Dear Sirs,

We thank the Reviewers and the Editors for their comments and suggestions regarding our submitted article No 61784. Please see below for our detailed responses.

Reviewer #2:

[1]. ***The abstract should be more clarified with current status, purpose and what are the main advanced knowledge or information.***

We have revised the abstract as follows:

"Women with polycystic ovary syndrome may be more susceptible to COVID-19, particularly because of the associated comorbidities of the former (alterations in the gut microbiome, obesity/metabolic syndrome and non-alcoholic fatty liver disease). An association between acute respiratory distress syndrome (as seen in severe cases of COVID-19) and altered intestinal microbiome has been noted. Excess body weight is associated with more severe COVID-19 and increased mortality. Obesity is a state of low-grade inflammation, which COVID-19 pushes to extremes (with a characteristic "cytokine storm"). The metabolic syndrome is characterized by hyperinsulinemia, which may be associated with COVID-19, particularly regarding microvascular dysfunction, systemic hypercoagulability and extensive micro- and macrovascular thrombosis. SARS-CoV-2 is pervasive and this virus is localized in abdominal and extraabdominal organs, including the liver, although there are conflicting reports regarding non-alcoholic fatty liver disease and COVID-19. Based on the available data, manipulation of the intestinal microbiome could possibly help in reducing the severity of COVID-19 in women with PCOS."

[2]. ***The title is confusing and should be revised.***

In the revised version of the manuscript the title has been changed to: "Polycystic ovary syndrome: pathways and mechanisms for possible increased susceptibility to COVID-19"

[3]. ***Part" PCOS AND THE GUT MICROBIOME": More attention should be paid to the relationship between host immunity and the gut microbiota.***

We have added the following in the revised version of the manuscript:

“…..Lipopolysaccaride in the circulation (attached to the glycoprotein LBP) binds to the CD14 toll-like receptor complex (TRL-4) on the surface of innate immune cells, leads to activation of a downstream signaling pathway and immune system activation{He, 2020 #152}. The latter impedes insulin receptor function and leads to hyperinsulinemia and glucose intolerance, which...”

[4]. ***Part" PCOS VS SARS-COV-2 INFECTION": This section needs to have more appropriate references. In fact, as the core content of the whole article, this part needs to add some more information.***

We have added the following in the revised version of the manuscript (citing a recent relevant article): “Obese patients with advanced NAFLD have been shown to have increased hepatic mRNA expression of ACE2 and TMPRSS2, the critical molecules for SARS-CoV-2 cellular entry (gender-specific differences may exist in the expression of these molecules)”.

[5]. ***Part" NAFLD AND THE GUT MICROBIOME": This part seems redundant for this review, which does not elaborate the authors' view very well.***

This part was deleted in the revised version of the manuscript.

Reviewer #3:

This topic is very interesting and need to publish it.

Thank you

Science Editor: 1

[1]. ***The abstract should be more clarified with current status, purpose and what are the main advanced knowledge or information.***

In the revised version of the manuscript we have changed the Abstract as follows:

"In 75% of women with polycystic ovary syndrome (PCOS), insulin action is impaired. In obesity, visceral adipose tissue becomes dysfunctional: chronic inflammation is favored over storage, contributing to the development of metabolic complications. PCOS, metabolic syndrome (MetSy) and non-alcoholic fatty liver disease (NAFLD) apparently share common pathogenic factors; these include abdominal adiposity, excess body weight and insulin resistance. Alterations in the gut microbiome have been noted in women with PCOS compared to controls; these may lead to deterioration of the intestinal barrier, increased gut mucosal permeability and immune system activation, hyperinsulinemia and glucose intolerance, which hamper normal ovarian function and follicular development (all being hallmarks of PCOS). It has been proposed that PCOS may entail higher susceptibility to COVID-19 via its associated comorbidities (NAFLD, obesity, MetSy and alterations in the gut microbiome). Studies have found an association between acute respiratory distress syndrome (seen in severe cases of COVID-19) and the intestinal microbiome. Furthermore, apparently, SARS-CoV-2 can gain entry to the gastrointestinal tract via locally-expressed angiotensin converting enzyme type 2 (ACE2) receptors. Excess body weight is associated with more severe COVID-19 and increased mortality. Although robust links between SARS-CoV-2 infection and PCOS/NAFLD/gut microbiome/metabolic consequences are yet to be confirmed, it seems that strategies for adapting the intestinal microbiome could help reduce the severity of COVID-19 in women with PCOS with or without NAFLD, MetSy or obesity."

[2]. ***The title should be revised.***

In the revised version of the manuscript we have changed the title to: "Polycystic ovary syndrome: pathways and mechanisms for possible increased susceptibility to COVID-19"

[3]. ***It would be worthwhile mentioning the need to better characterize patients beyond BMI and provide a supporting reference for the statement made and the relevance of dysfunctional visceral adiposity in relation to inflammation and how it has been shown in women to be associated with a decrease in lipogenic factors;***

We have added in the revised version of the manuscript the following (citing two supporting articles, including the one which was suggested by Reviewer#3): "We have to note that regarding obesity, women with PCOS present a challenge for researchers, since BMI may not characterize them adequately."

Additionally, we have added the following in the revised version of the manuscript, citing the suggested articles by Reviewer#3:

"Furthermore, in obesity, visceral adipose tissue becomes dysfunctional (with an increase in inflammatory molecules and a decrease in the expression of lipogenic enzymes); in this way – via various signaling pathways - chronic inflammation is favored over storage, contributing to the development of metabolic complications. These obesity-associated signaling pathways and mechanisms are not fully delineated. …….. Recent research indicates that in obesity, adipokine imbalance (low adiponectin and high leptin) modulates the activation of inflammasomes (receptors/sensors of the innate immune system that regulate caspase-1 activation and promote inflammation); thus the latter may be the connectors between excess adiposity and obesity-associated complications."

[4]. ***The authors need to provide the signed Conflict-of-Interest Disclosure Form and Copyright License Agreement.***

We are providing these forms along with the submission of the revised manuscript.

[5]. ***Please provide the original figure documents. Please prepare and arrange the figures using PowerPoint to ensure that all graphs or arrows or text portions can be reprocessed by the editor.***

We are providing the original Powerpoint figures for reprocessing, as suggested.