Anesthesiology and Pain Medicine
Volume 15 · Issue 4 · e162647

OPEN PEER REVIEW

Comparison of Serum Interleukin 6, Leptin, and Adiponectin Levels after Cesarean Section Under General Versus Spinal Anesthesia

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SUBMITTED	REVISED	ACCEPTED	DOI
27 May 2025	11 Aug 2025	16 Aug 2025	10.5812/aapm-162647

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1 Original submission

5 comments · 1 Jun 2025 – 10 Jun 2025

Referee 1 Reviewer

MINOR REVISION 1 Jun 2025

Dear Author
Comments are attached to the manuscript file.
Best wishes,

Arghavan Afra Reviewer

MINOR REVISION 4 Jun 2025

Dear Corresponding Author:
Thank you for submitting your manuscript and for your valuable contribution. The findings presented are compelling, and the research makes a meaningful contribution to the field by introducing novel insights. To strengthen the manuscript, please consider the following revisions:

The rationale and methodology for selecting the study samples should be clearly explained.
Each table should be accompanied by a detailed explanation to help readers clearly understand the findings presented.
The discussion section currently references a limited number of articles. It should be expanded to include more studies.
The conclusion section largely reiterates the findings. This section should be refined and extended to better align with the study's objectives and key outcomes.
Finally, all references published before 2015 should be removed and replaced with more recent sources to enhance the relevance and credibility of the literature review.

We greatly appreciate your efforts and look forward to receiving your revised manuscript.
Best regards

Referee 2 Reviewer

MAJOR REVISION 7 Jun 2025

Dear AE,
Thank you for the invitation. This article investigates how two anesthetic techniques—general anesthesia (GA) and spinal anesthesia (SA)—influence inflammatory markers (IL-6, leptin, and adiponectin) 24 hours after cesarean section (CS). It presents novel insights into the immunological impact of anesthesia methods on postpartum women.
There are some notes:
1-The rationale for choosing only a 24-hour post-CS timepoint lacks clarity. Cytokine responses are dynamic and may peak earlier or later.

2-While IL-6 is a well-accepted inflammatory marker, adiponectin, which is largely anti-inflammatory, showed increased levels in GA patients—this seems paradoxical and requires further explanation.

3-The inclusion criteria are vague. Were comorbidities (e.g., obesity, diabetes, preeclampsia) excluded or controlled for?
4-Correlation analysis is well presented but lacks multivariate analysis (e.g., linear regression) to adjust for confounders like BMI, age, baseline inflammation, and duration of surgery.

5-The manuscript discusses comparisons with previous studies well but omits deeper analysis of why adiponectin increased in the GA group despite its anti-inflammatory role.

6-The idea that general anesthesia provokes a greater systemic inflammatory response is not new, but combining this with adipokine profiling is a strength.

7-IL-6 is sometimes referred to without a definition of the abbreviation in later sections.

8-The manuscript needs professional English editing to improve grammar, flow, and readability.

Associate Editor

MAJOR REVISION 10 Jun 2025

Dear EIC,
Thanks to the authors and appreciation to the researchers. The manuscript presents valuable research. But some revisions are needed. The authors should revise it based on the comments. Also, a minor change should be made in the abstract:
*The study design should be mentioned in the first line of the methods section of the ABSTRACT.

Editor-in-Chief

MAJOR REVISION 10 Jun 2025

Dear Author,
Thank you for submitting the article. It needs some revision. Please revise it based on the reviewers' and AE's comments.

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Revision 1

AUTHORS' RESPONSE TO REVIEWERS

Authors' reply to reviewers

The next pages contain the authors' point-by-point reply to the comments of this revision round, as submitted with the revised manuscript. It is published as the authors wrote it.

Please find below a point-by-point response to the reviewers' comments.

#Reviewer 1#

Comment 1: Kindly, the keyword highlighted in yellow should be written based on the MeSH.

