

Dear Dr. Lian-Sheng Ma,

Science Editor, Company Editor-in-Chief, Editorial Office of BPG Inc,

We are very honored to submit our revised manuscript with the number 65789 and the title “Gut microbiota in gastrointestinal diseases during pregnancy” to the journal *World Journal of Clinical Cases*.

Thank you and two reviewers for spending valuable time reviewing our manuscript, giving positive evaluation and providing valuable comments. We believe that the suggestions made by the reviewers can improve the topic of our article and make the conclusion of the article more reliable. We carefully studied every suggestion given by reviewers, and revised our draft with strict reference to these suggestions. We are sure that the quality of the revised manuscript has been greatly improved.

In addition, we guarantee that all authors have read and agreed to submit the revised manuscript to the journal *World Journal of Clinical Cases*, and we guarantee that the manuscript has not been submitted to any other journals.

Thank you for your invitation and consideration,

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Manuscript Type: Review

Manuscript #65789: Gut microbiota in gastrointestinal diseases during pregnancy

Reply to the reviewers

Reviewers' Comments:

Reviewer 1

Reviewer's code: 05021511

SPECIFIC COMMENTS TO AUTHORS

In this paper, authors discussed the gut microbiota in pregnancy-related gastrointestinal diseases. This is an interesting and important issue, and authors provide useful information for readers to understand the role of gut microbiota in pregnancy-related gastrointestinal diseases. My comments are listed as below:

1, The abundance of Firmicutes and the F/B ratio was also found to be higher in overweight and obese pregnant women[75]. The F/B ratio is widely accepted to have an important influence on maintaining normal intestinal homeostasis. Detected this sentence, as the F/B ratio has been proven to be an unsuitable index for judge the health.

Answer: We thank the reviewer's suggestion. We have deleted the sentence "The F/B ratio is widely accepted to have an important influence on maintaining normal intestinal homeostasis." on page10.

2, *Akkermansia* was also observed to impair the integrity of the intestinal barrier, secrete LPS and induce tumor necrosis factor in the host circulation[82]. Most researches proven that AKK is a probiotics, especially in the diabetes and obesity. I suggested authors checked this.

Answer: We thank the reviewer's suggestion. We checked the function of *Akkermansia*, most studies proved *Akkermansia* is a probiotics other than pathogenic bacteria, so we deleted the description "*Akkermansia* was also

observed to impair the integrity of the intestinal barrier, secrete LPS and induce tumor necrosis factor in the host circulation. LPS can induce low-grade inflammation and insulin resistance by binding to the Toll-like receptor.” on page 11.

3, changes flora as microbiota in the whole paper.

Answer: We thank the reviewer’s suggestion and have changed all “flora” to “microbiota”.

4, just as authors indicated, “Research has mainly focused on changes in the structure and function of GM in gastrointestinal diseases during pregnancy”, and the mechanisms is lacks, but I think only discuss the changes of microbiota is insufficient, I suggested authors added a section on how to improve pregnancy-related gastrointestinal diseases via probiotics, or vaginal microbiota transplantation (Vaginal microbiota transplantation for the treatment of bacterial vaginosis: a conceptual analysis. FEMS Microbiology Letters; Vaginal microbiome transplantation in women with intractable bacterial vaginosis, Nature medicine; Dysbiosis of rat vagina is efficiently rescued by the vaginal microbiota transplantation or probiotic combination. International Journal of Antimicrobial Agents)

Answer: We thank the reviewer’s suggestion. We have a section on usage of probiotics to prevent bacterial vaginosis (page 18, ref.137-139).

Reviewer 2

Reviewer's code: 06044672

SPECIFIC COMMENTS TO AUTHORS

Generally, the topic is important and relatively well written. However, the authors need to discuss some other pregnancy related disease conditions (e.g. Anemia of pregnancy vs gut microbiota....).

Answer: We thank the reviewer's suggestion. We have added some other pregnancy related disease conditions including acute fatty liver of pregnancy (AFLP), anemia of pregnancy (page 12-13).

There are unnecessary statements included and must be removed, e.g. on page 15 ("Most of the symptoms of GI discomfort are mild (gastroesophageal reflux, constipation, etc.) and do not require intervention by a gastroenterologist, and there are few studies on their pathology and treatment. The balance between relief of the symptoms of GI discomfort and the side effects on the fetus should be taken into account when specific drugs are taken [94]. For serious complications of the GI tract during pregnancy, such as hyperemesis gravidarum (HG) and PE, which can result in fluid imbalance and metabolic disorders, and even endanger the lives of pregnant women, intervention by a gastroenterologist is essential. In addition, it is necessary to conduct in-depth research on the pathogenesis"). Similarly, there are more sentences that need to be avoided across the whole document.

