PROOF COVER SHEET

Author(s):	Mária Jakó, Andrea Surányi, Márta Janáky, Péter Klivényi, László Kaizer, László Vécsei, György Bártfai, and Gábor Németh
Article title:	Postnatal outcome and placental blood flow after plasmapheresis during pregnancy
Article no:	IJMF_A_1262344
Enclosures:	1) Query sheet 2) Article proofs

Dear Author,

1. Please check these proofs carefully. It is the responsibility of the corresponding author to check these and approve or amend them. A second proof is not normally provided. Taylor & Francis cannot be held responsible for uncorrected errors, even if introduced during the production process. Once your corrections have been added to the article, it will be considered ready for publication.

Please limit changes at this stage to the correction of errors. You should not make trivial changes, improve prose style, add new material, or delete existing material at this stage. You may be charged if your corrections are excessive (we would not expect corrections to exceed 30 changes).

For detailed guidance on how to check your proofs, please paste this address into a new browser window: http://journalauthors.tandf.co.uk/production/checkingproofs.asp

Your PDF proof file has been enabled so that you can comment on the proof directly using Adobe Acrobat. If you wish to do this, please save the file to your hard disk first. For further information on marking corrections using Acrobat, please paste this address into a new browser window: http://journalauthors.tandf.co.uk/production/acrobat.asp

2. Please review the table of contributors below and confirm that the first and last names are structured correctly and that the authors are listed in the correct order of contribution. This check is to ensure that your name will appear correctly online and when the article is indexed.

Sequence	Prefix	Given name(s)	Surname	Suffix
1		Mária	Jakó	
2		Andrea	Surányi	
3		Márta	Janáky	
4		Péter	Klivényi	
5		László	Kaizer	
6		László	Vécsei	
7		György	Bártfai	
8		Gábor	Németh	

Queries are marked in the margins of the proofs, and you can also click the hyperlinks below.

General points:

1. **Permissions:** You have warranted that you have secured the necessary written permission from the appropriate copyright owner for the reproduction of any text, illustration, or other material in your article. Please see http://journalauthors.tandf.co.uk/permissions/usingThirdPartyMaterial.asp.

2. **Third-party content:** If there is third-party content in your article, please check that the rightsholder details for re-use are shown correctly.

3. **Affiliation:** The corresponding author is responsible for ensuring that address and email details are correct for all the co-authors. Affiliations given in the article should be the affiliation at the time the research was conducted. Please see http://journalauthors.tandf.co.uk/preparation/writing.asp.

4. **Funding:** Was your research for this article funded by a funding agency? If so, please insert `This work was supported by <insert the name of the funding agency in full>', followed by the grant number in square brackets `[grant number xxxx]'.
5. **Supplemental data and underlying research materials:** Do you wish to include the location of the underlying research materials (e.g. data, samples or models) for your article? If so, please insert this sentence before the reference section: `The underlying research materials for this article can be accessed at <full link>/ description of location [author to complete]'. If your article includes supplemental data, the link will also be provided in this paragraph. See <http://journalauthors.tandf.co.uk/preparation/multimedia.asp> for further explanation of supplemental data and underlying research materials.

6. The **PubMed** (http://www.ncbi.nlm.nih.gov/pubmed) and **CrossRef databases** (www.crossref.org/) have been used to validate the references. Changes resulting from mismatches are tracked in red font.

AUTHOR QUERIES

Q1: Please check the article type for correctness.
Q2: Please provide the volume number and page range.

How to make corrections to your proofs using Adobe Acrobat/Reader

Taylor & Francis offers you a choice of options to help you make corrections to your proofs. Your PDF proof file has been enabled so that you can mark up the proof directly using Adobe Acrobat/Reader. This is the simplest and best way for you to ensure that your corrections will be incorporated. If you wish to do this, please follow these instructions:

1. Save the file to your hard disk.

2. Check which version of Adobe Acrobat/Reader you have on your computer. You can do this by clicking on the Help" tab, and then About".

If Adobe Reader is not installed, you can get the latest version free from http://get.adobe.com/reader/.

