

## Peer Review File

Article information: <https://dx.doi.org/10.21037/pm-21-72>

### Reviewer A

#### General comment:

The authors described a case of hemolytic disease of the fetus and newborn due to maternal anti-U. At GA of 26 weeks and a maternal anti-U titer of 64, MCA Doppler indices were within the severe range without fetal hydrops and IUT treatment was started. The fetus received a total of four IUTs. At 36 weeks GA cesarean section was performed and a healthy, although small for GA, child was born. Prophylactic phototherapy was initiated for 64 hours and no transfusions were given after birth.

The study is well performed and the manuscript is written according to CARE guidelines. However, some (minor) points need to be addressed.

#### Specific comments:

##### Abstract:

**Comment 1:** Main symptoms: Add main symptoms and clinical findings of the fetus.

**Reply 1:** We provided additional fetal symptoms.

Changes in the text: see Page 1, lines 14-20

**Comment 2:** Suggest to first describe the case and then the results of the review. Now it is somewhat mix-together

**Reply 2:** We restructure the abstract

Changes in the text: see Page 1, lines 14-28

##### Introduction:

**Comment 3:** Suggest to rewrite the first part of the introduction (or the abstract). Now it is copy-past from the abstract.

**Reply 3:** We rewrote the introduction to provide expanded background on Anti-U disease.

Changes in the text: see Page 2, lines 31-42

**Comment 4:** Add the following: 'This case report was prepared following the CARE Guidelines'. Include a citation of the CARE Statement publication.

**Reply 4:** We included a CARE statement and citation.

Changes in the text: see Page 3, line 49

##### Case presentation:

**Comment 5:** Line 73: What is meant by 'negative serologies'?

**Reply 5:** We defined this terminology with specific serologic results.

Changes in the text: see Page 3, lines 63-65

**Comment 6:** State if additional RBC antibodies were excluded.

**Reply 6:** We have included all the RBC antibodies that were tested for using

international nomenclature.

Changes in the text: see Page 3, lines 60-62

**Comment 7:** Lines 79-80: Use correct terminology for antigens, e.g. LC = c, FYA = Fya, etc

**Reply 7:** We have used the correct terminology.

Changes in the text: see Page 3, lines 57-58

**Comment 8:** Line 86: What were MCA Doppler indices?

**Reply 8:** We have included the MCA Doppler indices

Changes in the text: see Page 4, lines 70-72

**Comment 9:** Describe the IUT products more precisely.

**Reply 9:** We have described the IUT products used.

Changes in the text: see Page 4, lines 74-75

**Comment 10:** Were IUTs 1, 3 and 4 transfused intra-vascular?

**Reply 10:** We described how blood products were infused.

Changes in the text: see Page 4, lines 80, 90; Page 5, line 94

#### Discussion:

**Comment 11:** Briefly discuss difficulties finding U- donors. Were frozen and deglycerolized RBCs units used?

**Reply 11:** We described the blood products used in further detail.

Changes in the text: see Page 4, lines 74-75

**Comment 12:** Lines 141-143: The numbers of reports seem not to add up to 14, which are described in table 1.

**Reply 12:** We corrected the number of reports described in Table 1.

Changes in the text: see Page 6, line 127

#### **Reviewer B**

##### General comments:

The authors report a case of a patient presenting severe anti-U alloimmunization successfully managed by 4 intrauterine transfusions. They performed a literature review of anti-U hemolytic disease of the fetus and newborn.

For each IUT, the hemoglobin level of the fetus was normal for gestational age (between 5th and 95th percentile according to the paper of Mari et al, NEJM 2000). To my opinion, the intrauterine transfusions should not have been performed, because the fetus had no anemia at the time of the fetal blood samplings.

##### Abstract:

**Comment 1:** The abstract is clear but should be more precise concerning the number of IUTs, the gestational age of first IUT and the hemoglobin level at first IUT. These

three items are mandatory to illustrate the severity of the fetal hemolytic disease.

