5 October 2022

Editor in Chief

World Journal of Clinical Cases

Re: Manuscript ID: 68925

Dear editor:

On behalf of my co-authors, I am grateful for the opportunity to submit a revised version of our manuscript, now titled “Pregnancy-Induced Leukocytosis: Case report” for consideration for World Journal of Clinical Cases.

Please find attached to this letter point-by-point responses to your comments as well as those of our reviewers. We thank the Editor in Chief and reviewers for their positive and constructive comments and suggestions, which we believe have markedly improved the quality of our manuscript.

Please let me know if we can provide any further information. We trust that our manuscript is now suitable for publication, and look forward to your decision.

Thank you for your consideration. I look forward to hearing from you.

Sincerely,

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Point-by-Point Responses to the Reviewers

Reviewer Comments to the Author:

Reviewer: 1

Comments to the Author

1.Please add reference to the line in introduction - The normal range for WBC counts changes with age and pregnancy.

Answer： Thank you for this suggestion. We have added reference to the line in introduction - The normal range for WBC counts changes with age and pregnancy.

2. Please add reference to the line in introduction - Physiological leukocytosis often takes place and it is primarily related to the increased circulation of neutrophils, especially during the last trimester of pregnancy

Answer：We have added reference to the line in introduction - Physiological leukocytosis often takes place and it is primarily related to the increased circulation of neutrophils, especially during the last trimester of pregnancy.

3. I couldnt see Figure 1 in the submission files.

Answer：We have uploaded Figure 1 in the submission files.

4. Please provide also normal ranges of laboratory examinations in brackets including Leukocyte count, neutrophils, CRP, ESR, and PCT.

Answer：We have added normal ranges of laboratory examinations in brackets including Leukocyte count, neutrophils, CRP, ESR, and PCT.

5. Please provide differential diagnosis for the patient and also justify how you excluded all possible differential diagnosis in the patient to conclude asymptomatic leukocytosis as the final diagnosis for the patient. The diagnosis of asymptomatic leukocytosis is a diagnosis of exclusion and hence exploring differential diagnosis is pertinent in this case.

Answer： Leukocytosis response is similar in several non-obstetrical conditions, including: infection, inflammation, allergic reaction, malignancy, surgery, trauma ,somking and strenuous physical activity.She didn’t suffer from allergic reaction, malignancy, surgery, trauma and strenuous physical activity and smoke.She had no fever, the temperature being normal, and had no other symptoms

including oral ulcers, shivering, cough, and a small amount of white phlegm.And the patient went to the outpatient department of infection. The counts of C-reactive protein were 0.52mg/dl, the counts of erythrocyte sedimentation rate were 30mm/h, and the counts of PCT were ＜ 0.05 ng/ml， which showed no sign of infection. Then she visited the outpatient department of hematology. The patient refused bone marrow biopsy. Peripheral blood smear showed that mature neutrophils accounted for 73.2%, and The count of immature granulocytes was 0.95×109 per L, accounting for 3.7%. Conducted by another hospital showed that leukocytosis was detected, but the levels of red blood cell and megalokaryocyte were normal.Postpartum, her blood pressure gradually returned to normal with complete resolution of hypertension by six weeks postpartum, which illustrate that it is hardly to be malignant. We added this in the discussion.

6. Everything mentioned under the heading "Treatment" is patient history and not treatment. Please correct this heading and add a separate treatment section describing the treatment that was given to the patient post diagnosis of leukocytosis.

Answer：We adjust the content from "Treatment" to the patient history.

7.There is mentioned "Outcome and Follow-up" as heading 2 times. Please correct the headings.

Answer：We have corrected the heading, and removed the repetitive part.

8. I would recommend authors to remove the words "literature review" from the heading as they have not provided a review of literature. Its a case report.

Answer：We have removed the words "literature review" from the heading.

Reviewer: 2

Comments to the Author

This is known. Why TLC done at 27wks

Answer：We thank the Reviewer for the positive comments regarding our manuscript. TLC was done as a routine examination at 27weeks in the hospital.

Reviewer: 3

Comments to the Author

1.Abstract. -There was a similar sentence published in a previous case report. “Physiological leukocytosis often takes place and it is primarily related to the increased circulation of neutrophils, especially during the last trimester of pregnancy.” was found in an abstract of “Medicine (Baltimore) .

2016 Dec;95(52):e5717. doi: 10.1097/MD.0000000000005717. URL= https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5207571." Please consider rephrasing it.

