

Mar 14, 2021

Dear Editor,

I am writing to submit a revised version of our manuscript entitled “Acute myocardial infarction in twin pregnancy after assisted reproduction: a case report and literature review” (Manuscript NO: 62297).

We are grateful for your opportunity to revise our manuscript, and we would like to thank you and the reviewers for your review of our study. We have now addressed all the comments and suggestions made by the reviewers, and we believe this revised manuscript is significantly improved. A point-by-point response to the reviewer’s comments is enclosed, and we hope that this revised manuscript can now be reconsidered for publication.

Thank you for the time and effort you have spent on evaluating our paper. I look forward to hearing from you.

Sincerely,

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## Point by point response

Reviewer 1,

The authors showed myocardial infarction in a case with twin pregnancy after assisted reproduction. The case was properly diagnosed and treated without any serious complications.

General comment; The strong point of this study was to have an alert for a risk of acute coronary event in pregnant women who had twin pregnancy with assisted reproduction.

**Response: Thank you for your suggestion. In the discussion part, we deleted the mechanism of ovarian hyperstimulation syndrome (OHSS) leading to thrombosis, and added a risk of acute coronary events in pregnant women who had twin pregnancy with assisted reproduction.**

**In discussion part, we added the following alert: In recent years, with the extensive application of assisted reproductive technology (ART), mainly in vitro fertilization and embryo transfer (IVF-ET), there have been many published reports of thromboembolism[14], including venous thromboembolism (VTE) and arterial thrombotic (AT) events. The incidence of AT was low as compared to that of VTEs. Most people think it is related to superovulation during IVF-ET. But different studies had different results: A Danish national cohort study suggested that there was no evidence that assisted reproduction increases the risk of thrombosis[16]; A Southern India case series reported that among 12 cases of AMI during pregnancy, 8 patients had undergone IVF[17]. So the risk of AMI during pregnancy related to ART has not been determined yet.**

[14] Henriksson P. Cardiovascular problems associated with IVF therapy. *J Intern Med.* 2021;289(1):2-11. [PMID: 32592243 DOI:10.1111/joim.13136]

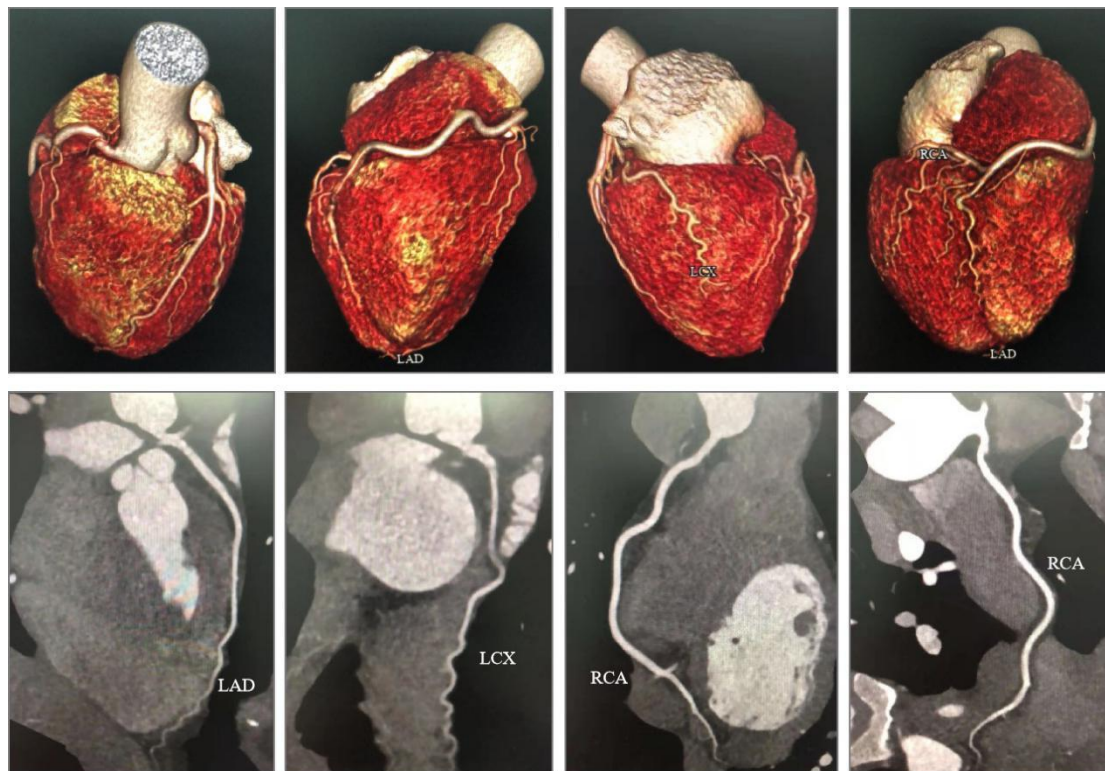
[16] Hansen AT, Kesmodel US, Juul S, Hvas AM. No evidence that assisted reproduction increases the risk of thrombosis: a Danish national cohort study. *Hum Reprod.* 2012;27(5):1499-1503. [PMID: 22357768 DOI:10.1093/humrep/des041]