- a. # of IUTs
- b. Age of first IUT
- c. Hgb level at first IUT

**Reply 1:** We added these components to the abstract.

Changes in the text: see Page 1, lines 14-20

**Comment 2:** Line 51: The authors could remove “In conclusion”

**Reply 2:** We have made this change.

Changes in the text: see Page 1, line 21

Case:

**Comment 3:** The abbreviation “G5P2022 » is not universal. “Gravida 5 Para 2” is easier to understand.

**Reply 3:** We changed the language to be universal.

Changes in the text: see Page 3, line 51

**Comment 4:** Lines 54 and 85: Doppler is a surname and should be written in the singular and with a first capital letter.

**Reply 4:** We corrected this throughout the manuscript.

Changes in the text: see Page 3, line 69; Page 4, lines 70, 81; Page 5, line 114; Page 7, line 147

**Comment 5:** Line 86: It would have been interesting to give the MCA measurement before first IUT (and before each IUT as well).

**Reply 5:** We provided MCA measurement before first IUT. Once we initiate IUT, we do not continue to follow MCA Doppler.

Changes in the text: see Page 4, lines 70-71

**Comment 6:** Did the sonographers confirm that MCA Doppler was still over 1.5MoM in a subsequent ultrasound examination after 24h or 48h before organizing the first IUT?

**Reply 6:** We provided MoM values.

Changes in the text: See Page 3, lines 70-71

**Comment 7:** Line 89: At first PUBS, the fetus had no anemia (see the article written by Mari et al, NEJM 2000). At 26 WG, mild anemia (fetal Hb between 0.65 and 0.84MoM, or under the 5th percentile) corresponds to a hemoglobin level under 10.3g/dL. The fetus should not have been transfused with this normal level of hemoglobin.

**Reply 7:** We provided rationale for our decision to transfuse.

Changes in the text: see Page 4, lines 71-72, 79-81

**Comment 8:** Line 95: At third intrauterine transfusion, the fetus still had no anemia (see the article written by Mari et al, NEJM 2000). At 31WG, mild anemia (fetal Hb

between 0.65 and 0.84MoM, or under the 5th percentile) corresponds to a hemoglobin level under 10.9g/dL. The fetus should not have been transfused with this normal level of hemoglobin.

**Reply 8:** We provided rationale for our decision to transfuse.

Changes in the text: see Page 4, lines 87-91

**Comment 9:** Line 97: At fourth intrauterine transfusion, the fetus still had no anemia (see the article written by Mari et al, NEJM 2000). At 31WG, mild anemia (fetal Hb between 0.65 and 0.84MoM, or under the 5th percentile) corresponds to a hemoglobin level under 11.2g/dL. The fetus should not have been transfused with this normal level of hemoglobin.

**Reply 9:** We provided rationale for our decision to transfuse.

Changes in the text: see Page 5, lines 92-94

**Comment 10:** Line 101: Apgar is a surname and should be written in singular and with a capital as first letter.

**Reply 10:** We corrected this.

Changes in the text: see Page 5, line 97

**Comment 11:** Line 124: The authors can not write “severe fetal anemia” because there was no fetal anemia at all.

**Reply 11:** We provided rationale on how we determined anemia and severity of disease in the newborn including consideration of MCA Doppler severity and fetal growth.

Changes in the text: see Page 4 for clinical rationale

**Comment 12:** Lines 149-150: The sentence “Severe cases resulting in fetal anemia were seen at maternal anti-U titers as low as 64” is conflicting with the sentence from the abstract “Uniquely, this case reports the lowest critical maternal anti-U titer to-date resulting in clinically significant fetal anemia” and with the sentence on line 126.

**Reply 12:** We observed clinically relevant anemia at a titer of 32.

Changes in the text: see Page 1, line 11

Case and Table 1:

**Comment 13:** DAT at birth is important to report. DAT on fetal blood sampling (and its intensity) is very interesting as well in case of IUT.

**Reply 13:** DAT at birth is included.

Changes in the text: see Page 5, line 100