Author's response to reviews

Title: Giant uterine artery pseudoaneurysm after a missed miscarriage termination in a cesarean scar pregnancy

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Author's response to reviews: see over
Dear Editor:

Thank you very much for your consideration of our manuscript. We have made revisions according to the reviewers’ comments and your suggestions. The paper has been edited carefully by a native English-speaking person.

In page 2 line 34, we revised “ultrasound” to “Doppler ultrasonography”.

In page 2 line 36, “a historectomy” was revised to “an emergency hysterectomy”.

In page 2 line 39, we changed Conclusions in the structured Abstract according to reviewers’ comments as: Ultrasound and Doppler ultrasonography are recommended to rule out uterine artery pseudoaneurysms, especially in cases such as a cesarean scar pregnancy.

For a giant uterine artery pseudoaneurysm, interventional embolization might be the first treatment option when the diagnosis is made, and, as in this case, hysterectomy is clearly possible when severe bleeding occurs.

In page 3 line 55, we added the information to explain the time interval of pelvic injury to hemorrhage caused by uterine artery pseudoaneurysm: “This delay is supposed to be caused by a gradual increase in the size of the pseudoaneurysm caused by a characteristic pressure increment. The blood flow into the pseudoaneurysm is greater during systole than diastole. This leads to a gradual pressure build up and eventual rupture.”

In page 3 line 61, we added “for this condition” in the end of the sentence “In
recent years, uterine artery embolization has become an accepted treatment method."

In page 3 line 70, we revised the sentence “She had a history of one elective cesarean delivery 2 years before and a missed miscarriage at 9 weeks of gestation 4 years before.” to “She had a history of one missed miscarriage at 9 weeks of gestation managed by surgical curettage 4 years before, and one elective cesarean delivery 2 years before.”

In page 4 line 75, we added “beta” in front of the word “human chorionic gonadotropin”.

In page 4 line 86, the sentence “......was proven by histopathology.” was revised to “proven as such by histopathology.”

In page 4 line 89 and line 92, the word “cyst” was changed to “cystic lesion”.

In page 4 line 95, “a hysterectomy” was revised to “an emergency hysterectomy”.

In page 4 line 96, “cyst” was revised to “pseudoaneurysm”.

In page 5 line 104, “this pseudoaneurysm” was changed to “the pseudoaneurysm in this case”.

In page 5 line 120, “we think it is necessary for patients to undergo an ultrasound examination within 24 h after curettage, especially in cases of cesarean scar pregnancy.” was revised to “we think it is necessary for patients to undergo a Doppler ultrasound examination as a required postoperative investigation especially in cases of cesarean scar pregnancy.”

In page 6 line 127, we revised “future fertility” to “preserving fertility”.

In page 6 line 129, No. 9 reference was changed to No.11 because we added 2 new references.

In page 6 line 129, we deleted the sentence “and much smaller than this case”.

In page 6 line 130, we added description to explain why we take hysterectomy in this case: “Our interventional radiologists lacked experience in treating such a giant lesion and thought that repeated treatment might be required. The serum β-hCG level was still high after curettage, suggesting there were retained chorionic villi in the pseudoaneurysm. Recanalization of the pseudoaneurysm might occur even after arterial embolization from rapid recruitment of collateral vessels. In this situation, repeated uterine curettage immediately after embolization or methotrexate therapy might decrease the
probability of recanalization. Therefore, in this case, the patient tried to seek admittance to an advanced institution to undergo embolization treatment. However, when waiting for this, massive bleeding occurred and we performed an emergency hysterectomy." We deleted the sentence “Such a giant pseudoaneurysm is difficult to treat with arterial embolization.” because no radiologists has the chance to try. In page 6 line 142, the reference No. 10 was changed to No. 12 because we added 2 new references as we revealed before. In page 6 line 143, we added “in the literature” in the end of the sentence “but no further experience has been reported”. In page 6 line 144, the word “resultant” was changed to “subsequent”, “and” was changed to “or”. In page 6 line 145, we deleted the sentence “In this case, we should performe hysterectomy as soon as we identified the pseudoaneurysm to avoid a dangerous hemorrhage” because we cannot make such a definite conclusion in a case report. In page 6 line 148, we revised the Conclusions as: It is highly advisable for patients to undergo a Doppler ultrasound examination as a required postoperative investigation to rule out a uterine artery pseudoaneurysm, in cases of a cesarean scar pregnancy. For such a giant uterine artery pseudoaneurysm, embolization might be the first treatment when the diagnosis is made, but hysterectomy is possible when severe bleeding occurs.
In page 9 line 202, we added 2 new references as No. 9 and No. 10.

