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: Helen Tremlett

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Very few studies have explored DMD exposure in MS fathers around the time of conception in relation to pregnancy outcomes. The authors report here on a small but important cohort of 78 such pregnancies; 42 exposed to a DMD (36 IFNB, 6 GA), 36 unexposed; 75 resulted in a live birth. There were no major safety signals observed with respect to DMD exposure, with the studied outcomes being similar between the exposed and unexposed groups (spontaneous abortion or malformations, mean gestational age, frequency of cesarean delivery, birth weight and birth length). However, there were some differences when compared to data from the general Italian population (with slightly higher numbers of pre-term deliveries and maternal complications than expected).

Strengths include novelty and study need – there are very few such studies in this area and the information provided by this study makes a major contribution to the field.

Main limitations include: potential for recall bias (all data were collected retrospectively, albeit within ‘6 months of delivery’); method of data collection: a lot of very detailed clinical information was collected all based on a semi-structured interview with the patient (fathers). Including Apgar scores and ‘ecographic alterations’. Unclear if this was a validated method of obtaining accurate information - would fathers / the parents be aware of data such as the babies 5 minute Apgar score or ‘ecographic alterations’?

Please number your comments and divide them into

- Major Compulsory Revisions

• 78 MS fathers were identified and 78 pregnancies – was it part of the inclusion criteria for this study that only singleton births would be considered and only one birth per father, or was this just a chance occurrence? If this was part of the inclusion criteria, this should be specified.

• As mentioned above, a lot of very detailed information was collected from the fathers – how many fathers were excluded because of missing data? Was the data collection 100% for all variables for all individuals included in this study? How did the authors deal with missing data?
On a related issue, the paper would benefit from a table outlining the broader characteristics of the cohort (e.g., with separate columns for the exposed vs unexposed fathers) with all the variables collected listed along with what was found (beyond what is in tables 1, 3, 4). Although some of this information is in the text (e.g., mean gestational age, mean birth weight etc), some results do not seem to appear anywhere, e.g., Apgar scores. It would also then be easier for the authors to state what information was missing/present for how many in each group. It would also be easier for the reader to have all this information in one easy to reference place. This table needs to include all the relevant data not already in table form as listed in the methods, i.e., all information listed in the second paragraph of the methods.

- The authors state in the methods that patients were administered a questionnaire within 6 months after delivery – but what if there was no delivery (no birth) and the pregnancy resulted in a miscarriage or abortion – did this 6 months time frame still apply? Perhaps this could be stated in the methods.

- The authors state in the results (3rd to last para): ‘median follow-up period of 1.8 years’ – what was the range? I.e., what was the shortest follow-up?

- Throughout the manuscript, the authors refer to others’ work (and theirs) as indicating that the drugs for MS are ‘safe.’ Because so many of these studies are small, and it takes much larger studies to identify even relatively common adverse events (‘Hanleys rule of three’), it is probably more accurate to report findings as indicating that ‘no major adverse safety signals’ were found. See also comments below.

- The authors do mention a limitation of their study was the small sample size – what was the a priori sample size calculation? Did they have power to conclude that:

‘Our data confirm the absence of association between paternal DMD exposure at time of conception and risk of spontaneous abortion, adverse fetal outcomes and congenital malformations’

Absence of a significant association in a small sample does not necessarily provide confirmation of there being no association period.

- Minor Essential Revisions

- Introduction: The authors state ‘Over the past few years, many papers have addressed issues of safety and tolerability of DMD at time of procreation and during pregnancy in MS mothers’

It’s probably more accurate to state:

‘Over the past few years, a number of papers have addressed issues of safety of the DMDs at the time of procreation and during pregnancy in MS mothers [2]

Rationale: 1. to avoid misinterpretation - the cited study only reviewed safety of the DMDs (not tolerability, least not tolerability defined as how well the women tolerated a DMD during pregnancy with respect to her own health eg flu like
symptoms etc)

2. ‘number of papers’ rather than many – because ‘many implies we have enough – but in reality there are relatively few papers and each paper only contributes a relatively small number of women / exposed pregnancies – ideally we would like many more studies with much larger cohorts to make any conclusive remarks regarding the safety of the DMDs

