Reviewer's report

Title: Understanding decreased fertility in women carriers of the FMR1 premutation: A possible mechanism for Fragile X Associated Primary Ovarian Insufficiency (FXPOI)

Date: 5 June 2014

Reviewer: Kerri Kissell

Reviewer's report:

I have reviewed the manuscript entitled ‘Understanding decreased fertility in women carriers of the FMR1 premutation: A possible mechanism for Fragile X Associated Primary Ovarian Insufficiency (FXPOI)’.

1. Does it address an important or timely issue?
   Yes, this research topic is relevant to reproductive health in a small population of women who have primary ovarian insufficiency due to FMR1 premutation. The author attempts to explain a genetic theory to the variability in primary ovarian insufficiency associated with fragile X FMR1 premutation beyond the related CGG repeats.

2. Is it well reasoned?
   Yes, overall, this is a well thought-out theory that will make a note-worthy publication. Overall, I would like to see the theory developed more.

3. Is it relatively balanced, or does it make plain where the author's opinions might not represent the field as a whole?
   I find this article to be well balanced.

4. Is the standard of writing acceptable?
   Yes. This article is expressing a biologically plausible theory behind the pathology of fragile X associated POI. Again, I think the theory could be expanded upon. For example, discuss possible mechanisms explaining the discrepancy seen in the monozygotic twin case. The writing itself requires fine tuning, for example, the word “interesting” is used three times in one sentence.
Minor Essential Revisions

1. References listed within manuscript: ‘(Woad et al., 2006, Coulam, 1982, Lu et al., 2012)”. Please adhere to guidelines for this journal for referencing articles and be consistent throughout.

2. This line: “Additionally, the length of the CGG repeat contributes to the variation observed in reaching menopausal age; currently the threshold for the onset of FXPOI is ambiguous [15-17]” is confusing in its reference to ‘reaching menopausal age”. I think what this author means to state is that the “length of the CGG repeat contributes to the variation observed in” age of ovarian dysfunction resulting in loss of reproductive capacity. POI associated with FX is different from typical menopause.


4. “One interesting case report described premutation monozygotic twins discordant for the FXPOI phenotype in which the woman with the FXPOI phenotype also had elevated FSH”. I fail to find the elevation in FSH interesting as this rise in gonadotropin is expected with ovarian failure associated with POI. Please revise this commentary.

5. The word interesting is stated three times in the last sentence of first paragraph under conclusions and significance.

**Level of interest:** An article of importance in its field

**Quality of written English:** Acceptable

**Declaration of competing interests:**

no competing interests