Author’s response to reviews

Title: Successful anticoagulant therapy for disseminated intravascular coagulation during conservative management of placenta percreta: A case report and literature review

Authors:

Shinya Matsuzaki (zacky@gyne.med.osaka-u.ac.jp)
Kiyoshi Yoshino (yoshino@gyne.med.osaka-u.ac.jp)
Masayuki Endo (endo@gyne.med.osaka-u.ac.jp)
Takuji Tomimatsu (tomimatsu@gyne.med.osaka-u.ac.jp)
Tsuyoshi Takiuchi (takkitakkitakki3@gmail.com)
Kazuya Mimura (kazuya.med_ob-gyne@hotmail.co.jp)
Keiichi Kumasawa (kumasawa@gyne.med.osaka-u.ac.jp)
Yutaka Ueda (ZVF03563@nifty.ne.jp)
Tadashi Kimura (tadashi@gyne.med.osaka-u.ac.jp)

Version: 1 Date: 28 Nov 2017

Author’s response to reviews:

28 November, 2017

Executive Editor
Nawsheen Boodhun
BMC Pregnancy and Childbirth

Dear Editor:

RE: PRCH-D-17-00510
Dear Editor

Thank you for the review of our manuscript titled “Successful anticoagulant therapy for disseminated intravascular coagulation during conservative management of placenta percreta: A case report and literature review” The editor’s and reviewer’s comments were very helpful, and we have revised our manuscript accordingly. Our point-by-point responses to the reviewer’s comments are provided below and highlighted in blue font in the revised manuscript.

We would like to take this opportunity to express our sincere gratitude to the reviewer who identified areas of the manuscript that needed corrections or modifications. We would also like to thank you for allowing us the opportunity to resubmit a revised copy of the manuscript.

We trust that the revised manuscript will now be suitable for publication in BMC Pregnancy and Childbirth.

Yours Sincerely,

Dr. Shinya Matsuzaki

Department of Obstetrics and Gynecology

Osaka University Graduate School of Medicine

2-2 Yamadaoka, Suita, Osaka 565-0871, Japan

Telephone: +81-6-6879-3355; Fax: +81-6-6879-3359

E-mail: zacky@gyne.med.osaka-u.ac.jp
Reviewer reports:

Thank you very much for your helpful comments. We have provided point-by-point responses to all comments and explanations regarding revisions made to the manuscript.

Wondimu Gudu, MD, MPH (Reviewer 1): Abstract section

- Background

* Unduly long.

Line 51-53 Stating "literature review was done" suffices rather than putting the long statement "Additionally, to understand this rare condition, we reviewed and discussed the related literature. For this, we performed an electronic literature search using the keywords "percreta" and "conservative management," "left," or "placenta in situ," including reports published between January 1995 and December 2016"

We appreciate your helpful comments. As suggested, we have revised the abstract section.

- Case presentation

Should be revised to highlight the most important clinical data related with the case.

Lines 59 to 68 should be removed (highlighted in the manuscript).

This section should be dedicated to brief description of clinical presentation, findings, work up and management of your case.

We appreciate your insightful comments. As suggested, we have revised the abstract section and added the clinical data.

Case presentation

G5 P2?? What about the other 2 pregnancies?
As suggested, we added the description in the revised version (line 87, page 5).

Revise "no medical history except for a history of two cesarean deliveries",
CD is an obstetric history, not medical

We appreciate your helpful comments. As suggested, we have revised the description in the revised version (line 88, page 5).

"The placenta was located along the entire anterior uterine wall". It is not a clear statement. Doesn't describe the exact location of the placenta (I.e was it a fundal anterior? Was it on the anterior wall of the lower uterine segment?). If the patient had placenta previa the relation of the lower edge of the placenta with the internal oss of the cervix should have been described or descriptive terms such as "placenta previa totalis, partialis….should be used.

The placenta covered the entire anterior wall of the lower uterine segment, and the patient was diagnosed with placenta previa marginalis. As suggested, we have revised the description in the revised version (line 90, page 5).

Discussion

- The definitive (preferred) management of placenta accreta in modern obstetrics is hysterectomy. Considering the following facts listed below, why was not hysterectomy performed in your case?

  * Patient being managed in a tertiary center with all specialties (surgeons, urogynecologist… ) and equipments required for handling any possible peri-operative complications.