Answer：We rephrase it-"Physiological leukocytosis often happens and it is primarily relevant to the increased neutrophils, especially during the last trimester of pregnancy"

2.Background. -There were some similar sentences published in a previous article without citation. "It is important for clinicians to be able to distinguish malignant from non-malignant etiologies, and to differentiate between the most common nonmalignant causes of leukocytosis." and "During pregnancy, there is a gradual increase in the normal WBC count (third trimester 95% upper limit = …" were found in "Am Fam Physician . 2015 Dec 1;92(11):1004-11. URL= https://www.aafp.org/pubs/afp/issues/2015/1201/p1004.html." Please consider rephrasing it.

Answer：We rephrase it- It is significant for clinicians to make a distinction between malignant and non-malignant etiologies, and to separate between the most common nonmalignant causes of leukocytosis.And We rephrase it- During pregnancy, normal WBC count increases gradually (third trimester 95% upper limit = 13.2 × 109 per L and 99% upper limit = 15.9 × 109 per L).

3.Methods. Does the manuscript describe methods (e.g., experiments, data analysis, surveys, and clinical trials, etc.) in adequate detail? Not applicable.

Answer：We have added the methods.

4.Results. -There were two "Outcome and follow-up" sections. In the first place, there seems to be summarized of this case again. Moreover, the "outcome and follow up" section was found that similar to the previous "treatment" section. Please improve the" Outcome and follow-up" section and may present it as a timeline table or figure.

Answer：Thank you for this suggestion. We have improved the" Outcome and follow-up" section.

5.Discussion. -Again, a similar sentence was published in a previous article without citation. "Hematological diseases in pregnancy should be carefully managed with a multidisciplinary approach, which should include obstetrics, hematology and, in selected patients, apheresis professionals." were found in an abstract of "Transfus Apher Sci . 2015 Dec;53(3):279-82. doi: 10.1016/j.transci.2015.11.007. URL= https://pubmed.ncbi.nlm.nih.gov/26621538." Please consider rephrasing it.

Answer：We rephrase it- Hematological diseases in pregnancy should be meticulously managed with a multidisciplinary cooperation, including obstetrics, hematology and so on.

6.Illustrations and tables. -The author mentioned that there was a figure in the manuscript. However, it was not available to review.

Answer：We have uploaded Figure 1 in the submission files.

7.Biostatistics. Does the manuscript meet the requirements of biostatistics? Not applicable.

Answer：Yes, the manuscript meets the requirements of biostatistics, which has been added in the manuscript.

8.Units. Does the manuscript meet the requirements of use of SI units? -Please use a unit of measurement consistently throughout the manuscript. The authors reported in the discussion section as "… the average WBC in a laboring patient was 12,450, with a range of 4,400 to 29,100." However, they presented as "x10^9 per L" in the others.

Answer：We have corrected it to keep it consistently-Molberg P, et al. found that the average WBC in a laboring patient was 12.45× 109 per L, with a range of 4.4 × 109 per L to 29.1× 109 per L. Patients with postpartum complications had a WBC similar to that of patients without complications (12.9 × 109 per L vs12.3× 109 per L p = 0.449).

9.Quality of manuscript organization and presentation. -Please recheck about the word "table" in the sentence in treatment section "…vitamin complex tablet 1 table a day until 12 weeks of gestation."

Answer：We correct it with-one vitamin complex tablet a day.

Reviewer: 4

Comments to the Author

1. [Infections] In some infections, typical symptoms such as fever and chills do not always present. Has culture testing of the patient's blood, urine and saliva samples been carried out?

Answer：She didn't have fever, symptoms of urgency and frequency，and culture testing of the patient's blood, urine and saliva samples didn't been carried out.

2.[Autoimmune diseases] The authors list infection, allergy, malignancy, surgery, trauma and heavy physical activity as causes of leukaemia syndromes. I suggest that autoimmune diseases, such as collagen diseases, should be added to them. In particular, it is recommended to identify antiphospholipid syndrome and systemic lupus erythematosus in patients with abnormal blood cell counts associated with pregnancy. Has the need to test for antinuclear antibodies in the patient been considered?

Answer：The patient didn't do test for antinuclear antibodies during pregnancy.

3.[Effects of pregnancy] In the discussion, the association between IVF and elevated white blood cell counts is discussed. Was the patient herself pregnant by IVF or not? The patient also had a history of polycystic ovary syndrome. Is there any association between the patient's changes of LH and FSH and her white blood cell count?

Answer：The patient herself was pregnant by IVF. Among components of the SAPS II score, the total leukocyte count (TLC) was negatively associated with serum FSH (beta coefficient = -0.635, P = 0.013). aikkakara S found that none of these parameters were determinants of LH（aikkakara S, Raj MN, Sachan A, Mohan A, Vengamma B, Rao PVLNS, Mukka A, Sravani C, Reddy AP. Impact of Severity of Illness on the Function of the Hypothalamo-pituitary-gonadal Axis in Postmenopausal Women with Acute Severe Illness: Implications for Predicting Disease Outcome. Indian J Endocrinol Metab. 2017 Sep-Oct;21(5):738-744.）The repeated blood routine tests showed that the counts of white blood cell and neutrophil granulocyte were within the normal range before 20 weeks of gestation.We think there is no exact relation between the patient's changes of LH and FSH and her white blood cell count.