In page 10 line 219 in the Figure legends, the word “cyst” was changed to “pseudoaneurysm”.

We revised our figures in this manuscript. We upload four figures and each figure includes an illustration. Figure 1 is 2-dimentional ultrasound image of the pseudoaneurysm. Figure 2 is Doppler ultrasonography of the pseudoaneurysm. Figure 3 is supplying artery velocity of the pseudoaneurysm. Figure 4 is gross specimen of the uterine artery pseudoaneurysm.

To reviewers

Reviewer 1: Shigeki Matsubara

1. You performed hysterectomy ONLY AFTER UAP has been ruptured; in other words, you looked and wait the situation even though you found it (gigantic!) a early as next day of D&C. Why? It is quite a dangerous scenario; if the rupture had caused 4000 mL bleeding (for example) at one time, the patients may have died!

Authors’ response: Thank you very much for your comment. Your question is valuable and reasonable. The situation was very dangerous. We sought interventional radiologists for help when we diagnosed a pseudoaneurysm. They agreed with us that the patient should be treated with embolization as soon as possible. But they did not have any experience in treating such a giant lesion with a patient showing an elevated serum β-hCG level. When the patient’s family knew that the radiologists were unsure about the best treatment, they decided to transfer her to an advanced hospital to receive embolization therapy. However, rupture of the pseudoaneurysm occurred while she was waiting for admittance to the advanced hospital. Hysterectomy was performed urgently.

We have added the following to the manuscript: “Our interventional radiologists lacked experience in treating such a giant lesion and thought that repeated treatment might be required. The serum β-hCG level was still
high after curettage, suggesting there were retained chorionic villi in the pseudoaneurysm. Recanalization of the pseudoaneurysm might occur even after arterial embolization from rapid recruitment of collateral vessels. In this situation, repeated uterine curettage immediately after embolization or methotrexate therapy might decrease the probability of recanalization. Therefore, in this case the patient tried to seek admittance to an advanced institution to undergo embolization treatment. However, when waiting for this, massive bleeding occurred and we performed an emergency hysterectomy.”

We revised the second sentence of the Conclusion as follows: “For such a giant uterine artery pseudoaneurysm, embolization might be the first treatment when the diagnosis is made, but hysterectomy is clearly possible when severe bleeding occurs.”

2. Why do you conclude that embolization is ineffective for “giant” UAP? If yours is the largest ever, then, we cannot conclude it because no interventional radiologists have never have had a chance to treat it. Your context lacks rationale.

Authors’ response: Thank you for your comments. We are sorry for our inappropriate expression. We cannot make this conclusion because no interventional radiologists had the chance to treat this case. Therefore, we have deleted this sentence in the paper.

3. You concluded, “hysterectomy should be performed as soon as possible. What do you mean? You did it 10 days after!; not at all “as soon as”. Do you mean, “as soon as possible only when bleeding occurs”? You did it long after you noticed UAP.

Authors’ response: Thank you for your comment. We are very sorry for the confusing explanation. We have revised the sentence as follows: “For such a giant uterine artery pseudoaneurysm, embolization might be the first treatment when the diagnosis is made, but hysterectomy is clearly possible when severe bleeding occurs.”

