

Peer Review File

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Reviewer A Comments:

ABSTRACT:

43: USE A PERIOD INSTEAD OF A COMMA (ADMISSION, LITTLE).

REPLY: WE MODIFIED OUR TEXT AS ADVISED.

CHANGES IN THE TEXT: PAGE 2, LINE 26

44: PERHAPS SEX/GENDER (AS OPPOSED TO “SEX AND GENDER”) IS LESS CONFUSING.

REPLY: WE ONLY INCLUDED THE "SEX" TERM.

CHANGES IN THE TEXT: THROUGHOUT THE WHOLE MANUSCRIPT.

46: SHOULD IT BE “TREATMENT EFFECTIVENESS” OR “TREATMENTS’ EFFECTIVENESS?”

REPLY: WE REPHASED THE SENTENCE AS “TREATMENT EFFECTIVENESS”.

CHANGES IN THE TEXT: PAGE 2, LINE 29

49: IS IT CONSEQUENCES “OF” OR “ON” CARDIOVASCULAR CONDITIONS? FROM THE PRECEDING DESCRIPTION ONE WOULD THINK THE LATTER.

REPLY: IT IS ‘CONSEQUENCES OF CARDIOVASCULAR DISEASE’.

CHANGES IN THE TEXT: PAGE 2, LINE 31

51: PERHAPS CHANGE TO “TO REVEAL”

REPLY: WE MODIFIED OUR TEXT AS ADVISED. WE ARE INCLUDING “HIGHLIGHT CRITICAL”

CHANGES IN THE TEXT: PAGE 2, LINE 33

55: THE PHRASE SEX DIFFERENCE IS USED, BUT PREVIOUSLY GENDER WAS ALSO BROUGHT UP... DO THESE TERMS NEED TO BE DISAGGREGATED?

REPLY: WE ONLY INCLUDED THE "SEX" TERM

CHANGES IN THE TEXT: THROUGHOUT THE WHOLE MANUSCRIPT.

57: INARTFUL WORDING, PERHAPS “CERTAIN ANESTHETICS” AS OPPOSED TO “ANESTHETIC CHOICES”

REPLY: WE MODIFIED THE TEXT AS ADVISED AND INCLUDED “SPECIFIC ANESTHETICS”

CHANGES IN THE TEXT: PAGE 2, LINE 41

58: “INDICATING THEIR.” TO WHAT DOES THIS REFER?

REPLY: WE INCLUDED THE PHRASE “SUGGESTING THE IMPORTANCE OF ANESTHETIC SELECTION”

CHANGES IN THE TEXT: PAGE 2, LINE 43

60: ARE THESE FOCI SEX SPECIFIC OR DIFFERENTIATED?

REPLY: THE IDENTIFIED LOCI HAVE BEEN STUDIED IN PRE-CLINICAL MODELS USING MALE AND FEMALE RODENTS. SEX DIFFERENCES HAVE NOT BEEN REPORTED; HOWEVER, IT IS POSSIBLE PRIOR STUDIES WERE UNDERPOWERED TO DETECT SEX DIFFERENCES. THEREFORE, WE INCLUDED THE FOLLOWING STATEMENT IN THE ABSTRACT: “. SEX DIFFERENCES HAVE ALSO BEEN OBSERVED IN SIDE EFFECTS ATTRIBUTED TO OPIOID ANALGESICS. WE SUMMARIZE SOME OF THE NEURAL CIRCUITS THAT MIGHT UNDERLIE THESE DIFFERENCES.”
CHANGES IN THE TEXT: PAGE 2, LINE 39-41

62: THE INCLUSION OF PRE-ECLAMPSIA SEEMS OUT OF PLACE.... ANY OBSTETRIC ANESTHETIC ISSUE IS POTENTIALLY AN INTERSECTION OF SEX AND ANESTHESIOLOGY... THIS OPENS UP THE RELEVANT FIELD OF INQUIRY TO ALL OF OBSTETRIC ANESTHESIOLOGY AS OPPOSED TO GENERAL ANESTHETIC ISSUES (PAIN, IMPACT ON WOMEN’S ONCOLOGIC CONDITIONS) WHICH SEEM TO BE THE THRUST OF THIS REVIEW.

REPLY: OUR GOAL WAS TO PROVIDE A REVIEW OF THE MOST RELEVANT TOPICS IN OBSTETRIC ANESTHESIOLOGY WHICH INCLUDE A SECTION ABOUT CARDIOVASCULAR DISEASE IN PREGNANCY—THE LEADING CAUSE OF MATERNAL MORBIDITY AND MORTALITY. FOR THESE REASONS, WE INCLUDED A SECTION ON PREECLAMPSIA, AN AREA IN WHICH SEVERAL OBSTETRIC ANESTHESIOLOGY RESEARCHERS ARE DEDICATED TIME AND EFFORT (CITED IN TEXT).
CHANGES IN THE TEXT: PAGES 18-23, LINE 366-464

68: AGAIN, SEX AND GENDER NEED TO BE DISAGGREGATED.

REPLY: WE ONLY INCLUDED THE "SEX" TERM.

CHANGES IN THE TEXT: THROUGHOUT THE WHOLE MANUSCRIPT.

75: WHAT PAIN DIFFERENCES? IS CARDIO-OBSTETRICS A NEOLOGISM OR AN ACTUAL PHRASE?