4.[Treatment] As the authors point out, termination of pregnancy is effective in refractory pregnancies complicated by leukaemia. In this case, the caesarean section improved the patient's leukaemia syndrome and neither the patient nor her baby had any adverse events. However, if a patient has leukaemia and her foetus is developing poorly at the time she has leukaemia, could the option of reducing the white blood cells with corticosteroids or immunosuppressive treatment and continuing the pregnancy be considered?

Answer：We wonder if you want to say leukocytosis, not leukaemia. Zhu D, et al. found that Acute leukemia (AL) occurring in pregnancy is extremely rare, and its treatment is a clinical dilemma.for patients diagnosed in early and late stages of pregnancy (>30 weeks), elective termination or induced delivery before chemotherapy may be a good choice for better maternal (and fetal) outcome.(Zhu D, Tang D, Chai X, Zhang G, Wang Y. Acute leukemia in pregnancy: a single institutional experience with 21 cases at 10 years and a review of the literature. Ann Med. 2021 Dec;53(1):567-575.)As for treatment of leukaemia, gestational age is also an important factor to be considered.

Reviewer: 5

Comments to the Author

1. Lines 30 - 31 : After 24 hours of cesarean section, neutrophil granulocyte returned to normal. Lines 157 etc: The first postoperative day, the counts of white blood cell were 14.71× 109 per L, the counts of the neutrophil granulocyte were 11.26×109 per L, So, there was no return to normality of the leucocyte count ! What do you mean by stating: "Next day she had a cesarean section because of fetal distress";

Answer:It means that she had a cesarean section because of fetal distress。The first postoperative day, the counts of white blood cell were 14.71× 109 per L, the counts of the neutrophil granulocyte were 11.26×109 per L. Although the counts of white blood cell and neutrophil granulocyte were high, but were decrease to the level that were acceptable after cesarean.

2.when at the conclusions, you say : We also suggest that termination of pregnancy may be an effective treatment for pregnancy complicated with leukocytosis. So, the cesarean section was due to fetal distress (which makes sense !) or to leukocytosis (which makes no sense at all!)

Answer:We want to express the meaning that,the cesarean section was due to fetal distress, but we observe that the termination of pregnancy may be an effective treatment for pregnancy complicated with leukocytosis.

3.Also, in the case report you say: complaining of leukocytosis with increasing blood pressure. There is no patient that can complain of leukocytosis !!! Please give instead complete details of the clinical symptomatology.

Answer:She didn't have any symptom because of leukocytosis, but she was tested leukocytosis in her 27 weeks of gestation and we will correct the Chief complaints with "A 33-year-old woman presented to the Emergency Department complaining of high blood pressure for 6 weeks,with leukocytosis for 13 weeks.

Reviewer: 6

Comments to the Author

1. Please mention the occupation of the patient. Excessive exposure to work related smoke can lead to leukocytosis which may have accentuated during pregnancy.

Answer：She is an employee of an Internet company, which has been added in the manuscript.

2. Please mention if the patient smoked or not, or if she was exposed to second hand smoking during pregnancy.

Answer：She did not smoke or was not exposed to second hand smoking during pregnancy, which has been added in the manuscript.

3. Please mention if there was a history of previous steroid use or hormonal therapy during pregnancy.

Answer：For her first implantation failure, she took aspirin one acetate orally at 5mg a day until 12 weeks of gestation, which is mentioned in the “History of present illness”.

4.Authors must review the causes of leukocytosis in a table. Please review and cite following article from PUBMED which described various causes of lymphocytosis. PMID: 31747226

Answer：We have reviewed and cited following article from PUBMED which described various causes of lymphocytosis.

Table 1. Causes of Leukocytosis

Infections	Lymphoproliferative disorders	other hematological systemic disease	Drugs and drug hypersensitivity reactions	Stress	Asplenia
Viral infections	Chronic Lymphocytic Leukemia	Monoclonal B Lymphocytosis (MBL)	allopurinol	cardiac conditions	
Bacterial Infections	Non-Hodgkin Lymphoma	Congenital B cell Lymphocytosis	carbamazepine	status epileptics	
Parasitic Infections	Adult T cell lymphoma/leukemia	Persistent B-cell polyclonal B-Lymphocytosis	vancomycin	epinephrine use	
Mycobacterial Tuberculosis	Large Granular Lymphocyte Leukemia		sulfa drugs		
	Acute lymphoblastic lymphoma				