

## REPLY TO REVIEWERS' COMMENTS

**NOTE: Corrections made in the text were highlighted in red.**

### Reviewer 1

**Comment 1:** The manuscript requires serious English editing. Grammar and style are below average. The very 1st sentence in the Abstract requires editing (“Epigenetic disruptions have been implicated in some cases of infertility, which can be targeted to help individuals expressing such an etiology conceive”). Wrong English grammar makes this sentence unclear for understanding (meaningless).

**Reply:** The manuscript has been edited by an expert. The screenshot of the profile of the grammar editor was uploaded for confirmation.

**Comment 2:** Abstract/Introduction are very vacuous and does not point to the main epigenetic targets associated with infertility. For instance, author could mention that epimutations (often hypermethylation) in several genes, namely MTHFR, PAX8, NTF3, SFN, HRAS, JHM2DA, IGF2, H19, RASGRF1, GTL2, PLAG1, DIRAS3, MEST, KCNQ1, LIT1, and SNRPN, have been reported in association with poor semen parameters or male infertility. See this publication <https://pubmed.ncbi.nlm.nih.gov/21540125/>.

**Reply:** Done as suggested. Please check the text.

**Comment 3:** Figure 3 and 4 should be combined.

**Reply:** Done as suggested.

**Comment 4:** Figure 7 is very poorly designed. Authors should improve or remove this figure.

**Reply:** It has been removed as suggested.

**Comment 5:** miRNA up- and down-regulation should be illustrated. A figure ( or table) should be designed.

**Reply:** Done. See table 2.

**Comment 6:** Successful epigenetic-targeting drugs as infertility treatment should be also organized in a table.

**Reply:** Done. See table 3.

**Comment 7:** Conclusions should be improved. Authors should provide solid data-supported insights ( not vacuous generalizations). The 1st sentence is very vacuous ( "The review established that normal epigenetic modifications are necessary for proper gametogenesis and embryogenesis"). What is "normal"? The phrase is poorly constructed. Your review did not "establish" anything. You just reviewed/discussed published data.

**Reply:** Corrected and improved upon as directed.

## **Reviewer 2**

**Comment 1:** 1. In page5, “These mechanisms may alter gene expressions individually or interact to control gene expressions” should be added with references.

**Reply:** Done as directed.

**Comment 2:** It is suggested that Figure 2, Figure 3 and Figure 4 should be merged into one figure. Also, the figure legends should be more detailed.

**Reply:** Done. Figures 3 and 4 had been merged. But figure 2 cannot be merged with them.

**Comment 3:** Carefully check all references in the article citation position are accurate, such as the Ref. 76 matches the content described in the article or not.

**Reply:** Done as directed.

**Thank you.**