Dear Editor：

On behalf of my co-authors, we thank you very much for giving us an opportunity to revise our manuscript, we appreciate editor and reviewers very much for their positive and constructive comments and suggestions on our manuscript entitled“Case report:Gestational diabetes mellitus combined with fulminant type 1 diabetes mellitus, four cases of double diabetes?”. (NO: 88226).

We have studied reviewers’ comments carefully and have made revisions which marked in red in the paper. We have tried our best to revise our manuscript according to the comments.

We would like to express our great appreciation to you and reviewers for comments on our paper. Looking forward to hearing from you.

Thank you and best regards.

Yours sincerely

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List of Responses

Dear Editors and Reviewers:

Thank you for your letter and for the reviewers' comments concerning our manuscript entitled"Case report: Gestational diabetes mellitus combined with fulminant type 1 diabetes mellitus, four cases of double diabetes?" (NO: 88226). Those comments are all valuable and very helpful for revising and improving our paper, as well as the important guiding significance to our report. We have studied comments carefully and have made correction which we hope meet with approval. Revised portion are marked in red in the paper. The main corrections in the paper and the responds to the reviewers' comments are as following:

Responds to the editor comments:

Comments:

(1) **Science editor:**

The manuscript has been peer-reviewed, and it is ready for the first decision.
Language Quality: Grade B (Minor language polishing)
Scientific Quality: Grade D (Fair)

Response: Thank you very much, we have send our revised manuscript to a professional English language editing company(Elsevier:https://webshop.elsevier.com/language-editing-services/language-editing/)and get the official manuscript language editing certificate.

(2) **Company editor-in-chief:**

I recommend the manuscript to be published in the World Journal of Clinical Cases. When revising the manuscript, it is recommended that the author supplement and improve the highlights of the latest cutting-edge research results, thereby further improving the content of the manuscript. To this end, authors are advised to apply PubMed, or a new tool, the RCA, of which data

source is PubMed. RCA is a unique artificial intelligence system for citation index evaluation of medical science and life science literature. In it, upon obtaining search results from the keywords entered by the author, "Impact Index Per Article" under "Ranked by" should be selected to find the latest highlight articles, which can then be used to further improve an article under preparation/peer-review/revision. Please visit our RCA database for more information at: https://www.referencecitationanalysis.com/, or visit PubMed at:https://pubmed. ncbi.nlm.nih.gov/.

Response: Thanks a lot for reminding us kindly, we visited the RCA database and get the latest highlight articles and enriched the content of the manuscript. We hope that we can meet with approval.

Responds to the reviewers' comments:

Response to the comments of Reviewer #1:

Comment No.1: Title: It seems to be appropriate. Abstract: Background is well written. However, case summary needs more elaboration as to what sort of insulin allergy was noticed which is actually so rare an entity.

Response: Thank you for the important question. That is a very sensitive topic. It was reported that a severe manifestation of drug allergy was previously reported as Drug-induced hypersensitivity syndrome(DIHS) or Drug reaction with eosinophilia and systemic symptoms (DRESS) can lead to FT1DM and autoimmune thyroid disease. DRESS syndrome is a severe drug hypersensitivity reaction with prominent cutaneous and systemic manifestations. Some drugs such as carbamazepine, phenytoin, lamotrigine, and sulfamethoxazole could cause DRESS. Insulin was not reported to cause DRESS before. Mechanisms that have been implicated in DRESS syndrome include immunologic mechanism and viral activation. DRESS syndrome usually begins within 2 months of ingestion of the offending drug, most often 2 to 6 weeks after its first use. As for our patients, they both allergic to *insulin detemir* for the symptoms of redness and swelling at the injection site, without

systemic manifestations which could not be diagnosed as DRESS, but presented FT1DM after about 4 weeks. Wu Han et al[1] reported that among six PF patients, three patients were diagnosed as gestational diabetes mellitus and were found to be allergic to insulin regimes during the treatment of multiple insulin injections, and two of them developed PF about one month after insulin allergy in 2019. Guo Weihong et al[2] also reported a case of multiple insulin allergy with FT1DM in late pregnancy in 2019. Both of the two articles are in Chinese language (listed below). That is the phenomenon we observed so far, but we cannot determine the causal relationship between insulin allergy and FT1DM, which needs more cases and more time to verify the relationship between them.