[17] Senthilkumaran S, Meenakshisundaram R, Osman W, Thirumalaikolundusubramanian P. Acute Myocardial Infarction During Pregnancy and the Puerperium: Experiences and Challenges From Southern India. *Mayo Clin Proc.* 2019;94(5):918-919. [PMID: 31054614 DOI:10.1016/j.mayocp.2019.03.005]

However, the lack of coronary imaging or follow up coronary angiography made the etiology of coronary events ambiguous in such patients.

**Response:** Thank you for your suggestion. We have added the follow up coronary imaging of the patient.. Combined with the clinical data of the patient's examination and follow-up, we considered that the etiology of the patient was more inclined to spontaneous coronary artery dissection (SCAD).

In the case presentation part, we added the following contents and a figure: Moreover, her coronary computed tomography angioplasty (CTA) suggested that there was no obvious abnormality on her right coronary artery (Figure 4).



**Figure 4.** Coronary computed tomography angioplasty showed that there was no significant stenosis on the left main coronary artery (LM), left circumflex branch (LCX) and right coronary artery (RCA). But the middle segment of the left anterior descending branch had mild stenosis (<50%).

**In the discussion part, we analyzed the etiology of the patient's AMI, and added the following contents: Unfortunately, IVUS and OCT were not made at that time. However, SCAD was more likely to be the etiology of the patient's AMI: The absence of chest pain during coronary angiography, right coronary stenosis and thrombus shadow on her coronary angiography were more prone to SCAD, whereas the coronary angiography of coronary spasm without chest pain was no significant abnormality. Furthermore, her absence of chest pain episodes and follow-up CTA were more prone to SCAD.**

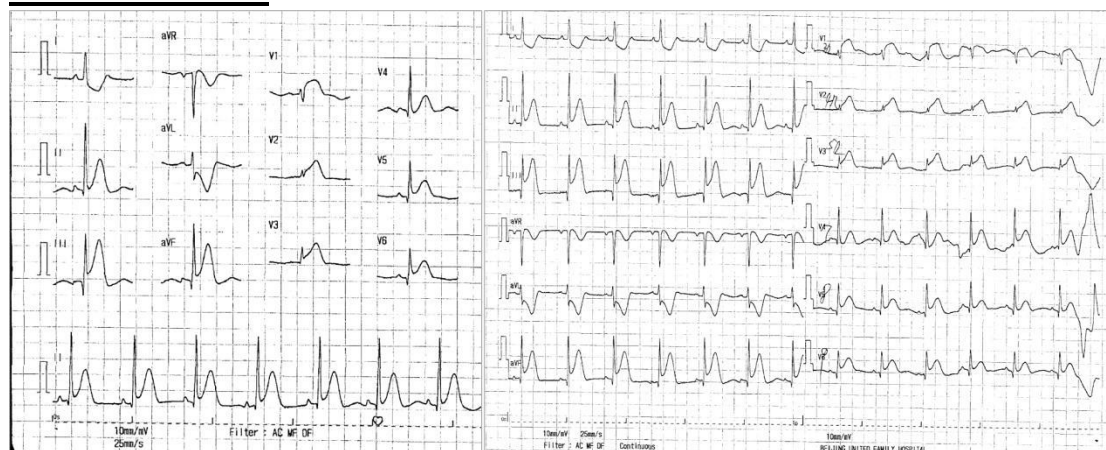
Specific comments; The discussion is too lengthy, and should be focused more on the strength and limitation of the present report. It is important to accentuate the risk of acute coronary event in assisted reproduction.

**Response: Thank you for your suggestion. We have revised the discussion part. We focused more on the risk factors and the identification of the patient's AMI, which suggested that although the patients during pregnancy had no cardiovascular disease risk factors, pregnancy, advanced age and other obstetric factors can increase the risk of AMI. Unfortunately, IVUS and OCT didn't be performed at that time, so we can't determine the etiology of the patient's AMI, just speculation based on the available data, which suggested that the etiology of AMI in pregnancy needs to be differentiated, especially between coronary spasm and SCAD.**

**And we added the risk of acute coronary event in assisted reproduction in discussion part.**

Figure 1; the leads should be clarified. Noisy parts of ECG should be omitted.

