Answers to Reviewer 1:

1) Although manuscript is divided into several sections, each section is quite long and narrative in nature, such as section "PCOS and insulin resistance" is 8 pages long. The section should be numbered and may further divided into more subsections to help readers to follow.

The main sections were numbered. Additionally PCOS section was further divided into four subsections (subsection headings appear in red color) along the suggestions of the referee. Therefore, the design/presentation of the manuscript (the places of some paragraphs within PCOS section) changed without making any change in the main topic. Added sentences to the revised manuscript were shown in red color.

2) Most of sections in manuscript are narrative and very long, since authors described one by one experiment. These information will be more readable and avoid reiterating in so many places if authors gather the information of each experiment into tables categorized by intervention method, key finding, whatever, and reference.

Along the suggestions of the referee we shortened the PCOS section (which is the longest section) of the manuscript by giving some details of the experimental and clinical studies in two tables. Tables 1 and 2 were added to the revised manuscript. By this way we removed some studies from the text to the tables. However, in order to keep the integrity of the manuscript we could not transfer all the studies to the tables and some of them still appear as a narrative form in the revised manuscript.

3) It may be helpful to general readers if most of narrative of describing individual experiment could be written in more succinct and overview of those individual experiments, as each study will be shown on tables already.

Along the suggestions of the referee, narrative nature of the manuscript was changed. A brief overview was given in page 8 (appeared as red color in the revised manuscript). A detailed explanation to this comment was also given in the previous comment of the referee.

4) Authors stated in several places that insulin resistance primarily reduces uptake glucose into liver (apart from skeletal muscle & adipose tissues). There are no good references so far that insulin resistance affect hepatic glucose uptake, as GLUT in the liver cells are insulin independence. Although some papers suggest the presence of GLUT4 in the liver, it does not play major role in hepatic glucose transport.

We removed the sentence that "insulin resistance primarily reduces uptake glucose into liver" in the revised manuscript.

5) The last paragraph in page 8 continued to page 8 about inflammatory cytokines may be relocated to other section (Insulin and insulin signaling), as it is well fit to other section.

In the section of "insulin and insulin signaling" we tried to give the basic (molecular) mechanisms of insulin resistance. However, the paragraph related to inflammatory cytokines and insulin resistance was given for one of the specific insulin resistantance mechanisms related to obese PCOS subjects. Thus, if the referee accept, we prefer to keep this paragraph in its present position but under a new subsection.

6) Authors may give some information of theca and granulosa cells about their relation of functions before insulin resistance affecting them.

Along the suggestions of the referee, a brief subsection was added (appears in red color) regarding the relationship between the theca and granulosa cells in normal conditions. This new subsection is located in page 5 (5i section) of the revised manuscript.

7) In last section of "how to translate in daily practice:" It seems authors giving quite an overstatement about requirement of accurate estimation of insulin resistance in order to use insulin sensitizer. Given that metformin is very safe drug. In clinical practice, metformin may be used for trial without some sophisticated lab workout if there is no other causes to concern.

Sorry for misunderstanding. We agree with the referee. We did not want to emphasize to make a test before giving metformin. That is why we wrote as "Therefore it is not suitable to give an insulin sensitizer relying on only some mathematical models. Instead, the decision of treatment should be based on the constellation of signs, symptoms and presence of obesity, acanthosis nigricans and some laboratory abnormalities such as impaired glucose tolerance, impaired fasting glucose."

However, we added the referee's suggestion to the revised manuscript (just to the end of the above mentioned paragraph. It appeared as red color in the revised manuscript).

Answers to Reviewer 2:

There were no specific comment from this reviewer.