3. If you have Adobe Acrobat/Reader 10 or a later version, click on the Comment" link at the right-hand side to view the Comments pane.

4. You can then select any text and mark it up for deletion or replacement, or insert new text as needed. Please note that these will clearly be displayed in the Comments pane and secondary annotation is not needed to draw attention to your corrections. If you need to include new sections of text, it is also possible to add a comment to the proofs. To do this, use the Sticky Note tool in the task bar. Please also see our FAQs here: http://journalauthors.tandf.co.uk/production/index.asp.

5. Make sure that you save the file when you close the document before uploading it to CATS using the Upload File" button on the online correction form. If you have more than one file, please zip them together and then upload the zip file. If you prefer, you can make your corrections using the CATS online correction form.

Troubleshooting

Acrobat help: http://helpx.adobe.com/acrobat.html
Reader help: http://helpx.adobe.com/reader.html

Please note that full user guides for earlier versions of these programs are available from the Adobe Help pages by clicking on the link Previous versions" under the Help and tutorials" heading from the relevant link above. Commenting functionality is available from Adobe Reader 8.0 onwards and from Adobe Acrobat 7.0 onwards.

Firefox users: Firefox's inbuilt PDF Viewer is set to the default; please see the following for instructions on how to use this and download the PDF to your hard drive: http://support.mozilla.org/en-US/kb/view-pdf-files-firefox-without-downloading-them#w_using-a-pdf-reader-plugin

THE JOURNAL OF MATERNAL-FETAL & NEONATAL MEDICINE, 2016
http://dx.doi.org/10.1080/14767058.2016.1262344

Taylor & Francis
Taylor & Francis Group

Q1 SHORT REPORT

Postnatal outcome and placental blood flow after plasmapheresis during pregnancy

Mária Jakó[a], Andrea Surányi[a], Márta Janáky[b], Péter Klivényi[c], László Kaizer[d], László Vécsei[c], György Bártfai[a] and Gábor Németh[a]

[a]Department of Obstetrics and Gynecology, University of Szeged, Szeged, Hungary; [b]Department of Ophthalmology, University of Szeged, Szeged, Hungary; [c]Department of Neurology, University of Szeged, Szeged, Hungary; [d]Department of Pathology, University of Szeged, Szeged, Hungary

ABSTRACT

Purpose: Plasmapheresis in pregnancy adversely affects maternal hemodynamics, however there are studies suggesting it to reduce pregnancy loss in immunological diseases when medication is more harmful to the fetus. The overall optimal plasmapheresis treatment protocol remains unknown.

Materials and methods: A pregnant with neuromyelitis optica was followed up after receiving six volumes of fresh frozen plasma.

Results: The placenta compensated the hemodynamic change until the 33rd week of gestation, resulting a small for gestational age, otherwise healthy girl.

Conclusions: More research is needed on plasma exchange during pregnancy because in our observation placental circulation can adapt to the change in blood pressure.

ARTICLE HISTORY
Received 6 October 2016
Accepted 15 November 2016
Published online ▮▮▮

KEYWORDS
Plasmapheresis; placental vascularization; intrauterine growth restriction; neuromyelitis optica

Introduction

Plasmapheresis is the removal of whole blood from the patient, its separation by machine into component parts, and then the return of certain of those components or replacement with albumin or plasma protein fractions in combination with sterile saline. This procedure is used in immunological diseases to eliminate antibodies. The side effects are mostly mild; fainting, tingling of limbs, coagulopathy, bleeding, drop in blood pressure and allergic reaction to frozen plasma can adversely affect pregnancy [1]. In clinical researches concerning plasmapheresis they found that in case of antiphospholipid syndrome (APS) this method can be used as a treatment if first line (aspirin or heparin) fail to prevent pregnancy loss. In a series of 18 cases, when one plasmapheresis per month was performed, the live birth rate increased to 100% from the usual 10–50%. There was one mild preeclampsia, three fetal distress, four preterm deliveries, one thrombocytopenia, and two cases of uteroplacental insufficiency. The uterine artery pulsatility index (PI) was reduced and umbilical artery PI was >95th percentile. At 16th week of gestation 44% of women had bilateral uterine artery notch, by the 28th week only 11% [2]. A patient with familial hyperchylomicronemia received 41 courses of plasmapheresis during pregnancy and delivered a healthy boy at the 41st week of gestation [3].

