Format for ANSWERING REVIEWERS

May 13, 2014

Dear Editor,

Please find enclosed the edited manuscript in Word format (file name: 10093-review.doc).

Title: Acute fatty liver pregnancy associated with severe acute pancreatitis: a case report

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Name of Journal: *World Journal of Hepatology*

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The manuscript has been improved according to the reviewer's suggestions as follows:

1. The format of the manuscript has been updated.

2. Revisions have been made according to the suggestions of the reviewer.

3. The article was rewritten, and the grammar, style, spelling and syntax were corrected by a native speaker of English.

(1) Answers to the reviewer No. 503536

Thank you for all of your comments. We have addressed each of your concerns separately in a point-by-point manner.

Major points:

1 . Alkaline phosphatase and g-GTP were increased and now their values were included in the Table 1. The jaundice was really caused by liver failure and not by constriction of biliary tract, since imaging tests (ultrasound and computed tomography) did not reveal any kind of biliary obstruction. Adittionally, the liver function tests demonstrated severe hepatic impairment, which was the cause of the jaundice. This comment is now in the article discussion.

2 . We agree that the main illness was the hepatic disease, demonstrated by the severe hepatic impairment reported. The pancreatitis was a superimposed complication that is uncommonly reported. This statement is now well described in the discussion.

3 . We also agree that it is not possible to see the steatosis in the CT image, and it is not so prominent in the routine histological stains showed in the article. The reason is probably that the liver steatosis in acute fatty liver of pregnancy is described as being only microgoticular. Thus, it cannot be always recognized in CT exams or in routine histological stains (hematoxylin-eosin and Masson). Our aim was to show that the diagnosis is difficult and must be made by specific methods such as the oil red stain used in this case. Unfortunately, we do not have molecular exams to show in the article, but we performed the gold standard method of diagnosis.

4 . The mechanism by which pancreatitis may develop as a complication of fatty liver of pregnancy is not well

understood in the literature because this association is rare. We raised a hypothesis on the possible physiopathology involved that is now inserted in the article discussion. Our hypothesis is that the accumulation of long-chain metabolites of 3-hydroxyacyl produced by the fetus or placenta is toxic not only to the liver, but to the pancreas too. Thus, the pancreas could be affected when a big degree of these metabolites accumulation is present, as occurs in cases of severe hepatic disease. It could be a reasonable explanation for the pancreatic impairment showed in this case of hepatic failure.

Minor points:

1 . The abdominal ultrasound was performed before the CT scan, and the findings were now included in the case description.

2. The discussion is now more concise and the focus is more aimed to the physiopathology of the diseases. However, some of the other reviewers asked for more information, so we included more explanations and data in the article.

(2) Answers to the reviewer No. 73425

Thank you for all your comments. We tried to answer each of them separately in a point-by-point manner.

We agree with the reviewer that the diagnosis of pancreatitis was not so clear in the first description we sent to the World Journal of Gastroenterology. To show more details about the pancreatitis we included the ultrasonography findings in the case description and more laboratorial exams in the table 1. Unfortunately, at the time of the patient admission we still not had lipase exams available at our hospital. However, the abdominal pain presented by our patient was clearly different of the cases presented only with acute fatty liver of pregnancy without pancreatitis. The pain findings at the physical exam were the reason for her referral to our hospital, because the first doctor who saw her raised the possibility of acute appendicitis. The amylase increasing was of more than six fold the upper limit of normal, and the pancreatic edema was well documented at ultrasonography and computed tomography exams, so there were no doubts about the presence of pancreatitis. Now all these findings are highlighted in the article.

The acute renal failure was a complication of the pancreatitis. According to the Ranson criteria she had a severe disease, reaching 3 points at the admission, given by the leukocyte count, AST and Lactate dehydrogenase values (Table 1). Additionally, she achieved 14 points in the APACHE II criteria, corresponding to an estimated risk of hospital death of 18.6%. Her renal failure was treated only by supportive measurements and the delivery, confirming that it was a consequence of the underlying disease. No renal replacement therapy was needed. We included some comments about it in the article discussion.

The article was totally rewritten. English grammar, style and syntax were corrected by an English professor, avoiding misspellings.

New references were also included to update the article.

(3) Answers to the reviewer No. 1350278

Thank you for all your comments. We tried to answer each of them separately in a point-by-point manner.

We agree with the reviewer that the diagnosis of pancreatitis was not so clear in the first description we sent to the World Journal of Gastroenterology. To show more details about the pancreatitis we included the ultrasonography findings in the case description and more laboratorial exams in the table 1. Unfortunately, at the time of the patient admission we still not had lipase exams available at our hospital. However, the abdominal pain presented by our patient was clearly different of the cases presented only with acute fatty liver of pregnancy without pancreatitis. The pain findings at the physical exam were the reason for her referral to our hospital,

because the first doctor who saw her raised the possibility of acute appendicitis. The amylase increasing was of more than six fold the upper limit of normal, and the pancreatic edema was well documented at ultrasonography and computed tomography exams, so there were no doubts about the presence of pancreatitis. Now all these findings are highlighted in the article.

We also have to agree with the reviewer that the HELLP syndrome could not ruled out according to the first version of our article. Information about the blood pressure and proteinuria was now included in the case description. Furthermore, specific findings that can be used to differential diagnosis between these two diseases were also included in the article introduction, clarifying the diagnosis of acute fatty liver of pregnancy.

The upper endoscopy was performed to investigate the possibility of peptic ulcer or other gastroduodenal disease, since the patient had severe abdominal pain with no relief after common analgesics received before admission. We kept this information to show that her symptoms were not caused by a gastroduodenal disease. Now we insert this explanation in the paper.

The article was totally rewritten. English grammar, style and syntax were corrected by an English professor, avoiding misspellings.

(4) Answers to the reviewer No. 729478

Thank you for all your comments. We felt encouraged to find more things in the article that could be improved. So we hope you like this new version after some little changes that we did in the paper.

(5) No. 289477

Thank you for all your comments. We tried to answer each of them separately in a point-by-point manner.

The article was totally rewritten. English grammar, style and syntax were corrected by an English professor, avoiding misspellings.

The outcome of the fetus was included in the article.

The patient indeed had symptoms one week before her admission at our hospital, but unfortunately we have not results of lab tests performed in her city.

The physical examination at presentation was depicted, improving the case description.

3 References and typesetting were corrected

Thank you again for considering our manuscript for publication in the *World Journal of Gastroenterology*.

Sincerely yours,

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