Attach:

[1]吴晗,于淼,肖诚,等. 妊娠相关性暴发性 1 型糖尿病患者临床特点分析[J]. 中华糖尿病杂志,2019,11(11):720-724. DOI:10.3760/cma.j.issn. 1674-5809.2019.11.005.

[2] 郭伟红,崔瑾,杨玲,等.妊娠后期胰岛素过敏合并暴发性 1 型糖尿病一例[J]. 中华糖尿病杂志, 2019, 11(9) : 630-632. DOI: 10.3760/cma.j.issn. 1674-5809.2019.09.012.

Special thanks to you for your good comments.

Comment No.2: Introduction: More introductions regarding clinical presentation of pregnancy-associated FT1DM (PF) is needed.

Response: Dear professor, Thank you very much for your prompt. We are sorry we didn't make it clear in the paper. We have added more introductions regarding clinical presentation of pregnancy-associated FT1DM (PF) and marked in yellow in revised manuscript.

Comment No.3: Cases: Regarding the cases, few clarifications need to be addressed: In all the cases, there is no mention of serum bicarbonates and Pco2. Were serum beta hydroxybutyrate levels ever measured in any of the patients? Does Urinary ketones of 1+ in pregnancy qualify for ketosis? Which method was used to measure urinary ketones? Nothing is mentioned regarding follow up of the babies of the affected mothers.

Response: We are very sorry for our incomplete description due to space constraints. The case one, who presented with the high glucose level and urinary ketone body level of 3+ was first admitted to obstetrics and gynecology department for fear of an accident to the fetus. She had a cesarean section soon and didn't test blood gas analysis or OGTT or pancreatic antibodies at that time. Eight weeks later, her blood glucose level fluctuated widely although with insulin therapy. The laboratory tests found extremely low C-peptide levels and negative CAD/ICA antibodies. Therefore, we concluded that she suffered from PF due to the sudden spike in blood sugar and urinary ketone body level of 3+(HbA1c 6.1%) then. For the second patient, her CO2CP was 21mmol/L while the urinary KET 3+; For the third patient, her random BG level was 28 mmol/L, urinary KET 4+, CO2 combining power 13 mmol/L, and arterial pH 7.30; For the last patient, her random BG level was 21.4 mmol/L with the urinary KET 1+. She was first admitted to obstetrics and gynecology emergency for the fluctuated glucose level and didn't received the blood gas analysis. For a pity, we didn't measure serum beta hydroxybutyrate levels since it is not a routine test in our hospital at that time. If the patient suffered from urinary ketones of 1+~4+ in pregnancy, we think she has ketosis in different degree. We use the dry chemistry method to measure urinary ketones. We followed up the babies of the affected mothers. The offspring of the Case 1 is a healthy girl who was 2 years old now with the Hight 1 meter and Weight 13 kg. The offspring of Case 2was a healthy boy who was 2 years old now with the Hight 1 meter and Weight 13 kg. The baby of the Case 3 was a healthy girl who was 1 years old with the Hight 75.5cm and Weight 10.82kg.The offspring of Case 4was a healthy boy who was 5 months old with the Hight 68cm and Weight 8.4kg. We just describe the birth situation because the follow-up was normal. As your suggested, we have added some detailed information in the revised version. Thanks again.

Comment No.4: Results: Results seem to be well summarized. Discussion: This portion seems to be well written but labeling FT1DM and GDM as double diabetes needs more caution.

Response: Thank you very much for your valuable suggestion, labeling FT1DM and GDM as double diabetes is our creative propose and really want

your support and recognition. As we wrote in our article, Pozzilli and Buzzetti described diabetes with both islet autoantibody positivity and characteristics of metabolic syndrome as double diabetes in 2007. The cases of double diabetes with FT1DM based on T2DM were reported in Japan in 2013, mentioning that double diabetes have clinical features of both T1DM and T2DM.The combination of GDM with FT1DM, i.e., two different types of diabetes, occurs in the same patient during pregnancy and has a lifelong impact. The pathogenesis of GDM is regarded as insulin resistance and β-cell dysfunction, while the pathogenesis of FT1DM results in β-cell destruction. We propose that GDM combined with FT1DM as a subtype of PF has its own characteristics and should be classified as double diabetes occurring during pregnancy. However, further studies involving more clinical cases are required.

Comment No.5: Table: Table 1 is too busy and may be put in a more comprehensive way. No mention of P values wherever relevant.

Response: Thanks for your suggestion. We have revised Table 1. We streamlined content to make our report clear and easy to read. Thank you again for your kind remind.