Answer: We thank the reviewer's suggestion. We deleted the aforementioned unnecessary statements as follows:

Page 13, "Most of the symptoms of GI discomfort are mild (gastroesophageal reflux, constipation, etc.) and do not require intervention by a gastroenterologist, and there are few studies on their pathology and treatment. The balance between relief of the symptoms of GI discomfort and the side effects on the fetus should be taken into account when specific drugs are taken"

Page 1, "Research has mainly focused on changes in the structure and function

of GM in gastrointestinal diseases during pregnancy.”

Page 6, “GI diseases are common in humans, and affect millions of people worldwide. Dysbiosis of the GM in the pathology of GI diseases has been extensively studied.

Treatment of GI diseases with probiotics has been conducted, and they provide an ideal choice with few side-effects.”

Page 7, “The beta diversity in T1 is similar to that in non-pregnant women, and the beta diversity in T3 is much higher.”

Page 7, “The mechanism underlying the promotion of Bifidobacterium by progesterone is not yet fully known.”

Page 9, “There are many factors that can affect the GM composition during this period.”

Page 9, “The GM in pregnant women is very important to colonization of the GM in neonates. Undoubtedly, GM dysbiosis in disease during pregnancy will affect the GM of neonates for a long time. “

Page 9, “Obesity during pregnancy has increased recently, especially in developed countries.”

Page 10, “It is unclear whether the change in GM is the cause or just the result of GDM.”

Page 12, “ The increase in hormone levels in women during pregnancy, such as progesterone, reduces the contractility of smooth muscle in the GI tract, leading to delayed gastric emptying. Additional gastrin produced by the placenta leads to an increase in gastric acid. In addition, during pregnancy, growth of the fetus, enlargement of the uterus and thickening of the uterine wall also change the relative position of abdominal organs. For example, the appendix may move up during the third month. With the development of the fetus during pregnancy, enlargement of the uterus and thickening of the uterine wall, at 9 months of pregnancy, the uterus occupies almost the entire abdominal cavity, directly compressing the stomach, diaphragm and heart. Under the influence of these factors,”

Page 13, "The relationship between GM dysbiosis and GI disorders has been extensively studied. The shift in the composition of GM during pregnancy has also been investigated systematically. It is reasonable to deduce that pregnancy-related GI disorders are associated with GM dysbiosis during pregnancy."

The conclusion should be re-written, it is not clear and needs a concrete summary.

Answer: We thank the reviewer's suggestion. We have re-written the conclusion in page 19.

Moreover, the paper needs minor language polishing.

Answer: We thank the reviewer's suggestion. We have corrected (in red) some spelling and grammatical errors.

Page 6, "A series of clinical trials have proved that *Escherichia coli* Nissle 1917 ~~was~~ effective in the maintenance of IBD remission."

Page 6, "which contains 8 lactic-acid producing bacteria, can reduce ~~the rate of~~ IBD relapses in 9 months from 100% to 15%"

Page 8, "The uterus was initially considered ~~as~~ a sterile environment, which excluded the probability of GM colonization prior to delivery"

Page 9, "GDM is characterized by increased insulin resistance and ~~increased~~ blood glucose during pregnancy."

Page 15, "~~In addition,~~ the immune imbalance at the maternal-fetal interface also plays an important role in PE"

Page 15, "At 16 weeks of pregnancy, the numbers~~s~~ of butyrate-producing bacteria in the GM are negatively correlated with blood pressure"

Page 16, "GM are negatively correlated with blood pressure and ~~the level of~~ plasminogen activator inhibitor 1 ~~level~~ in overweight and obese pregnant"

Page 15, "A large number of bacteria ~~was~~ ~~were~~ observed in the placenta of PE mice."

Page 16, “Experiments in mice have shown that the intake of probiotics can maintain the stability of the intestinal microbiota, enhance vascular endothelial function, and ~~keep~~ lower blood pressure.”

Page 17, “A recent study indicated that in pregnant women with HG, the alpha diversity of GM is higher, with a higher average numbers ~~s~~ of different OTUs.”