Reviewer’s report

Title: Paternal therapy with disease modifying drugs in multiple sclerosis and pregnancy outcomes: a prospective observational multicentric study

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Reviewer: Katelyn Kavak

Reviewer’s report:

This paper is an interesting study addressing the potential negative effects of paternal use of disease modifying drugs (DMDs) on outcomes of pregnancies (birth length and weight, spontaneous abortion, congenital malformations among others). The authors take a multicenter approach and aggregate data across 21 centers. The main findings indicate that there are no or only minor adverse effects of DMD use among fathers with MS on the fetus. I have several comments:

Major Compulsory Revisions:
1) The introduction needs more information about why the authors feel paternal DMD use could potentially influence pregnancy outcomes. At the moment the hypotheses are not sufficiently supported. This issue can be addressed by describing other studies (not necessarily related to MS) that report an association between paternal factors and pregnancy outcomes. The discussion also needs to be expanded and biological, underlying reasons of why paternal exposure could even have an effect on the fetus must be discussed further. Three mechanisms of potential influence are mentioned (genetic, epi-genetic and non-genetic), however, this is not discussed in detail.

2) Authors have mentioned that the development of spermatozoa to germ cells takes approximately 64 days, and while they mention (as an afterthought) that results were similar when they compared fathers who were exposed to DMDs to those who were unexposed to DMDs longer than 3 months. It is unclear why this definition of exposed vs unexposed was not used throughout the paper (instead of DMD exposure >4 weeks prior to conception). The study would improve substantially if the main findings were described using the >64 days definition. At the moment the decision to use the >4 weeks cut-off is unclear.

3) It is unclear which variables were used as confounders, e.g. gestational age and cesarean delivery were mentioned both as confounders as well as outcome measures.

Minor Essential Revisions:
1) The methods section lists spontaneous abortions, pre-term delivery, cesarean delivery, birth weight and birth length as factors that were compared to the Italian population. While the first three (all categorical) are compared using a binominal test, the latter is continuous and would therefore not be able to be analyzed the
same way. It should be made clear that while all these factors are compared between exposed and unexposed fathers, only the first three are compared to the Italian population.

2) Mann-Whitney U tests were used on continuous variables but it is unclear which data was not normally distributed. As most of the variables that are continuous (age, weight, height) usually follow a normal distribution it is unclear why Mann-Whitney U was chosen over the use of independent samples t-tests. If data was indeed not normally distributed, please describe in the methods section.

3) Figure 1 can be found on both page 23 as well as the last page.

4) There are some spelling, (e.g. “mean” of instead of “means” on page 6, “woman” instead of “women” on page 8) punctuation, (e.g. capitalization of the word “author” on page 5, “country on page 6, remove comma from “128,09” on page 10) and grammatical errors (e.g. “deriving” instead of “derived” on page 7) that need to be addressed.

5) In table 3, the significant results of the logistic regression analyses show that there is a relationship between cesarean and pre-term delivery as well as gestational age and cesarean delivery. These results appear to be redundant and measure (arguably) the same thing. Consider omitting one of the two, and describing the other in-text only, as the table would be much clearer by only including 1 analysis type (linear regression).

**Level of interest:** An article whose findings are important to those with closely related research interests

**Quality of written English:** Needs some language corrections before being published

**Statistical review:** Yes, and I have assessed the statistics in my report.

**Declaration of competing interests:**

I declare that I have no competing interests