4. If you expected “spontaneous absorption (disappearance) of UAP”, then write so. Even in that occasion, discussion on whether such a “gigantic” UAP can be absorbed or not is required; this should be deeply and completely discussed.

Authors’ response: Thank you for your comment. We are very sorry for the confusing expression in the report. We did not expect a spontaneous absorption of the UAP. In fact, the patient’s family decided to transfer to an
advanced hospital for embolization because our interventional radiologists lacked experience in treating this lesion. We waited for the acceptance of the advanced hospital and watched the patient carefully. However, we were forced to carry out an emergency hysterectomy.

5. There are many wrong English. Even though the grammar may be right, it is not “comfortable” English from paper writing point of view.

Authors’ response: Thank you for your comment. The paper has been edited carefully by a native English-speaking editor from a professional editing group. We hope it will meet the requirements of publishing.

6. You can never say “US SHOULD be done within 24 hours”. As indicated in Author Guideline of this Journal, you had better quite cautious to say the actual way of practice. Why 24 hours? 12 hours in not good? 36 hours is not good? Single case report cannot allow such a definite conclusion.

Authors’ response: Thank you for your comment. Your suggestion is correct. We cannot make a definite conclusion from a single case report. We found the pseudoaneurysm at 18 h after curettage, but we cannot assert that US should be done within 24 hours. We think ultrasound and Doppler ultrasonography will be helpful in diagnosing uterine artery pseudoaneurysms in the postoperative care of caesarean scar pregnancies. We revised the sentence as follows: “It is highly advisable for patients to undergo a Doppler ultrasound examination as a required postoperative investigation to rule out a uterine artery pseudoaneurysm, especially in cases of a cesarean scar pregnancy.”

Reviewer 2: Nidhi Sharma
1. In the conclusion of the structured abstract, please mention Doppler ultrasound in the preoperative work up in addition to the postoperative management of caesarean scar pregnancy. This will help us to decide if any arteriovenous malformations were formed as result of previous caesarean section or curettage done for previous missed abortion. We will also know if the pseudo aneurysm resulted as a result of curettage done for this gestation or an earlier one. We recommend Doppler in all cases of undiagnosed vaginal bleeding to rule out arterio venous malformations of uterine vascular architecture.

Authors’ response: Thank you for this advice. The previous missed abortion occurred 4 years before. It was managed by surgical curettage. The patient had undergone an elective cesarean delivery 2 years before. Doppler ultrasonography did not identify any blood signal in an echo-free area in the cesarean scar before this curettage. We think the
pseudoaneurysm formed afterwards. We have added this information to the Conclusion of the structured abstract as follows: “Ultrasound and Doppler ultrasonography are recommended to rule out uterine artery pseudoaneurysms, especially in cases such as a cesarean scar pregnancy.”

2. In the background, the cause of onset of symptoms after 1 week to 3 weeks after pelvic surgery needs to be speculated. A word about a gradually increase in the size of pseudo aneurysm due to characteristic pressure gradient can be mentioned. The flow into the pseudo aneurysm is more during systole. This leads to a gradual pressure build up and eventual rupture.

**Authors’ response:** Thank you very much for this helpful advice. We have added sentences such as this in the background to speculate on the cause of onset of the symptoms: “This delay is supposed to be caused by a gradual increase in the size of the pseudoaneurysm caused by a characteristic pressure increment. The blood flow into the pseudoaneurysm is greater during systole than diastole. This leads to a gradual pressure build up and eventual rupture.”

3. In case presentation kindly mention if the previous missed abortion was also managed by a surgical curettage.

**Authors’ response:** Thank you for this advice. The missed abortion 4 years before this case was managed by surgical curettage. We added this information into the manuscript: “She had a history of one missed miscarriage at 9 weeks of gestation managed by surgical curettage 4 years before, and one elective cesarean delivery 2 years before.”