Neuromyelitis optica (NMO) is an autoimmune disorder with prevalence of 0.5–4.4/100,000 inhabitants, it is mainly sporadic with female predominance and the median age of onset is 35–45 years. A significant breakthrough in the research of NMO was the description of circulating IgG auto-antibody (AQP4-IgG) that blocks Aquaporin-4-channel in oligodendrocytes [4]. Lesions start with the perivascular deposition of immunoglobulins, complement mediated cytotoxicity and the loss of AQP4 channel and glial fibrillary acidic protein [5]. To date no acute therapy has demonstrated significant benefit in improving visual outcome in NMO or preventing optic nerve atrophy. It can be managed through years with mild symptoms, but the medication has to be stopped for family planning. Current treatment for acute attacks includes corticosteroids and plasmapheresis. High dose of intravenous methylprednisolone (IVMP) results in faster recovery and improved color vision. Plasmapheresis after IVMP reduces the circulating AQP4-IgG resulting in long term improvement in visual acuity.

CONTACT Mária Jakó jmarica8@gmail.com Department of Obstetrics and Gynecology, University of Szeged, 1. str. Semmelweis, Szeged H6725, Hungary

Supplemental data for this article can be accessed here.

Immunosuppressive drugs are used as long term preventive therapies. Intravenous immunoglobulin and interferon beta appear to be ineffective in preventing relapses [6].

Only a few reports describe the negative effect of pregnancy on NMO, and there is no overview of data or consensus in therapy. In a retrospective study, it has been shown that pregnancy may have proinflammatory effects on autoimmune demyelinating diseases suggesting that NMO onset is more likely to occur during the postpartum year and that the relapse increases in the first 3–6 months after delivery [7]. In NMO-IgG seropositive patients, the annualized relapse rate during pregnancy did not differ from that before pregnancy, but it increased significantly during the first six months postpartum. Moreover, 77% of the deliveries were associated with postpartum relapses suggesting that delivery adversely affects NMO [8,9]. We first describe a case in the literature [10,8], when plasmapheresis was administered during pregnancy for a patient suffering from NMO and a live infant was born. There is no information about plasmapheresis in pregnancy complicated by maternal NMO based on PudMed, Sciencedirect, MeSH Database till now.

Materials and methods

Instead of teratogenic medication or leaving the mother without therapy, we chose plasmapheresis where the removed plasma was substituted with fresh frozen plasma. Ethics approval (Registration number: 49870-3773/2014/EKU (586/2013)) was obtained and the patient signed an informed consent on 21 January 2014.

Gestational age, fetal biometry and the flow S/D ratio of umbilical and uterine arteries were determined by conventional 2-D and color Doppler ultrasound measurements (Voluson 730 Expert ultrasound machines (GE Medical Systems, Kretztechnik GmbH&Co. OHG, Zipf, Austria)). Fetal weight was calculated by Hadlock B formula.

The 3-D static volume box was placed over the umbilical cord insertion. The maximum sweep angle was 70°. The stored volumes were analyzed using the Virtual Organ Computer-aided Analysis program (GE Medical Systems, Zipf, Austria, version 10.4). The "Merce-type sonobiopsy" is a validated method, that is applicable throughout the whole pregnancy.

