Author's response to reviews

Title: Incidence of obstetrical thrombotic thrombocytopenic purpura in a retrospective study within thrombocytopenic pregnant women. A difficult diagnosis and a treatable disease

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Author's response to reviews: see over
Dear Editor

Please find a revised manuscript (MS: 2010880102144814) for “Incidence of obstetrical thrombotic thrombocytopenic purpura in a retrospective study within thrombocytopenic pregnant women. A difficult diagnosis and a treatable disease” with a point by point response to the reviewers comments.

We hope that this new version improved by the reviewers careful reading and fruitful comments will be suitable for publication acceptance.

Thank you for considering our work.

Sincerely

Yahsou Delmas and co-authors

Note: the lines and pages number in the responses are related to the new version of the manuscript
Reviewer's report
Title: Incidence of Obstetrical Thrombotic Thrombocytopenic Purpura in a Retrospective Study within Thrombocytopenic Pregnant Women. A Difficult Diagnosis and a Treatable Disease
Version: 1 Date: 28 November 2014
Reviewer: marie scully
Reviewer's report:
Minor essential revisions:
A very well described cohort of obstetric thrombocytopenia and the relatively high risk of TTP, given it is a rare disease.

Points that need addressing:

1. Can the authors confirm where they got samples from? Were the patients identified ie the 50 cases, called back to the unit?

Response:
Indeed, as the study was retrospective, ADAMTS13 activity assessment was mostly performed from serum samples initially used for systematic viral serologies during obstetrical unit hospitalization. In the remaining cases, patients were called back to the unit. Before doing this systematic approach within the two studied years, only one deficient patient was diagnosed at post-partum consultancy. We explained more clearly this point in the revised version of the manuscript. (Line 205-210 page 9).

2. Conclusion: page 12 line 296, the authors may need to consider another word rather than 'deep' thrombocytopenia, do they mean severe?

Response:
Yes indeed, deep has been replaced by severe, as recommended by the reviewer.

3. Figure 3 is unnecessary and should be described in the text.

Response:
We feel that the description of patient B sibling is complicated and we thought that a pedigree might be clearer. As genetic sequencing for this patient shows no mutation and supposed bigger rearrangement is hypothesized but unproven, the pedigree reinforces the recessive and constitutive origin of TTP. We propose to show this figure as a supplemental data.

Level of interest: An article of importance in its field
Quality of written English: Acceptable
Statistical review: No, the manuscript does not need to be seen by a statistician.
Declaration of competing interests: no conflicts of interest
Reviewer's report
Title: Incidence of Obstetrical Thrombotic Thrombocytopenic Purpura in a Retrospective Study within Thrombocytopenic Pregnant Women. A Difficult Diagnosis and a Treatable Disease
Version: 1 Date: 27 December 2014
Reviewer: Paula Bolton-Maggs

Reviewer's report:

1. The authors have made a retrospective diagnosis of TTP in pregnancy by reviewing cases of thrombocytopenia in pregnancy during 2008-2009 (so now more than 5 years ago).

Response:
Indeed, it took a long time to finalize this work. One reason is that we wished to have the complete follow-up of our patients. The other reason is that we needed to have a complete genetic analysis.

2. The title makes the point that the diagnosis is difficult and that the condition is treatable, but the paper rather loses this focus. Those women without a clear reason for the low platelet count had measurement of ADAMTS13. This was not during the pregnancy but later (when the assay became available?).

Response:
Indeed, ADAMTS13 activity was only assessed at the nephrologist post-partum consultancy, as obstetric unit practitioners were unaware of this rare disease at the time patients were managed. We specified this point in the revised version of the manuscript. (Line 207-211 page 9). The assay was available routinely from 2007 in Bordeaux.

3. Four cases were established by this assay plus thrombocytopenia in pregnancy. Here lies the first major weakness of this account: there is no comment on the presence or absence of schistocytes which are a key feature of the diagnosis because the authors noted that films were rarely examined for this.

Response:
Indeed, we agree with the reviewer’s comment. Unfortunately, films were only sparsely examined and as this was a retrospective analysis (usually more than one year after delivery), this information is not available. However, this also emphasizes the importance of our work, since it illustrates that in practice a peripheral blood smear is not systematically performed in patients with thrombocytopenia, as this should be performed in clinical practice. We insisted on this point in the revised version of the manuscript (Line 285-287 page 12).