Response: The keywords were revised and "spinal" was removed and replaced with the two keywords "spinal anesthesia" and "general anesthesia."

Comment 2: Kindly, Given the title of this manuscript, which is in the category of cellular anesthesia, and is somewhat about the effects of various anesthetic drugs for inducing anesthesia, I recommend that you also use these articles in the introduction:

"Nazemroaya B, Taei S. Comparison of the Impact of Atracurium and Cisatracurium on the Neutrophil-To-Lymphocyte Ratio in Addition to Hemodynamic Changes during Anesthesia Induction. Arch Anesth & Crit Care. 2024;10(Supp. 2):608-614."

"Behzad Nazemroaya, Mahmoud Falamarzfouladi, Leyla Rafiei. Rate of changes in Neutrophil-to-Lymphocyte ratio in patients with and without nausea and vomiting after spinal anesthesia: a clinical trial. AMJ 2023; 63(2): 7767 –74."

Response: Both studies mentioned were added to the introduction section (references 7 and 8).

Adverse effects that have been related to GA are typically caused by the drugs used in this anesthesia method. Some of these drugs, such as cis-atracurium and atracurium, have been shown to have different effects on blood pressure and alter the composition of white blood cells, including neutrophils and lymphocytes (7). Even in surgeries under spinal anesthesia, these changes have been associated with adverse postoperative outcomes such as nausea and vomiting (8).

Comment 3: Kindly, considering that you did not use the same medications to induce anesthesia, is this not a confounding factor in the research? If so, please mention it in the discussion section as one of your limitations.

Response: This study employed two distinct anesthesia methods that utilized different drugs with varying mechanisms of action in various local areas. In fact, the goal was to investigate and compare the effects of the drug combinations used in these two anesthesia techniques during cesarean sections.

Comment 4: Kindly, Draw the study flowchart as Figure 1.

Response: The flowchart was drawn as Figure 1.

#Reviewer 2#

Comment 1: The rationale and methodology for selecting the study samples should be clearly explained.

Response: We appreciate the reviewer's detailed feedback. The selection and inclusion criteria for the study have been revised, and these changes are highlighted in the article, specifically in the opening paragraph of Section 2.1. The revised text is as follows:

In this cross-sectional study, pregnant women who were scheduled for elective CS were recruited from the outpatient antenatal clinic to participate in this study. All participants satisfied the criteria for both general and spinal anesthesia, and the method of anesthesia was randomly assigned to each participant. Parturients with autoimmune diseases, preeclampsia, hypertension, gestational diabetes, a gestational age of less than 37 weeks, those who received blood transfusions during surgery, and those who underwent intubation were excluded from the study. After the CS, based on the anesthesia method administered, participants were divided into two groups: general anesthesia (GA) and spinal anesthesia (SA).

Comment 2: Each table should be accompanied by a detailed explanation to help readers clearly understand the findings presented.

Response: All tables include legends that clarify the type of statistical test used, the interpretation of the results presented, and the abbreviations found in the tables. These legends are highlighted for each table.

Comment 3: The discussion section currently references a limited number of articles. It should be expanded to include more studies.

Response: Although more studies have been conducted on the relationship between serum levels of interleukin-6 and anesthesia method in cesarean section, this study has investigated for the first time the relationship between serum levels of two cytokines, leptin and adiponectin, and two methods of general and spinal anesthesia in cesarean section. Almost all recent studies on interleukin-6 have been discussed. However, in the case of leptin and adiponectin, due to the limitations of similar studies, we went to related studies. We provided explanations about the correlation between cytokine levels and the existing contradictions.

Comment 4: The conclusion section largely reiterates the findings. This section should be refined and extended to better align with the study's objectives and key outcomes.

Response: The conclusion was revised to highlight that cesarean sections under general anesthesia show higher levels of the cytokines interleukin-6, leptin, and adiponectin compared to those performed under spinal anesthesia.