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Response to the comments of Reviewer #2:

Comment No.1: Li et al. reported that four GDM patients developed fulminant type 1 diabetes. There are few reports of GDM patients developing fulminant type 1 diabetes, and in that sense, this report is valuable. However, as the authors have stated, there are already reports of GDM patients developing fulminant type 1 diabetes (References 5, 6), so this report lacks novelty. In addition, GDM is considered to have insulin resistance, and its complication with fulminant type 1 diabetes is discussed as "double diabetes," but in what way did insulin resistance develop in the four patients presented by the authors? That hasn't been measured, so it's only a speculation.

Response: Thank you very much for your valuable advice. GDM is always with insulin resistance. In order to ensure the energy needed for fetal growth and development, the mother will develop physiological insulin resistance, which is closely related to the function of the placenta. This resistance appeared from the placenta formation, increased with the extension of gestational weeks, rapidly increased at 24-28 weeks of pregnancy, reached a peak at 32-34 weeks, and gradually disappeared after the delivery of the placenta. In healthy pregnant women, insulin sensitivity decreases by 50% to 60% during pregnancy. The worst is in the third trimester, and compensatory insulin secretion of islet beta cells increases to maintain normal blood sugar. GDM occurs if insulin resistance is more severe and/or islet beta cells fail to compensate. GDM is the result of a combination of insulin resistance and/or inadequacy of islet beta cell function, but their contributions vary in different patients. The contribution of insulin resistance was greater in overweight and obese GDM patients before pregnancy, and the contribution of islet beta cell dysfunction was greater in normal-weight GDM patients, both of which appeared in early pregnancy. So we just want to say that GDM and FT1DM are different types of DM, and they happened on one patient. This situation should be named as 'double diabetes'. Thank you very much for your comments again.

Comment No.2: They also reported that IAA was positive in all four patients, but they were measured after the start of insulin treatment, so they were not valid. Similarly, the data for insulin in table 1 were measured during insulin treatment, and the significance of presenting them is unclear.

Response: We are sorry that we may have not expressed it clearly. We mean that there was no reason to monitor IAA during the period of GDM that precedes a sudden spike in blood sugar, what these four patients have in common is that they were diagnosed with GDM during pregnancy, then treated with insulin, then appeared FT1DM, and then IAA was found to be positive.We're not saying cause and effect, we're just observing this phenomenon,Not all patients taking insulin are positive for IAA, but these patients with GDM combined with FT1DM showed positive IAA. Yes,,insulin

level during insulin treatment is affected by the exogenous insulin. If it is to avoid misleading readers, we will mark 'the OGTT test done during insulin treatment' in the following. Thank you so much!

Comment No.3: Furthermore, the data in table 2 clearly includes data other than the data of the four patients, but the details are not described in this paper.

Response: We really thank you very much for this question. We are very sorry for our incomplete description due to space constraints. As we wrote in our article, The clinical characteristics and laboratory data of three similar cases reported previously plus the four patients presented here are summarized and compared with patients with classical PF in Table 2. Three similar cases could be checked in the article ***Wu H,Yu M,Xiao Ch,Li NS,Fu Y,Mao JF,et al. Clinical characteristics of pregnancy- associated fulminant type 1 diabetes-a single center experience.Chin J Diabetes Mellitus.2019,11(11):720-724 [DOI: 10.3760/cma.j.issn.1674-5809.2019.11.005]'***.We list the information in Table1 below.

Table 1 Information of 3 patients of GDM combined with FT1DM in reference

Case No.	1	2	3
Age	40	28	31
BMI	19.6	16.85	25.76
Family history	Yes	No	Yes
Drug allergy	Various Insulin	Insulin detemir and glargine	Various Insulin
Onset time	6 days Postpartum	13 days Postpartum	35weeks Pregnancy
Influenza-like Symptom	No	Yes	Yes
DK/DKA	Yes	Yes	Yes
Ketones	3+	4+	4+
Glucose（mmol/L）	18.6	44.9	19.1
HbA1c	6.0	5.6	5.4
Fasting C-Peptide(ng/ml)	< 0.05	< 0.01	< 0.01
Postprandial C-Peptide(ng/ml)	< 0.05	< 0.01	< 0.01

We tried our best to improve the manuscript and made some changes in the manuscript. These changes will not influence the content and framework of the paper. We appreciate for Editors and Reviewers' warm work earnestly, and hope that the correction will meet with approval.

Once again, thank you very much for your comments and suggestions.