  * The degree of placental adherence/invasion was already known preoperatively in this case. (One of the indications to leave the placenta in situ is when unsuspected placenta accreta is diagnosed intaoperatively and the necessary preparations were not made). Even then subsequent hysterectomy is recommended)
We appreciate your insightful comments. As suggested, we have added the description “the management of placenta accreta in modern obstetrics is hysterectomy” in the background section (line 77, page 5). Although we diagnosed placenta percreta before cesarean delivery, intraoperative findings revealed strong and broad adhesion between the placenta and bladder wall; these findings were relatively more explicit than what we preoperatively considered. Thus, we decided to perform conservative management in patients presenting intraoperative findings. We have added perioperative MRI and intraoperative images in new Figure 1 and have replaced old Figure 1 with Figure 2 to illustrate perioperative and intraoperative findings. Previous data about planned subsequent hysterectomy were limited, and no data were available about ideal timing and complications. Therefore, we continued the conservative management. Hope, this explains our situation well.

* The reason of differing hysterectomy cited by authors was the fact that the placenta invaded into the bladder. But, If muti-speciality care was planned hysterectomy could have been done leaving the part of the myometrium attached with the bladder intact.

We appreciate your helpful comments and agree with your suggestion. In our case, intraoperative findings revealed strong and broad adhesion between the placenta and bladder wall with approaching pelvic sidewall and filling the cul de sac. Accordingly, we have added the image as Figure 1 to illustrate the difficulty. We believed that despite performing hysterectomy with a multidisciplinary team, the urologic complication of hysterectomy was very high. In addition, massive hemorrhage and a high rate of urologic complications had been reported; thus, we decided to perform conservative management to avoid surgical complications of hysterectomy for placenta percreta.

* The woman is mutiparous (3). Conservative management leaving the placenta insitu is rarely recommended in women desiring future fertility

- Was the patient counseled and involved in the clinical decision making process.

We appreciate your helpful comments. As mentioned earlier, we performed conservative management to avoid severe urologic complications during hysterectomy and not to preserve fertility. Accordingly, we have added the description in the revised version (line 95, page 5).
DIC is a condition involving both the activation of coagulation cascade with concurrent fibrinolytic events. Considering that heparin can precipitate bleeding from the placental attachment site, Do you recommend the use of heparin as a novel therapy?? Most standard text books do not recommend heparin in cases like presented here. The only possible indication is in patients who are at risk of thrombo-embolism. Gabbe's text book of obstetrics even states that the use of heparin is condemned!!

We appreciate your insightful comments. As suggested, since our treatment posed the risk of bleeding from the placental attachment site, we considered that our treatment could not be offered as a novel therapy and should be left at the discretion of well-informed patients. Our patient was well informed and strongly desired to continue conservative management. Therefore, we reviewed a previous study about fetal death syndrome and consulted the use of heparin administration. Consequently, the patient desired using heparin. Accordingly, we have added the description in the text (line 130, page 7).

As suggested, our treatment posed the risk of bleeding. Thus, we administered intravenous heparin so as to be able to stop heparin administration and immediately neutralize its effect using protamine sulfate in case of hemorrhage. Our treatment poses a high risk and needs intensive care. Accordingly, we have added the description (line 216, page 10).

- Why was not postoperative prophylactic antibiotics administered?? I think the woman is a candidate for prophylactic antibiotics considering that a potential site (media) of bacterial proliferation (placenta) is left in uterine cavity.

We appreciate your helpful comments. Our literature review revealed 30 cases of conservative management of placenta percreta that mentioned about the antibiotics and 10 cases that did not receive postoperative prophylactic antibiotics. Because we found no incidence of endometritis within one week after CD in prophylactic antibiotics cases, we considered prophylactic antibiotics as nonessential. Accordingly, we have added the description (line 250, page 11).

Some of the concepts are repeatedly mentioned in the discussion section (especially related with fever and heparin)
Thank you for your advice. As suggested, we have revised the redundant sentences in the discussion section.

- Authors conclude that DIC and Fever are not absolute indicators for conservative management of placenta accrete

* But clinical recommendations are to target the underlying condition (in this case retained placenta) in the treatment of DIC (especially in your patient who had very low fibrinogen level)

We appreciate your helpful comments. As suggested, if we encounter complications associated with conservative management, we should consider hysterectomy. In our case, the patient strongly desired to continue the conservative management, and we had no previous data that detailed the duration of heparin administration to improve DIC. We anticipated improving DIC in a short duration. However, our case revealed that the treatment duration extended to about 3 weeks, which, in turn, might be a high-risk treatment. We believe that our data is informative for readers. Accordingly, we have revised the sentence with a weakened expression about these comments (line 269, page 12).

- Line 14 to 15 "Conservative management of the placenta accreta crucial to avoid the listed complications. Page 6 line 102 to 103 " to avoid surgical morbidity"

* But literature evidence is to the contrary where hysterectomy is actually indicated to avoid other potential life threatening complications

We appreciate your insightful comments and agree with your suggestion. Accordingly, we have revised the sentences (line 77, page 5) with a weaker expression because conservative management of placenta percreta is a relatively high-risk management.

- The reason given to start heparin was that the fibrinogen level didn't improve after administration of FFP. Why was FFP not given before heparin?