Results

Patient history before pregnancy

In 2009, the patient was referred to neurological consultation due to paraesthesia and numbness of limbs spreading from her left upper limbs downwards, and loss of vision for 30 s. Family history was unremarkable. Ophthalmological examination revealed no pathologic changes, the MRI showed no alteration in the brain while in the neck revealed T2 hyperintense lesion in the cervical spinal cord at the level of C2–5. The cerebrospinal fluid analysis tested negative for oligoclonal bands. After high (3×1000 mg) dose of IVMP, the patient experienced complete remission. In 2010, symptoms reappeared on her left side and she received another high dose (this time 3×500 mg) of IVMP. All clinical features pointed to neuromyelitis, and in 2011 seropositivity for AQP4-IgG was confirmed. According to the revised diagnostic criteria for NMO, this case met the three benchmarks [9] and the diagnosis was settled. In 2012 her neurological symptoms returned but were eliminated quickly by steroids, but in December MRI showed T2-weighted relatively large lesion in the spinal cord extending over C3 and Th5–6 vertebral segments. In the first half of 2013, the patient had no symptoms due to azathioprine (100 mg). In April 2013, she quitted therapy for family planning.

Patient history until the 16th week of pregnancy

The patient's last menstrual period was on 11 July 2013. In September paraesthesia returned in her lower limbs followed by urine retention, dysesthesia and loss of vision on the right side. Ophthalmologic examinations showed signs of demyelination, and neuronal degeneration. She received five plasmapheresis. First ultrasound was performed on 9th October for establishing the gestational age and genetical ultrasound screening was performed on 11th October. Nuchal translucency and crown-lump length of the fetus were measured in normal range for gestational age, and a retroplacental hematoma was discovered. Due to her symptoms, she received one scheduled plasmapheresis in October and low dose of oral methylprednisolone every second day to prevent relapse and she had no complaints until the end of November. All together she has received six courses of fresh frozen plasma.

Patient follow up until delivery

The patient's previous symptoms reoccurred and persisted until the end of pregnancy and she lost her vision on the right side. On 33rd week of gestation, the patient complained of rare fetal activity and the ultrasonographic examination showed intrauterine growth restriction, oligohydramnion, and calcificated placenta.

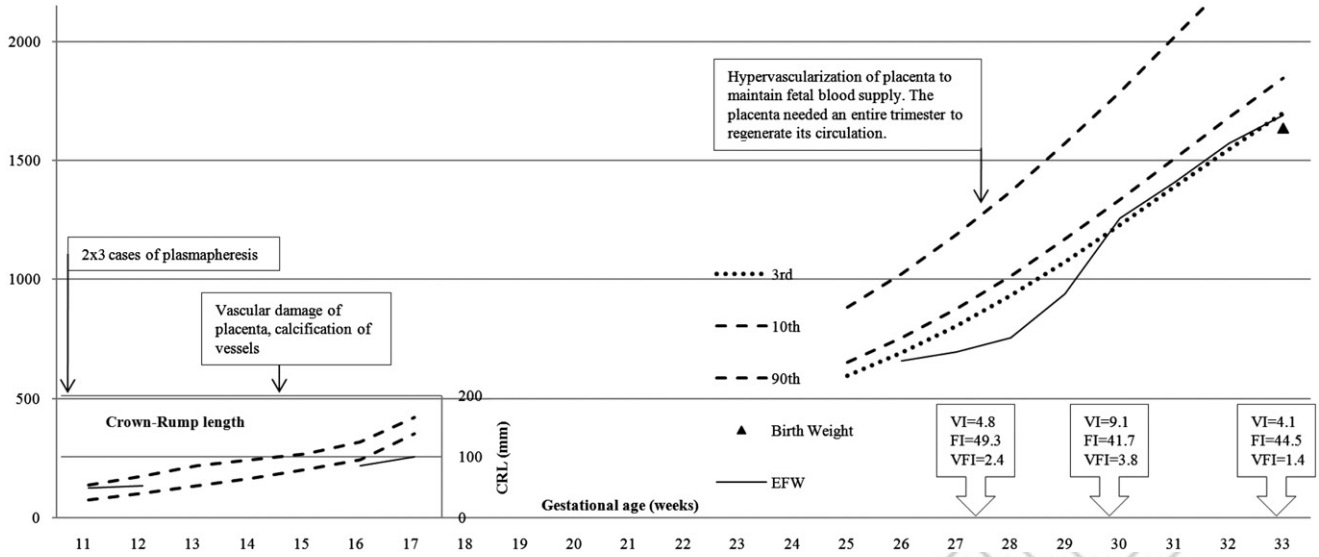

Figure 1. Fetal growth and fetoplacental circulation after plasmapheresis.

