it is not a primary side effect of the drug.
ANSWER: We deleted the statement that lymphoma is the primary side effect of ADA from the text.

The effects of adalimumab on ovarian ischemia: For practical purposes all the data given in this section on the possible effects of adalimumab on ovarian ischemia is based on animal experiments and the presented hypothesis that TNFalpha blockers may be used to prevent ischemia in women is simply too speculative based on very limited evidence. I don´t think this section should be included.
ANSWER: We included the section, but as you suggested, noted that nowadays data is very limited and changed the section as well.

The sections describing the possible effects of adalimumab and other TNFalpha blockers on endometriosis should be combined.
ANSWER: We merged these sections into one.

It should be clearly noted that there is a profound lack of knowledge on the matter and that most data comes from animal experiments and that besides the cited study on infliximab no human studies specifically addressing the issue is available.
ANSWER: We noted that information is limited and most of the data come from animal studies.

Reviewer #2:
The review paper evaluates the gynecological disorders in inflammatory bowel disease with special emphasis on effects of anti-TNF therapy and menstrual abnormalities. Could authors comment whether studies evaluated the effects of severity or response to anti-TNF therapy on the menstrual abnormalities. Are the menstrual abnormalities more related to the severity of the IBD or negative or positive effects of anti TNF?

ANSWER: Most of the studies focused on patients who were in remission, therefore (for example, in the Saha et al. manuscript that focused on women with Crohn’s disease, the mean Harvey - Bradshaw index was 3.1 in all patients) so it is not possible to assess the severity of the disease in menstrual abnormalities.