We appreciate your comments. Because we considered the side effects of subcutaneous heparin to be limited, we first administered heparin subcutaneously. However, we performed transfusion because subcutaneous administration of heparin was ineffective. In addition, the administration
of FFP did not improve fibrinogen level either. Thus, we initiated the intravenous administration of heparin to improve fibrinogen level, and this treatment was successful. Accordingly, we have revised the sentences in the revised version (line 137, page 7).

- Any concern with the prolonged administration of heparin (18 days)??

Although heparin-induced thrombocytopenia is one of the side effects of administering heparin, it was not observed in our case. Accordingly, we have added this description in the text (line 142, page 7).

- Line 232
  * Authors suggested IC without infection can be treated with heparin but in the previous paragraph anticoagulant treatment of DIC irrespective of other clinical conditions was recommended

We appreciate your helpful comments and have revised the sentences in the revised version (line 228, page 11).

- Line 236
  * How do you explain the raised CRP and WBC??

We appreciate your helpful comments. As added in the discussion section, placental blood flow disappeared, and the placenta might be necrotic around day 70 after the cesarean delivery. The inflammatory response to infection and tissue injury supports host defense, clearance of necrotic tissue, adaptation, repair, and absorption of hematoma caused the WBC and CRP elevation. Hence, we speculated that the elevation of WBC and CRP was induced by the absorption of necrotic placenta such as the absorption of hematoma or the clearance of necrotic tissue in our patient. Accordingly, we have added the discussion in the revised version (line 240, page 11).
General comments

1. I think Some of the files are bulky and better be put as supplementary files (e.g. findings of the literature review)

2. The literature review is more of a narrative synthesis which could be submitted as a separate manuscript. The case report can be submitted by revising the discussion part of the manuscript so as it is focused on the summarized findings of previous literature data in light of the current case report.

We appreciate your comments. As suggested, we have revised the literature review and considered re-submitting it as a separate manuscript to omit some bulky files. Instead of removing two tables, we have added perioperative MRI and intraoperative images as Figure 1 and have revised the discussion to improve the manuscript.

Reviewer 2 reports:

Thank you very much for your helpful comments. We have provided point-by-point responses to all comments and explanations regarding revisions made to the manuscript.

Valerie Smith, PhD (Reviewer 2): The authors present an interesting case with an associated literature review. I have some minor comments only; 1. Lines 88-90; you describe a Gravida 5, Para 2 woman, but state she had no medical history except for two cesareans; so what happened with the other two pregnancies? Did these end with miscarriages? If yes, perhaps include here so as to clarify.

We appreciate your helpful comments and have revised the description in the revised version (line 87, page 5).

2. Line 103; the estimated blood loss of 200mls seems fairly low for a CS birth; how was this estimated; e.g. swab weights, visually, etc.; please state.
We appreciate your insightful comments. As suggested, we have added the description about the method for the estimation of blood loss because a transverse uterine fundal incision exhibited minimal blood loss, as previously reported (Kotsuji F et al. BJOG. 201; 120: 1144-9.). In addition, the placenta was not separated; thus, blood loss was relatively small. Accordingly, we have revised the description (line 106, page 6) and we have added the description in the discussion section (line 172, page 9)

3. Line 104; where you state the woman was not administered prophylactic antibiotics post-operative; is this usual/routine procedure in your unit or a deviation from same? Please clarify

We appreciate your comments. At our institution, we do not administer post-operative prophylactic antibiotics after the cesarean delivery without pre-operative infection. Regarding conservative management of placenta percreta, our literature review revealed 10 cases of conservative management of placenta percreta that did not receive prophylactic antibiotics. Because we found no incidence of endometritis within 1 week after CD in prophylactic antibiotics cases, we considered prophylactic antibiotics to be nonessential. Accordingly, we have added the description in the revised version (line 250, page 11).

4. Line 107; as the woman is described as discharged on day 14, where and why was the blood taken on day 42? For example, was it during a follow-up clinic visit? Was it by her general practitioner? Please clarify

We appreciate your helpful comments. We examined the patient weekly and observed a decrease in the serum fibrinogen level on day 42. Because this was an outpatient follow-up visit, the patient was asymptomatic. Accordingly, we have added the description in the revised version (line 116, page 6).

5. Lines 169-172; regarding the literature review - you divide the reports by DIC and fever; so was yours the only case that experienced both? Can you clarify in the text please
We appreciate your insightful comments. As mentioned, to the best of our knowledge, our case is the only one in which the patient experienced DIC and fever and was successfully treated by medical treatment. Our case could reveal interesting findings to discuss DIC induced by residual placenta, and we believe that our case is useful for readers. Accordingly, we have added the description in the revised version (line 190, page 9).