**Response: Thank you for your suggestion. We changed the ECG based on the data that we can collect.**



**Figure 1. Eighteen-lead ECG showed ST-segment elevation in II, III, aVF, V3R-V5R, and V7-V9.**

Figure 2; CAG was shown in only one direction. At least two directions should be shown with clear information. Furthermore, images of RCA in figure 2 look like TIMI 1 or 2 flow grade.

**Response: Thank you for your suggestion. However, we only collected the CAG in this direction. As for the TIMI flow grade of RCA in figure 2, the data we collected shows that it is TIMI 3 flow grade. Furthermore, we would provide the CAG videos we collected as supplementary materials.**

**冠脉造影结果**

编号	血管名称	病变性质	病变长度	病变形状	TIMI	最重狭窄程度	其他异常类型
1	右冠状动脉近段	-	-	-	III级	90%	-
其他血管无明显异常。							

Table 1; in the last 2 cases, the risk factors for coronary events were not determined.

**Response: Thank you for your suggestion. We deleted the last 2 cases, and added other cases, in which the risk factors were determined. In Table 1, we added the following contents:**

<b><u>O Fayomi, et al. 2007[8]</u></b>	<b><u>Case Report</u></b>	<b><u>A 33-year-old gravida 7 para 6 woman at 32 weeks' gestation was diagnosed with anteroapical myocardial infarction, more likely due to atherosclerosis. She had a 15 cigarettes per day smoking habit.</u></b>
<b><u>Yu-Ching Chen, et al. 2009[9]</u></b>	<b><u>Case Report</u></b>	<b><u>A 27-year-old gravida 1 woman at 34 weeks' gestation presented with acute myocardial infarction, Although having unremarkable medical history and no risk factors for cardiac disease, she was under the impression of antepartum hemorrhage, preterm labor, the use of ritodrine, and pregnancy-related elevations in cholesterol and triglyceride.</u></b>
<b><u>Murat Baskurt, et al. 2010[10]</u></b>	<b><u>Case Report</u></b>	<b><u>A 24-year-old woman in her 18th week of pregnancy was diagnosed with myocardial infarction. She had two abortions during the last years and had received hydroxyprogesterone caproate treatment. Also, she presented with high lipid levels.</u></b>
<b><u>Murat Akcay, et al. 2018<sup>[12]</sup></u></b>	<b><u>Case Report</u></b>	<b><u>A 34-year-old female patient in her 36<sup>th</sup> week of pregnancy presented with acute anterior myocardial infarction. She had no known risk factor foe coronary artery disease, no history of substance abuse and no any problems related to the pregnancy. But it was noted that this was her second pregnancy.</u></b>
<b><u>Souleymane Diakite, et al. 2019<sup>[13]</sup></u></b>	<b><u>Case Report</u></b>	<b><u>A 34-year-old female, pregnant of 35 weeks, was diagnose with myocardial infarction. Her past medical history revealed no previous hospitalizations and no cardiovascular risk factors. But her laboratory tests revealed transient protein S deficiency. Deficits in protein S could result in thrombosis.</u></b>

Discussion: the authors should discuss more with regard to the safety and risk of medications for the mother and fetus.

**Response: Thank you for your suggestion. In discussion part, we added the following contents to discuss the safety and risk of medications for mother and fetus:**

**In medication, safety of standard medical treatment in infarction remains uncertain for pregnant patients. Low-dose aspirin seems safe, as are nitrates, heparin, nifedipine and certain beta blockers (metoprolol, atenolol). There are no case reports linked to the use of aspirin at low dose of 80-150mg per day, and in most opinions the potential benefits of aspirin usage far outweigh the risks[24]. Clopidogrel is also recommended and is still the most widely used thienopyridine, although case reports have demonstrated an association between the use of clopidogrel and maternal thrombocytopenia, maternal hemorrhage and fetal demise[24]. But we should note that statins are contraindicated during pregnancy, so this patient was given statins after delivery.**

Editorial office's comments:

Authors must revise the manuscript according to the Editorial Office's comments and suggestions.

**Response: Thank you for your suggestion. We have revised our manuscript according to the comments and suggestions, including the case representation, references, author contributions, figures and table. We also provided the approved grant application form and the signed informed consent form.**