In this study, we found that 24 hours after a cesarean section, the proinflammatory cytokines interleukin-6 and leptin, as well as the anti-inflammatory cytokine adiponectin, were higher in women who received general anesthesia compared to those who received spinal anesthesia. This suggests that spinal anesthesia may be more beneficial than general anesthesia for cesarean sections. To the best of our knowledge, this study is the first to examine the relationship between serum leptin and adiponectin levels with general or spinal anesthesia in cesarean sections. Further research is needed to explore the relationship between the serum levels of these cytokines and post-cesarean complications, including those affecting both mothers and newborns.

Comment 5: All references published before 2015 should be removed and replaced with more recent sources to enhance the relevance and credibility of the literature review.

Response: In this manuscript, there was only one reference older than 2015 (reference number 17), which was removed and replaced with a more recent article.

#Reviewer 3#

Comment 1: The rationale for choosing only a 24-hour post-CS timepoint lacks clarity. Cytokine responses are dynamic and may peak earlier or later.

Response: As mentioned in the previous study, the increase in cytokine concentrations during inflammatory responses is variable, but their increase reaches its peak after 24 hours and remains high for the next 48 to 72 hours.

The increase in cytokine concentrations during inflammatory responses is variable, but it has been shown that their increase peaks after 24 hours and remains high up to 72 hours (17).

Comment 2: While IL-6 is a well-accepted inflammatory marker, adiponectin, which is largely anti-inflammatory, showed increased levels in GA patients—this seems paradoxical and requires further explanation.

Response: This contradiction has been observed in previous studies, and the explanation of which has been added in the text. However, discovering the exact mechanism of this synergy between two pro-inflammatory and anti-inflammatory cytokines requires basic studies and investigation of molecular signaling, which is beyond the scope of this study.

Previous studies have demonstrated a simultaneous increase in both proinflammatory and anti-inflammatory cytokines. For instance, Novak et al. found that 6 and 12 hours after CS, the serum levels of proinflammatory cytokines,

including interleukin-6, tumor necrosis factor alpha (TNF-α), and interleukin-8, as well as anti-inflammatory cytokines, including interleukin-10 (IL-10) and interleukin-4 (IL-4), were significantly higher in parturients who underwent general anesthesia compared to those who received spinal anesthesia (18). As previously shown, the heightened secretion of adiponectin by macrophages serves as an essential stimulus for the expression and increase in serum levels of IL-10 (24). However, serum levels of IL-10 were not assessed in the present study.

Comment 3: The inclusion criteria are vague. Were comorbidities (e.g., obesity, diabetes, preeclampsia) excluded or controlled?

Response: We appreciate your attention to detail. The study's inclusion criteria are already clearly outlined in the text and applied accordingly:

In this cross-sectional study, pregnant women who were scheduled for elective CS were recruited from the outpatient antenatal clinic to participate in this study. All participants satisfied the criteria for both general and spinal anesthesia, and the method of anesthesia was randomly assigned to each participant. Parturients with autoimmune diseases, preeclampsia, hypertension, gestational diabetes, a gestational age of less than 37 weeks, those who received blood transfusions during CS, and those who underwent intubation were excluded from the study. After the CS, based on the anesthesia method administered, participants were divided into two groups: general anesthesia (GA) and spinal anesthesia (SA).

Comment 4: Correlation analysis is well presented but lacks multivariate analysis (e.g., linear regression) to adjust for confounders like BMI, age, baseline inflammation, duration of surgery.

Response: As stated in the discussion section, a limitation of the study was that we did not measure BMI or baseline inflammation in the participants. In the linear

regression model analyzed for the three cytokines—interleukin-6, leptin, and adiponectin—none of the demographic, laboratory, or clinical variables significantly predicted the values of these cytokines. Consequently, these data are not presented.

Comment 5: Discusses comparisons with previous studies well but omits deeper analysis of why adiponectin increased in GA group despite its anti-inflammatory role.