The ultrasonographic data are shown in Figure 1. The uterine arteries on both sides showed an early diastolic reduction of the blood flow. Cesarean section was performed immediately. A female neonate was delivered weighing 1635 g (<3rd percentile) with Apgar scores of 5–6–7 at 5–10–15 min respectively, and later she was transferred to perinatal intensive care unit. Extended confluent infarctions were detected on the surface of the placenta. Histological examination revealed a placental tissue as in third trimester with accelerated maturation and calcification, and the vessels were far from the villous surface, reducing the blood nutrient exchange. No chorioamnionitis or funisitis could be detected. On the third postnatal day, the patient became anemic, refused transfusion, received ferric-sodium-glucuronate and folic-acid.

Postpartum follow up

She could breastfeed the newborn. Three months after delivery, the patient lost her vision on the left side as well. After the initialization of rituximab (100 mg and six months later 500 mg), the patient experienced no relapse and her status remained stable. Although she lost her vision almost completely on the left side, ophthalmologic examinations of October 2014 revealed some improvement on the left eye.

Discussion

Our patient did not receive intravenous immunoglobulin for the reasons mentioned in the introduction. Immunosuppressive drugs could control her symptoms for three years with short term relapses. Quitting steroid therapy in order to have a baby caused dilemma both for the patient and the doctor. In our case, the fetus was small for gestational age but regarding literature data it is still a successful case, hence only 65% of such pregnancies end with livebirth. The sudden change in maternal blood pressure during plasmapheresis damages the newly forming capillaries (retroplacental bleeding), that can be compensated by the excessive vascular branching afterwards. The new vessels are overwhelmed and more likely to calcificate. Corticosteroid or immunosuppressive drugs in pregnancy also may lead to intrauterine growth restriction and major malformations. With this short report, we would like to highlight the ability of the placenta to compensate the drop in blood pressure during plasmapheresis and that there should be a way of combination of therapies to reach the best possible outcome.

Compliance with ethical standards

All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

Disclosure statement

The authors report no conflicts of interest. This research work received no funding, it was conducted within a PhD

program in Reproductive Medicine (ID number: 5T472), University of Szeged.

ORCID

Andrea Surányi http://orcid/org/0000-0002-1168-7261

References

1. Royal College of Obstetricians and Gynecologists. Blood Transfusion in Obstetrics. Green-top Guideline No. 47; 2015.
2. El-Haieg D, Zanati MF, El-Foual FM. Plasmapheresis and pregnancy outcome in patients with antiphospholipid syndrome. Int J Gynaecol Obstet 2007;99:236–41.
3. Djelmis J, Ivanisevic M, Kosi N. Plasmapheresis in pregnant patient with familial hypertriglyceridemia. Eur J Obstet Gyn Reprod Biol 2016. http://dx.doi.org/10.1016/j.ejogrb.2016.03.042
4. Drori T, Chapman J. Diagnosis and classification of neuromyelitis optica (Devic's syndrome). Autoimmun Rev 2014;13:531–3.
5. Matthews LA, Palace JA. The role of imaging in diagnosing neuromyelitis optica spectrum disorder. Mult Scler Relat Disord 2013;3:284–93.
6. Uzawa A, Mori M, Kuwabara S. Neuromyelitis optica: concept, immunology and treatment. J Clin Neurosci 2014;21:12–21.
7. Langer-Gould A, Beaber BE. Effects of pregnancy and breastfeeding on the multiple sclerosis disease course. Clin Immun 2013;149:244–50.
8. Kim W, Kim SH, Nakashima I, et al. Influence of pregnancy on neuromyelitis optica spectrum disorder. Neurology 2012;78:1264–7.
9. Wingerchuk DM, Lennon VA, Pittock SJ, et al. Revised diagnostic criteria for neuromyelitis optica. Am J Ophthalmol 2006;142:715–6.
10. Shang W, Liu J. Neuromyelitis optica during pregnancy. Int J Gynaecol Obstet 2011;115:66–8.

Q2