Author’s response to reviews

Title: The effect of gestational diabetes mellitus on sufentanil consumption after cesarean section: A prospective cohort study

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Version: 1 Date: 09 Nov 2019

Author’s response to reviews:

Dear Editor:

Thank you for giving us an opportunity to revise our manuscript.

The details of the amendments according to the reviewers’ opinions are provided below.

Naida Cole, M.D. (Reviewer 1)

Introduction

1. The first sentence might read better if changed to "Gestational diabetes mellitus (GDM) is defined as high blood glucose caused by an impaired glucose tolerance detected and diagnosed during pregnancy."

Thank you for your valuable comments. This section has been revised.
2. In the first paragraph, the second sentence might well include how the diagnosis is made.

Thank you for your valuable comments. “GDM is characterized by elevated fasting blood glucose and impaired glucose tolerance during pregnancy. The reference values used in the oral glucose tolerance test for pregnant women are as follows: fasting, 5.6 mmol/L; 1-hour postprandial, 10.3 mmol/L; 2-hour postprandial, 8.6 mmol/L; 3-hour postprandial, 6.7 mmol/L. GDM is diagnosed when two or more test values reach or exceed the reference values.” has been added to the Introduction.

3. In the 2nd paragraph, move the reference [4] to follow the 2nd sentence instead, so it is clear that those first 2 sentences are both referring to that paper.

Thank you very much; what you said is correct. The suggested change has been made.

4. You may want to add a few more references to support the statements in paragraph 2. For example, PMID 30963325 (and other studies) also showed the higher postoperative opioid requirement in DM patients. Same thing with the proposed mechanisms at the end of this paragraph. Another paper on this is from the journal Diabetes 2015; 64: 3987-9.

Thank you very much for providing the latest reference support. These references have been added to the manuscript.

5. In the last paragraph, change the second sentence to: "...gestational diabetes is usually briefer and its association with opioid consumption is unclear."

Thank you very much for your valuable comments. This section has been revised.

6. As you correctly state later in the paper, this design cannot address a cause-effect relationship between GDM and opioid consumption. Please change and make this clear in the Introduction final paragraph (line 43).

Thank you very much for your valuable suggestion. This part of the paragraph has been revised to “Therefore, we conducted a prospective observational cohort study in which we investigated the correlation between gestational diabetes and sufentanil consumption during the immediate postoperative period after cesarean section.”
Methods

7. Why was an epidural placed purely for opioid administration (which could have been given intrathecally) or is this your standard practice in case of a failed spinal?

Thank you very much for your valuable comments. This is currently our standard practice in case of a failed spinal; meanwhile, a single analgesia after surgery.

8. Under Procedure, in the 4th paragraph, please specify the concentration of the 3mL/h sufentanil PCIA infusion.

Thank you very much for your valuable suggestion. ”The sufentanil concentration was 1 mg/ml”, has been added to the manuscript.

9. Did any patients receive any other postoperative analgesics during the study period in addition to the sufentanil PCIA? If so, were these standing orders or on demand? Please describe this or if none were given, please mention this.

Thank you very much for your valuable suggestion. To reduce the confounding factors, only PCIA analgesia with sufentanil, it has been added to the manuscript.

10. Did any patients receive other medications through the epidural intraoperatively besides sufentanil?

No drugs other than sufentanil were given intraoperatively through the epidural.

Patients who received other medications were excluded from the study.

Results

11. Were there any surgical or medical complications (especially within the first 24 hrs) in any study patients?

The study only recorded anesthesia-related complications; patients who had severe surgical or medical complications that required discontinuation of the anesthesia were excluded from the study.
12. Were there any patients who required multiple attempts for their neuraxial technique?

The anesthesia was administered by a senior anesthesiologist. Whether or not there were multiple attempts was not recorded.

13. It would be very helpful to also know the size of the neonates at birth, patient comorbidities (or at least their ASA class), patient psychiatric history if any, history of substance or opioid use or chronic pain issues. Assuming these were well-matched between groups, it would reduce some obvious confounding factors. If this data is unobtainable, it should be mentioned that this is a limitation, as any of these could affect opioid use.

Thank you very much for your valuable suggestion. The pregnant women included in our study were all ASA II (this description has been added to the revised manuscript). Pregnant women who had other comorbidities, chronic pain, history of opioid use, or other factors affecting opioid consumption were excluded. Your suggestion regarding the neonatal factors is very valuable. We collected the newborns' weight data from the electronic medical record and conducted a statistical analysis of the data. The results have been added to the revised manuscript.

14. In the last paragraph, the subanalysis is interesting, but it should be qualified that the study was not powered for this outcome.