Response: Further explanations regarding studies to clarify why adiponectin, an anti-inflammatory cytokine, increased simultaneously with interleukin-6 and leptin, which are pro-inflammatory cytokines, in the general anesthesia group, are added in the discussion section as follows. However, a thorough investigation of the molecular mechanisms underlying this phenomenon will require laboratory-based studies.

Previous studies have demonstrated a simultaneous increase in both proinflammatory and anti-inflammatory cytokines. For instance, Novak et al. found that 6 and 12 hours after CS, the serum levels of proinflammatory cytokines, including interleukin-6, tumor necrosis factor alpha (TNF-α), and interleukin-8, as well as anti-inflammatory cytokines, including interleukin-10 (IL-10) and interleukin-4 (IL-4), were significantly higher in parturients who underwent general anesthesia compared to those who received spinal anesthesia (18). As previously shown, the heightened secretion of adiponectin by macrophages serves as an essential stimulus for the expression and increase in serum levels of IL-10 (24). However, serum levels of IL-10 were not assessed in the present study.

Comment 6: The idea that general anesthesia provokes a greater systemic inflammatory response is not new, but combining this with adipokine profiling is a strength.

Response: We appreciate your attention. This study is the first to evaluate two lipid tissue cytokines, leptin and adiponectin, in cesarean sections using general and spinal anesthesia.

Comment 7: IL-6 is sometimes referred to without abbreviation definition in later sections.

Response: The correction was successfully implemented. After its first mention in the text and its abbreviation in parentheses as (IL-6), interleukin 6 was subsequently referred to as IL-6 in other parts of the manuscript.

Comment 8: The manuscript needs professional English editing to improve grammar, flow, and readability.

Response: The entire manuscript has been edited for grammar and vocabulary by a professional English-language editor. https://shopping-articlex.brieflands.com (Verification Code: 4 8 0 5 v 5 f d 0 b 2 2 a). The certificate for native language editing is attached.

#Reviewer Assistant Comments#

Major Comments: The abstract lacks information about the setting, specific locations, and dates of the study, which are important for understanding the context and applicability of the findings.

Response: The correction was made as follows, and the date and location of the study were included in the abstract.

This cross-sectional study was conducted at Sayad Shirazi Hospital in Gorgan, IR.IRAN, in 2024.

Minor Comments: The abstract does not specify how the participants were selected, which could be relevant for assessing the study's validity and potential biases.

Response: The selection method and criteria for participation in the study were added to the abstract.

Eighty pregnant women who were scheduled for CS were enrolled in the study. All participants satisfied the criteria for both general and spinal anesthesia, and the method of anesthesia was randomly assigned to each participant. Exclusion criteria included autoimmune diseases, preeclampsia, hypertension, gestational diabetes, a gestational age < 37 weeks, those who received blood transfusions and/or intubation. Participants were divided into two groups based on the anesthesia method after the CS: general anesthesia (GA) and spinal anesthesia (SA).

2 Revision 1

5 comments · 12 Aug 2025 – 16 Aug 2025

Referee 1 Reviewer

ACCEPT 12 Aug 2025

Dear Author

I must thank you for answering the comments carefully and patiently.

Best wishes,

Referee 2 Reviewer

ACCEPT 16 Aug 2025

Thank you for correcting pitfalls and answering my questions.

Referee 3 Reviewer

ACCEPT 16 Aug 2025

The findings being presented by the author(s) are interesting and the research indeed contributes new findings. They have made the necessary changes to the document. The manuscript has been improved by the revision.

Associate Editor

ACCEPT 16 Aug 2025

Dear EIC.
Previous errors have been corrected, and there are no further recommendations.

Editor-in-Chief

ACCEPT 16 Aug 2025

Dear Authors,

Thank you for addressing the identified issues and responding to my queries. Your revisions have substantially improved the manuscript, and it is now considered acceptable for publication. Congratulations on your hard work and commitment to enhancing the quality of your research.