4. In Discussion, paragraph 1, line 21 please add doppler with ultrasound examination as a required postoperative investigation.

**Authorsʼ response:** Thank you for your suggestion. We have added this into the Discussion: “Therefore, we think it is necessary for patients to undergo a Doppler ultrasound examination as a required postoperative investigation especially in cases of cesarean scar pregnancy.”

5. In Conclusion, please add doppler with ultrasound for post operative care of caesarean scar pregnancy.

**Authors’ response:** Thank you for your comment. We have added this in Conclusions as follows: “It is highly advisable for patients to undergo a Doppler ultrasound examination as a required postoperative investigation...”
to rule out a uterine artery pseudoaneurysm, in cases of a cesarean scar pregnancy."

Discretionary
The author is also welcome to speculate the role of intraoperative ligation of feeding vessel of the pseudo aneurysm. The possibility of securing hemostasis with plication should be considered before a radical decision of hysterectomy is made.

Authors’ response: Thank you for this suggestion. Securing hemostasis with plication of the pseudoaneurysm might possibly be performed after successful ligation of uterine artery. However, we did not find any references on this aspect and we did not try this method. In this case, the hemorrhage was abrupt and abundant, so we used emergency hysterectomy because the operation was simple and time saving. It stopped the bleeding rapidly. Therefore, we are sorry we cannot speculate further on this.

Reviewer 3: Beatriz Rojas
I do not see any changes necessary.

Authors’ response: Thank you very much for this comment.

Reviewer 4: Lorraine Corfield
Major Compulsory Revisions:
1) The key message is that these uterine pseudoaneurysms must be treated urgently. Many will be amenable to endovascular treatment which can include stents as well as embolization and thrombin. Therefore the conclusions should be changed to reflect this—an opinion from an interventional radiologist and /or vascular surgeon should be sought prior to resorting to hysterectomy where time allows.

Authors’ response: Thank you very much for your comment. We sought interventional radiologists for help when we diagnosed a pseudoaneurysm. They agreed with us that the patient should be treated with embolization as soon as possible. But they did not have any experience in treating such a giant lesion with a patient showing an elevated serum β-hCG level. When the patient’s family knew that the radiologists were unsure about the best treatment, they decided to transfer her to an advanced hospital to receive embolization therapy. However, rupture of the pseudoaneurysm occurred while she was waiting for admittance to the advanced hospital. Hysterectomy was performed urgently.

We have added the following to the manuscript: “Our interventional
radiologists lacked experience in treating such a giant lesion and thought that repeated treatment might be required. The serum β-hCG level was still high after curettage, suggesting there were retained chorionic villi in the pseudoaneurysm. Recanalization of the pseudoaneurysm might occur even after arterial embolization from rapid recruitment of collateral vessels. In this situation, repeated uterine curettage immediately after embolization or methotrexate therapy might decrease the probability of recanalization. Therefore, in this case the patient tried to seek admittance to an advanced institution to undergo embolization treatment. However, when waiting for this, massive bleeding occurred and we performed an emergency hysterectomy.”

We revised the second sentence of the Conclusion as follows: “For such a giant uterine artery pseudoaneurysm, embolization might be the first treatment when the diagnosis is made, but hysterectomy is clearly possible when severe bleeding occurs.”

2) It is not clear from the report whether this was a pseudoaneurysm or a cyst which was highly vascular. I am sure the diagnosis was clear at hysterectomy and it appears that the authors were convinced this was a pseudoaneurysm-hence the use of the word ‘cyst’ in the uterine wall is misleading-if it was a pseudoaneurysm this should be called a pseudoaneurysm rather than a cyst.

Authors’ response: Thank you very much for your comment. You are right and we are sorry for these mistakes. The lesion was a cystic area as seen by ultrasonography. We revised the word “cyst” to “cystic lesion” in page 4 lines 89 and 92 in the Case presentation and to “pseudoaneurysm” in line 96, and in page 10 line 219 in the Figure legend.