ANSWERING REVIEWERS

August 6, 2017

Timothy Pawlik, MD, Director, Professor

Editors-in-Chief, World Journal of Gastrointestinal Surgery

8226 Regency Drive Pleasanton, CA 94588 USA

Dear Dr. Pawlik:

Please find enclosed the edited manuscript in Word format (file name: 34762-Revised manuscript.doc).

Title: Mesenteric vein thrombosis following impregnation via in vitro fertilization-embryo transfer

Author: Masaaki Hirata, Hiroko Yano, Tomoe Taji, Yoshiharu Shirakata

Name of Journal: *World Journal of Gastrointestinal Surgery*

ESPS Manuscript NO: 34762

The manuscript has been improved according to the suggestions of reviewers:

1 Format has been updated

2 Revision has been made according to the suggestions of the reviewer

Point-by-point replies to the comments made by the reviewers.

In Response to Reviewer #03650239's Comments:

1) On page 6, as part of the discussion regarding her risk factors for venous thromboembolism (VTE), I would also mention whether the patient had a family history of VTE.

R: She had no family history of coagulopathies or thromboembolic events.

2) Pursuing thrombolysis in this case was undoubtedly a difficult decision as there are few data to guide its use during pregnancy. Recurrent SMV thrombosis itself is not surprising given the inflammation following surgery. It would be useful if the authors could expand upon their decision making in terms of pursuing thrombolysis. This is not meant to ignite a debate, but more information could help readers making a similar decision in a different patient.

R: Thrombolysis therapy via a catheter placed in the SMA may be recommended if the thrombosis worsens despite anticoagulation with heparin, although urokinase carries the risk of fetal hemorrhagic complications. Thrombosis due to underlying prothrombotic states, including pregnancy, begins in the small vessels and progresses to involve larger vessels. Considering

this pathogenesis, thrombolysis therapy at the SMA may be recommended.

3) Similarly, I think the authors need to explain why abortion was recommended, as the thought process behind this decision is not discussed.

R: The reasons why we selected abortion are as follows:

-Screens for inherited thrombotic disorders were negative, and pregnancy itself may have caused thrombosis.

-The thrombosis recurred despite heparin administration.

-The patient was in early pregnancy, and thrombosis may recur during pregnancy.

-The health of the mother is given priority.

4) It would be useful for the authors to state how long they plan to continue anticoagulation in the patient.

R: We planned to continue anticoagulation therapy for one year.

Life-long anticoagulation is warranted in patients with inherited thrombophilia, whereas anticoagulation therapy for at least 6 months to one year is recommended for patients with reversible predisposing causes, including pregnancy.

In Response to Reviewer #02904354's Comments:

1) The liver, renal, and coagulation function data should be presented at her admission. PLT data should be also presented.

R: Liver function: aspartate aminotransferase level, 23 U/L (normal, 13-30 U/L); alanine aminotransferase level, 29 U/L (normal, 7-23 U/L).

Renal function: serum creatinine level, 0.58 mg/dL; blood urea nitrogen level, 14.3 mg/dL.

Coagulation function: prothrombin time, 13.4 sec (normal, 10.2-13.6 sec); activated partial thromboplastin time, 24.1 sec (normal, 23.0-36.0 sec).

Platelet count, 142000 /μL.

2) Other thrombotic risk factors were missing, such as JAK2 V617F mutation, FV Leiden mutation, and FII G20210A mutation. These thrombotic risk factors should be reviewed in the Discussion. Indeed, EASL and AASLD guidelines have some clear recommendations regarding risk factors. Some high-quality evidence from meta-analyses should be reviewed. These limitations regarding absence of relevant data should be discussed.

R: In general, FV Leiden and FII G20210A mutations should be investigated as causes of mesenteric vein thrombosis. We proposed this to the patient, but she

refused this testing. In addition, many reports have stated that these risk factors are not found in Japanese people. The JAK2 V617F mutation is found in myeloproliferative neoplasm patients, and it is one cause of mesenteric vein thrombosis. Hemoglobin and platelets were in the normal range in this case, and we did not include myeloproliferative neoplasm as a differential diagnosis.

3) It should be better if there are some pictures regarding surgerical procedures and resection of gangrenous portion of the small intestine.

R: We have included pictures of the surgical removal of superior mesenteric vein thrombi (Figure 2) and the gangrenous portion of the small intestine (Figure 3).

4) Is preoperative anticoagulation given?

R: No, we started it just after surgery.

5) Follow-up CT scans showing the patency of SMV should be provided.

R: We have included CT scans from four months after surgery (Figure 4). These scans revealed complete recanalization of the portal vein and partial recanalization of the SMV.

6) Follow-up laboratory data should be provided. Did she have ascites?

R: We have included laboratory data from four months after surgery.

Liver function: aspartate aminotransferase level, 19 U/L (normal, 13-30 U/L); alanine aminotransferase level, 17 U/L (normal, 7-23 U/L).

Renal function: serum creatinine level, 0.54 mg/dL; blood urea nitrogen level, 11.1 mg/dL.

Coagulation function: prothrombin time on warfarin, 19.3 sec (normal, 10.2-13.6 sec); activated partial thromboplastin time, 31.5 sec (normal, 23.0-36.0 sec).

Platelet count, 260000 /μL; D-dimer level, 0.5μg/mL (normal, < 1.0 μg/mL).

She had normal liver function, no symptoms of portal hypertension and no ascites.

7) I do not know the meanings of these words "partial recanalization of the SMV with persistent occlusion". Please clarify these words.

R: The SMV was completely occluded from the distal to the 1st jejunal branches. The 1st jejunal vein was expanding and functioning as a collateral pathway.

<u>In Response to Reviewer #00613748's Comments:</u>

I appreciate your polite review.

3 References and typesetting were corrected

I checked the whole sentence again, and I revised grammatical errors.

Thank you again for publishing our manuscript in the *World Journal of Gastrointestinal Surgery*.

Yours sincerely,

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