Reviewer's report

Title: Reproductive life disorders in Italian celiac women. A case-control study.

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Reviewer: Jonas Ludvigsson

Reviewer's report:

Reviewer: 2
Comments to the Author

Domenico: reproductive life disorders in Italian Celiac women

I would like to thank the editor for asking me to review this paper. This paper concerns an important paper but could be improved. I have reviewed this paper for another journal before. Since then it has been improved, but further revisions are needed. This is especially true regarding the description of the statistics. I have recalculated some of the ORs and these do not turn out as in the paper. This worries me and the authors need to explain this.

e.g. main outcome measure amenorrhea: abstract OR is 33. When I calculate it based on the data 12-50 (cases) and 4-182 (controls) I get 11 (?).

and similarly when I calculate the odds ratio for at least one pregnancy complication I get 2.5 instead of 4.1.

I cannot rule out that I have misunderstood something but I would be interested to know how the authors calculated these ORs. Did the use a matched approach (they do not state that), or?

I appreciate that the authors have included ORs, confidence intervals and p-values in their presentation (including in the abstract). Another change of major importance is that “oats” is not included among the grains containing gluten. I also urged the authors to define their main outcomes.

ABSTRACT:

Two outcomes are reported with ORs etc in the abstract, “amenorrhea” and “at least one complication during pregnancy”. However in your methods section in your abstract you list five main outcome measures. Although I feel five main outcome measures is a lot, I accept it, but urge you then to present ORs for all these main outcome measures. Presenting more detailed data (ORs+95% CI+p-value if you like) will occupy some space and I suggest you skip the list of all other outcomes.

"in a sample of childbearing age women" is not specific enough, please state the number of women and their ages (median and range). Was this a matched case-control study? If so, state that and for what the women with or without CD were matched (age?, other?) smoking?).
Conclusion. You state that the correlation between CD and reproductive disorders could explain fertility problems in CD. However, what is very important is that the largest study until this date (Tata et al) actually found not association between CD and infertility! Actually we do not know if there is any link between CD and infertility.... Hence I suggest that you do not refer to infertility in your conclusion.

INTRODUCTION.

The abstract may be shortened by 30-50%, The prevalence on different continents is not necessary, neither the absolute number of individuals with CD in the united states.

I suggest skipping the references by Baldassare and Malamut. These were not original works. If you want a review on the prevalence of CD, try Dube et al 2005.

You cite a paper by Ciacci (reference 17), please note that the shorter breastfeeding duration in mothers with untreated CD was not statistically significant (p-value <0.10 but not <0.05). The same was true for the increased risk of low birth weight that was not statistically increased in the Ciacci paper (p-value above 0.05, but below 0.10).

METHODS

Omit the words about privacy law watchdog

What proportion of women had undergone biopsy, and for women with biopsy did you require villous atrophy for the diagnosis?

Enrolling women from an Italian association of CD meeting is risky. It is possible that participants at such a meeting either have: a more severe disease (why else would you engage in such an organization), or that they are socially more talented, or less often have children (because than you cannot travel as freely as if you have children....)?

What were the educational levels of women with and without CD?

I am afraid that the sampling was inappropriate, that you were able to enroll all participants at the Apulia meeting and then had a 100% response rate is extraordinary.

compare: 85% of controls accepted to participate,

Regarding the statistics, it may be that you should have used Fisher's exact test since the expected number of women in the CD group should have been less than "5" on several occasions??

Did you use a conditional logistic regression when you evaluated the case-control study? controls were matched for cases.

A clear description of the statistics is very important.
RESULTS
Please see my comments below “Tables”.
Either the OR or the 95% CI of your data on miscarriages (page 7) is incorrect, OR cannot be 1.2 if the 95% CIs are 0.9-4.6 (2.1 ??).
In the results section you present a large number of absolute data (e.g. 25 women had diarrhea, 11 had vomiting etc. Please write: (n=25) and not only “(25)” since the latter may be misinterpreted as a reference even if BMC uses [xx].

DISCUSSION
You suggest that women with menstrual disorders should be screened for CD. But do we know (and do you show??) that a gluten-free diet will lead to less menstrual disorders?
Another weakness was that only women that could be reached by phone were included as controls. You did not report how many could not? This is of some importance since cases were not reached by phone. It should also be noted that data from cases and controls were obtained in different ways (or???). Cases were interviewed at the Apulian meeting while controls were interviewed over the phone. It cannot be ruled out that phone interviews were shorter, that participants did not have the time to recall all negative pregnancy outcomes and menstrual disorders and therefore underreported such events. That will lead to an overestimation of relative risks among women with celiac disease diagnosis.
Another weakness is that you did not consider smoking status. In most studies, smoking is negatively associated with CD (although Ludvigsson et al in their study in Clinical Gastroenterology Hepatology 2005 vol. 3 (9) pp. 869-74 found no association between CD and smoking in pregnant women). If there is no association between CD and smoking then lack of smoking data is no problem (as in the Ludvigsson paper – not the same paper that you have already referred to, published in Gastroenterology), but if there is a negative association this could have influenced your risk estimates. Please comment on this.
Finally it should be commented that only 41.9% of the women with CD in this study had undergone small intestinal biopsy. That is a weakness.

TABLES
Please include the data on at least one pregnancy complication in Table 2, or better create a new table (third table, see below). These pregnancy complications should also be defined. Did the interviewed women themselves define “severe anemia” ? or did you have a certain hemoglobin cut-off? What was “threatened abortion” – did the women themselves define this? And what is uterine hyperkinesias? Gestational hypertension. All these concepts should be defined in the methods section, or you should state that they were self-reported and not confirmed by patient charts. If so, this should also be listed among the limitations of this paper, in the discussion section.
Third table. I also suggest that you create a third table for pregnancy complication.

FIGURES
the figures are really nice. But please define the outcomes of your study, e.g. threatened abortion?

REFERENCES
Since you wrote your paper, an excellent paper has been published based on Danish data:
Khashan et al. PMID. 19939833. (at least I believe it is published) Please refer to that paper.

Several of the references in your manuscript are misspelled. E.g. title of ref 11. Journal of ref 1 etc.
Please check all the references again.

LANGUAGE
A professional language review of this paper would improve the paper.

**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, but I do not feel adequately qualified to assess the statistics.

**Declaration of competing interests:**
I declare that I have no competing interests