4. Every case of thrombocytopenia should have a bloodfilm examination, this is basic good practice.

Response:
Yes, we do agree with this statement. As discussed in point 3., we added a sentence in that way, line 286 page 12.
5. The diagnosis of TTP should be treated as a medical emergency and treatment with plasma exchange started within 8h (Scully et al. 2012). This paper must stress this point and not imply that ADAMTS13 should be assayed in every thrombocytopenic patient. This assay is not generally available as an urgent test.

Response:
We fully agree with this statement. We therefore modified our manuscript accordingly and insisted on the fact that plasma exchange should be started as soon as TTP is diagnosed (ie, ADAMTS13 activity is not required to start plasma exchange) (line 59 page 3 in the abstract and lines 303-305 page 13). In clinical practice, the difficulty lies in the fact that TTP and HELLP syndrome both display haemolysis, thrombocytopenia and schistocytes. However, plasma exchange is mandatory in the first, whereas pregnancy termination is required in the second. So far however, clinical and standard biological features cannot be used to distinguish one disease from the other; on the opposite, ADAMTS13 activity is the only reliable tool to distinguish accurately both diseases. Even performed retrospectively, we believe that ADAMTS13 assessment is of particular importance to identify patients with a congenital TTP (lines 312-315 page 13).

6. In the subsequent pregnancies women with congenital TTP received plasma infusions as prophylaxis. On what basis was the particular regimen chosen?

Response:
The plasma infusion regimen was chosen empirically, and based on the reported experience in pregnancy cases of Upschaw-Schulman syndrome (Fujimura et al.; British journal of haematology 2009, 144(5)). The dose and the schedule of administration were increased throughout pregnancy, and further intensified in case of haemolysis and/or thrombocytopenia. Also, we empirically defined a residual ADAMTS13 activity of >10% as a target value.

7. What were the results of the ADAMTS13 measurements with this therapy?

Response:
ADAMTS13 residual activity before plasma administration was usually comprised between 10 and 15 %.

8. The authors have not described the progress during pregnancy of these 4 women, in particular at what point the thrombocytopenia was found and what action was taken. Three had a diagnosis of HELLP syndrome. The account of these patients is confusing and the differential diagnosis should be more clearly discussed since TTP is uncommon and, as in these cases, misdiagnosed.

Response:
We fully understand the reviewer’s comment. We therefore specified that thrombocytopenia was identified the day of admission for these three patients, and that caesarian was performed in less than 24 hours. This point has been clarified in the revised version of the manuscript (page 9, lines 211-213).
9. There are several places where the term 'plasmatherapy' is used. The authors should be clear when they mean plasma exchange and when they mean plasma infusion since plasmatherapy might mean either. Plasma infusion is no longer considered sufficient treatment for TTP, exchange is essential in the acute setting. I do not agree with the statement in line 142 page 6 about 'infusion or exchange'. Clearly the authors mean 'plasma exchange' in line 274 page 11.

Response:
We verified all the manuscript and homogenized the terminology. We used the term plasma exchange lines 143 and 284, as requested by the reviewer. Patient's type of plasma treatment has been precised with additional sentence lines 247-248 page 10. Also this has been changed in figure 3 and legend line 550 page 24.

10. Plasma infusion or other ADAMTS13-containing products (e.g. plasma-derived factor VIII concentrates) may be used for known congenital cases but not in the acute setting in pregnancy when the full diagnosis (i.e. congenital or acquired) is not yet established. The paper and the conclusion assumes that every obstetric unit has access to urgent ADAMTS13 assays but that is not true. The diagnosis is suspected on the basis of thrombocytopenia and fragmented red cells which should trigger urgent plasma exchange while awaiting results of the enzyme assay which may have to be sent away.

Response:
We fully agree with this statement. This point has been underscored lines 303-305 page 13.

11. Minor points: The language needs revision to better English, e.g. ADAMTS13 'dosages' is better expressed as 'levels'. Page 7 line 162 'severe' is better than 'deep'. Thrombocytopenia is usually spelled now without the 'a', i.e. thrombocytopenia'. It is better to call the 'Coombs' test the 'direct antiglobulin' test.

Response:
All these points have been addressed. We thank the reviewer for these comments.

12. I do not think figure 2 is necessary.

Response:
As the scope of the journal is obstetrical unit physicians, placenta pathologies are original data; therefore we feel that they could be of interest for these practitioners. We suggest to present this figure as a supplemental data.

12. In table 1 the abbreviations should be spelled.

Response:
This has been done (line 522 page 22).

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:** No, the manuscript does not need to be seen by a statistician.

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