Thank you very much for your valuable suggestion. Indeed, it is impossible to determine the relationship between the level of glycated hemoglobin and the consumption of opioid analgesics based on our existing data. We are continuing to collect data on postoperative analgesia use by pregnant women with gestational diabetes. We hope that the use of a large sample size will yield significant results.
Adam Jacob (Reviewer 2)

In the research article "The effect of gestational diabetes mellitus [GDM] on sufentanil consumption…", the authors describe a single center, prospective, observational cohort study to describe the association of GDM and post-cesarean opiate use. A cohort of 64 women undergoing cesarean delivery (32 with GDM, 32 without GDM) was followed after surgery to determine the amount of postoperative opiate use. Specifically, the primary endpoint was sufentanil consumption 6 hours after the operation. Secondary endpoints included 24 hours sufentanil consumption, frequency of PCA use, pain scores, adverse effects, and patient satisfaction. Patients with GDM used statistically significantly more sufentanil (24.0 vs 20.1 mcg) at 6 hours compared to non-GDM patients. Remaining secondary outcomes were not clinically different. Ultimately, authors concluded that "pregnant women with GDM require more opiates during the immediate postoperative period after cesarean section than those without GDM."

Though the difference in opiate use in the present study is only modest (at best), the results are provocative and reinforce the association between diabetes and higher postsurgical opiate needs demonstrated in previous research. Therefore, I would consider this hypothesis-generating research which requires more investigation.

General Questions/Comments:

1. The manuscript would benefit from review and editing for English language.

   Thank you very much for your valuable suggestion. The manuscript was translated and edited for English language usage by AJE. The verification code is 9F39-F159-AEAD-E323-F01P.

2. Could you subdivide the GDM cohort by White Classification? Any impact on results?

   Thank you very much for your constructive suggestions. All pregnant women included in the GDM group were class A according to the White Classification. We collected fasting blood glucose data on the pregnant women only on the morning of the surgery. There were no statistical data on blood glucose level two hours after a meal. Therefore, the A1 and A2 subgroup analysis could not be performed.
3. Why exclude patients that required epidural top-ups?

This was done to eliminate a possible confounding factor; epidural top-ups may affect later analgesic consumption.

4. How strictly did you match by height and weight? For example, did you match weight exactly? Or perhaps + / - 1 kg? Would you have sufficient numbers to match 1:2 to increase power?

We matched by height ±2 cm and weight ±1 kg. Because of the need to match height, weight, and parity simultaneously, there was not a sufficient number of eligible pregnant women undergoing elective cesarean delivery to create a 1:2 matched sample during the time-limited study.

5. Did you include urgent and emergent cesarean sections? Only elective?

No, we included only elective cesarean sections.

6. Did you exclude women with pre-existing diabetes?

Yes, we included women who had been diagnosed with gestational diabetes during pregnancy and excluded women with pre-existing diabetes.

7. Can you surmise what other unmeasured confounding variables might lead to small difference in early postsurgical opiate use?

In addition to the factors that were considered in the study (height, weight and parity), I believe that psychological factors such as postoperative care by family members or anxiety status may also affect opioid consumption and pain scores. Another reviewer suggested factors such as fetal size. The results of a statistical analysis of the fetal weight data were added to the revised manuscript; however, no statistically significant differences were found.

8. Unless patients are receiving opiates from a source other than the sufentanil PCA, PCA use (i.e., number of times patients press the PCA button) as an outcome is redundant. Both are objective measures that reflect the same outcome. I would suggest removing PCA use as one of your secondary outcomes, and just include opiate use.
These two sets of data, sufentanil consumption and number of times the patient pressed the PCA button, measure different parameters. Sufentanil consumption is the actual consumption of analgesics, while the number of times patients press the button on the PCA device records the total number of times that the pregnant women attempted to administer the drug themselves. However, the drug was not administered at each press because the device had a 15-minute lockout time. Therefore, the total number of times a patient pressed the PCA button reflects the patient’s subjectively perceived need for analgesics rather than the amount of analgesic administered.

Specific Questions / Comments:

1. Introduction - Please review and reorganize this section. I believe all the appropriate content to justify the study is there, but I think it could be presented a bit more logically.

   Thank you for your valuable comments. This section has been revised.

2. Introduction (lines 21-23) - Please include a reference for this sentence.

   Thank you for your valuable comments. This section has been revised.

3. Methods (lines 50-51) - Please clarify what you mean by "maternal circulation state."

   Thank you very much for your valuable suggestion. The expression we used is not very accurate; we revised the statement to “the infusion speed was then adjusted by the anesthesiologist according to the maternal circulation state.”

4. Results - Please avoid redundant presentation of results in Tables and text. One location is sufficient.

   Thank you very much for your constructive suggestions. The redundant presentation has been deleted.
5. Results - Given how few women had HbA1c > 6, the results in the final paragraph are not very meaningful and could be deleted. Instead consider comparison by GDM White Classification?

All pregnant women were diagnosed with class A gestational diabetes based on the White Classification. We collected fasting blood glucose data on the pregnant women only on the morning of surgery. The blood glucose levels two hours after meals were not recorded. Therefore, the A1 and A2 subgroup analysis could not be performed.

6. Results - The data presented in Table 3 may be better summarized in text.

Thank you for your valuable comments. This section has been revised.