Response to reviewers

Revisions to the text based upon the reviewers suggestions are highlighted in yellow in the main text.

Reviewer 1

A subchapter considering the pharmacological treatment of Post-partum psychosis should be added. Indeed the mechanism of action of drugs used to treat PP will shed light on its own mechanism of action.

I don't feel that this topic warrants an additional subchapter given that pharmacotherapy for PP is described comprehensively in references that are already cited (Jones et al., Sit et al., Bergink et al.), and because the precise biological mechanisms by which drugs used to treat PP exert their therapeutic influence is uncertain. I have already stated the following: 'The fact that PP is often responsive to antipsychotic treatment indicates that abnormal serotonergic and/or dopaminergic function may play a role in its pathogenesis' which, given the poor state of knowledge about the condition, is about all that can be currently asserted.

Editorial comments

Why mood stabilizers may be useful in a psychotic condition? What he specifically intended with prophylactic pharmacotherapy? Psychotherapy and psychoeducation have been also generically reported without providing details/information to support their potential in women with postpartum psychosis.

I have now included the following to explain why mood stabilisers may be used: '(given that mood fluctuations, or bipolarity, may precede and/or be exacerbated by PP)'. I believe that the reference to prophylactic pharmacotherapy in women at high risk of PP is self-explanatory, particularly in combination with the associated references. Details of the psychotherapy and psychoeducation approaches to managing PP are beyond the scope of this review; I have already included citations to reviews where this topic is discussed at length (Jones et al. and Sit et al.).

Within the "Biological basis to risk?" section, the author should in my opinion describe more appropriately the biological pathways underlying postpartum depression and postpartum psychosis. What are the main differences according to the differential oestrogen supplementation that may be beneficial for some patients in these two different conditions? The most relevant aims of the present section need to be more specifically provided as well.

I believe that in-depth discussion of postpartum depression would only serve to reduce the focus of the review; the pathogenesis of PD is likely to be different from PP given differences in the two conditions' prevalence and symptoms, although there may be some common underlying aspects of biology. The primary purpose of this section is simply to emphasise that there is evidence for a biological role in PP risk, and to allude to some reasonably well-supported risk mechanisms.

Furthermore, when the author reported that neuroimaging studies are difficult to perform due to issues with participant recruitment and testing, and hence, are currently scarce, he should also report the main references to support this assumption.

I have now amended this sentence as follows: 'Neuroimaging studies in this area are scarce, presumably due to issues with participant recruitment and testing.'

Overall, the main text is long and difficult to follow for the general readership; thus, I suggest to include one or more Tables in order to summarize the main information according to the most relevant take-home messages included within the manuscript.

I have now summarised the advantages and limitations of the various approaches for understanding PP pathophysiology in Table 1 as suggested. The risk pathways suggested by the novel mouse model are already summarised in Figure 1.

Finally, the paper well describes, in my opinion, the biological (in particular, genetic) substrates underlying the postpartum psychosis but the clinical details of postpartum psychosis onset/ maintenance could be more extensively developed.

My intention was to focus on the biological underpinnings of PP, and how we might investigate these, rather than describing the clinical details of PP (which, as discussed above, have been reported elsewhere in several excellent reviews).

Additional minor changes based upon recently-published information

I have included five additional new references which, in my view, strengthen the circumstantial evidence implicating STS and CCN pathway disruption in PP pathogenesis, and reinforce the idea that the two pathways may interact.