• Introduction: The authors state ‘In particular, prospective cohort studies reported an overall safety of Interferon-beta (IFN-beta) exposure, compared with outcomes of unexposed pregnancies in MS patients…’

Consider revising to the following (for a similar rationale as outlined above and to be consistent with the authors following sentences in which they outline hints of some adversity, although small):

‘In particular, prospective cohort studies observed no major adverse safety signals associated with Interferon-beta (IFN-beta) exposure, compared with outcomes…’

• Introduction: The authors state:

‘Despite limited sample size, studies on Glatiramer Acetate (GA) exposure showed its safety, in terms of main fetal and pregnancy outcomes, that were comparable to those observed in the general population’

consider revising to:

‘Despite limited sample size, studies on glatiramer acetate (GA) exposure also reported no strong adverse safety signals, with the main fetal and pregnancy outcomes being comparable to those observed in the general population’

• Introduction: The authors cite the one known study on DMD exposure in MS fathers. There is now one additional study which the authors will not have known about, but has just been published. This should now be included in the paper:

CNS Drugs. 2014 Mar 19. [Epub ahead of print]

Birth Outcomes in Newborns Fathered by Men with Multiple Sclerosis Exposed to Disease-Modifying Drugs. Lu E1, Zhu F, Zhao Y, van der Kop M, Synnes A, Dahlgren L, Sadovnick AD, Traboulsee A, Tremlett H.

• Methods, end of second paragraph. The authors state: ‘In case of problems, the baby’s clinical charts were reviewed.’

Please clarify – in the case of what kind of problems? Do they mean if a) data were missing e..g the parents did not complete that section of the questionnaire / interview or b) any malformation was identified from the questionnaire or c) major developmental problems were identified from the questionnaire or d) something else?

• results, second paragraph, the authors state:

‘Forty-two patients (53.8%) were taking DMD at the moment of conception..’
Probably better to state:

‘Forty-two patients (53.8%) were taking a DMD around the time of conception…’

• Clarification of factors related to the father vs mother:

The paper would benefit from some clarification as to whether a measured factor was related to the father or the mother. This would be helpful for the reader:

Eg.

- Methods, last paragraph – factors are clearly labelled as being the fathers (conception, education, disease duration….presumably the next factors are related to the mother – previous pregnancies etc, smoking and alcohol – it would be nice to label them explicitly - especially as earlier it is stated that some of the factors were collected for both the mother and the father (eg smoking, alcohol)

- Table 3: specify in the table that ‘education’ and ‘age at conception’ related to the father

• Table 1 : just to clarify, please specify that the p-value related to the exposed vs unexposed group comparison. Please also provide a key under the table indicating which statistical test was used to compare which variable

• Tables 2 and 4: please specify (under table) which chi-square test was used – presumably given the very small numbers the Fishers exact test was used?

• Table 3: This table would benefit from a little more detail – e.g. the title needs to be more specific – does this include all pregnancies or only live births?

How many individuals were included in each of the models shown?

Is it possible to report ORs and 95%CI for all, rather than Beta for some and ORs for others?

A comprehensive list of all factors included in each model would be helpful, even if listed under the table.

• Table 4: just avoid any confusion, it would be helpful to specify in the title that the exposure was related to the father and at the time of conception

Eg instead of:

‘Maternal complications in exposed and unexposed pregnancies’

‘Maternal complications in pregnancies where the father was exposed or unexposed to a DMD for MS at the time of conception’

• Discussion: rather than inferring these drugs are safe, better to replace:

‘Previous studies have indicated no effect of interferon beta or glatiramer acetate…..’

To

‘Previous studies have not reported any major adverse safety signals associated with the mothers exposure to interferon beta or glatiramer acetate….’
There are other places in the discussion that the drugs are referred to as safe – these should be re-phrased.

• Discussion: it would be helpful to have a brief discussion on the limitations of comparing to the Italian general population – eg how demographically comparable were they to the study subjects? How might that affect the comparisons?

Also the topics of recall bias and validity of collecting very detailed complex medical data directly from the fathers (as stated in the methods) needs to be discussed.

Level of interest: An article of importance in its field

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

Statistical review: Yes, but I do not feel adequately qualified to assess the statistics.

Declaration of competing interests:

I declare that I have no competing interests