

Dear Editor in Chief,

We thank the Reviewers for evaluating our manuscript, "Surgical and nutritional interventions for endometrial receptivity: report of a case" (Manuscript NO.: 78279, Case Report). We have considered the comments and have taken the appropriate actions. For each of the comments, we have written a reply below.

Reviewer 1

The key question is why the article didn't address the role of Metformin (a beneficial insulin sensitizer in PCOS) either in its mechanistic or discussion, particularly as this case has IR primarily with prediabetes, along with the failure of the diet regimen in the second cycle?

Response: The reviewer correctly posits the use of Metformin as a treatment for insulin resistance, which we did consider. The patient presented with a glucose level higher than normal and insulin resistance, and both of these parameters prompt a pharmacological treatment of Metformin, a classical and very commonly employed election. Even when Metformin's role has been widely described as an insulin sensitizer, the prescription of this drug alone does not produce a fast improvement in IR, unless a well-designed nutritional intervention can be added and followed for the patient. The dosage (posology) can have many different effects, some of which, nausea and diarrhea, can be problematic for IVF. Moreover, a recently published systematic review of 12 studies (doi: 10.1080/09513590.2021.1913114) demonstrated that Metformin does not improve insulin sensitivity over hypocaloric diets in women with polycystic ovary syndrome. When pre- and post-intervention values for fasting plasma glucose, fasting plasma insulin, and IR indices (HOMA1-IR, ISI, and QUICKI) were compared, any benefit of using Metformin was already achieved when a diet intervention was implemented. This means that adding Metformin to hypocaloric diets did not improve serum glucose or insulin concentrations, or IR in PCOS women. For these reasons, we decide against using Metformin for this patient, but we will not exclude using Metformin for future patients under similar conditions. Here, our goal was to achieve a long-lasting and more permanent change in IR for PCOS women, and we proposed to do so by lowering the carbohydrate content. This is supported by a previous meta-analysis, which indicated that diets with lower carbohydrate concentrations improved insulin sensitivity in women with PCOS (doi: 10.1016/j.ejogrb.2020.03.010). We believe this case represents a success in our proposal of using a nutritional intervention in conjunction with IVF to generate a better pregnancy. This information was added to the discussion section.

With respect to "the failure of the diet regimen in the second cycle", the diet regimen did not exactly fail. The decrease in weight was present, but maybe not sufficient, as indicated by the BMI not changing, when considering the World Health Organization classification (overweight). That is why the type of diet was changed, and the improvement was significantly better, achieving BMI classification of "normal" as well as improved (corrected) insulin resistance. This suggests that using Metformin for this patient was not needed.

The second question is about the manifestations of hyperandrogenism in the case which has been omitted.

Response: The reviewer does point out that this information was omitted and should be include here as with any other PCOS assessment. Therefore, we have included all characteristics of clinical hyperandrogenism that were recorded for this patient as part of the diagnosis.

Reviewer 2

1. The background of the abstract mentions that a "coordinated definition of metabolic syndrome is used," and it is suggested to expand and explain the specific content of this definition.

Response: We agree with the reviewer that this information should be included in the abstract; however, we cannot find the phrase “coordinated definition of metabolic syndrome is used”. Nevertheless, in the abstract, we referred to the Harmonized definition of metabolic syndrome (doi: 10.1161), which defines five specific parameters of metabolic syndrome, and, according to the definition, having 3 of them makes the diagnosis. As PCOS women have metabolic issues, it is important to consider the possible metabolic alterations concurrent with insulin resistance. We measured and considered those criteria to evaluate the patient metabolic status—this is why we mention them in the abstract. We added this explanation of this into the appropriate sections (pathological examination, laboratory analysis, etc.).

2. History of present illness is incomplete, so the patient's previous medical history of therapeutic intervention can be added.

Response: We have added all relevant medical history for this case.

3. References are in an incorrect format; please refer to the author guidelines or the published articles for modification.

Response: We reviewed and corrected the format of the references. They are now in the correct format. PubMed and DOIs citation numbers were checked in the reference list, as well as we verified all authors of the references.

Language evaluation:

Response: Classification: Grade A was given by both reviewers. Concerning the certificate, we already provided a statement that one of our collaborators, Dr. Leonardo M. Porchia, who revised the document, and is a Native English Speaker. In any case, we added a letter about Dr. Porchia with this statement.