REPLY: WE REPLACED THE KEYWORD TO “CARDIOVASCULAR” AND “REVIEW”
CHANGES IN THE TEXT: PAGE 3, LINE 55

INTRODUCTION:

78-81: THE TERM FEMALES AND WOMEN ARE BEING USED INTERCHANGEABLY, THESE TERMS SHOULD BE DEFINED AND DISAGGREGATED FOR THE PURPOSE OF THIS PAPER.

REPLY: WE ONLY INCLUDED THE "FEMALE" TERM.

CHANGES IN THE TEXT: THROUGHOUT THE WHOLE MANUSCRIPT.

85: REPLACE “AND” WITH “OR”

REPLY: WE MODIFIED OUR TEXT AS ADVISED AND INCLUDED “ACKNOWLEDGING DIFFERENCES BETWEEN FEMALES AND MALES RELEVANT TO ANESTHETIC MANAGEMENT IS PARAMOUNT TO OPTIMIZE PERI-HOSPITAL OUTCOMES AND IMPROVE HUMAN HEALTH”

CHANGES IN THE TEXT: PAGE 4, LINE 62-64

91: IS THIS TRUE? MEN GET MASTECTOMIES. ALSO, THE TERMS MEN AND WOMEN FOR REFERRING TO CHILDBIRTH AND LABOR ARE RECENTLY PROBLEMATIZED.

REPLY: WE DELETED “EXCLUSIVELY” AND INCLUDED AT “PERIOPERATIVE AND PERIPARTUM PROCEDURES THAT AFFECT PRIMARILY FEMALES (E.G., MASTECTOMIES FOR BREAST CANCER, NEURAXIAL ANESTHESIA DURING LABOR AND DELIVERY) REQUIRE CUSTOMIZED PAIN MANAGEMENT PLANS.”

CHANGES IN THE TEXT: PAGE 4, LINE 74-76

102: IS THIS TERMINOLOGY CONSISTENT: IF “WOMEN” REFERS TO SEX AND SEX (HERE) IS DEFINED AS THE BIOLOGIC DIFFERENCES INCLUDING CHROMOSOMAL MAKE-UP, THIS CONTRADICTS MANY CURRENT AND ESTABLISHED USES OF THE TERMS “MEN” AND “WOMEN.”

REPLY: WE ONLY INCLUDED THE "FEMALE" TERM.

CHANGES IN THE TEXT: THROUGHOUT THE WHOLE MANUSCRIPT.

METHODS:

EVEN WITH THE TABLES SUPPLIED, IT IS DIFFICULT TO ASCERTAIN HOW ARTICLES WERE EXCLUDED. HOW MANY ARTICLES WERE INCLUDED IN THE END? DID THE AUTHORS REVIEW OVER 11,000 ARTICLES?

REPLY: WE UPDATED TABLE S1 WITH DETAILS OF THE SEARCH.

CHANGES IN THE TEXT: PLEASE REFER TO SUPPLEMENTARY MATERIAL TABLE S1

DISCUSSION:

120: THIS CLAIM REQUIRES A CITATION.

REPLY: WE INCLUDED THE REFERENCE TO THE PHRASE “MOST FINDINGS ARE SKEWED TOWARD MALE-PREVALENT DISEASES” (6).

CHANGES IN THE TEXT: PAGE 7, LINE 99

127: CHANGE TO “HAVE SHOWN”

REPLY: WE MODIFIED OUR TEXT AS ADVISED AND INCLUDED “DEMONSTRATED”

CHANGES IN THE TEXT: PAGE 7, LINE 107

128: THE WORD “SHOWED” IS INARTFUL.

REPLY: WE MODIFIED OUR TEXT AS ADVISED AND INCLUDED “THEREFORE, MORPHINE PROVIDES BETTER SOMATIC (11) AND VISCERAL PAIN (12) RELIEF IN MALE RATS THAN IN FEMALE RATS.”

CHANGES IN THE TEXT: PAGE 7, LINE 108-109

162-184: IS THIS A DESCRIPTION OF A SEX DIFFERENCE?

REPLY: YES. WE MODIFIED THE SUBTITLE TO “THE ROLE OF GENE-ENVIRONMENT AND EPIGENETICS IN FEMALES.”

CHANGES IN THE TEXT: PAGE 9, LINE 150

215: IT IS TRUE THAT BREAST CANCER IS MUCH MORE COMMON IN WOMEN THAN MEN. HOWEVER, WOULD THE SCOPE OF THIS REVIEW BETTER APPLY TO BREAST CANCERS WITH SPECIFIC GENETIC MARKERS EXCLUSIVE TO WOMEN?

REPLY: YES. BREAST CANCER IS 100-FOLD MORE PREVALENT IN FEMALES THAN MALES; MALE BREAST CANCER'S MOLECULAR AND GENETIC COMPOSITION GENERALLY MIMICS THAT OF FEMALE DISEASE (64).

CHANGES IN THE TEXT: PAGE 13, LINE 250-252

243-321: THIS IS AN EXCELLENT REVIEW OF POST MASTECTOMY PAIN MANAGEMENT. HOWEVER, IT DOES NOT FIT SEAMLESSLY WITH THE OTHER TOPICS.

REPLY: WE WORKED ON THE TRANSITIONS BETWEEN SECTIONS. BECAUSE THE SCOPE OF THIS REVIEW WAS TO HIGHLIGHT AREAS IN WHICH ANESTHESIOLOGY RESEARCH HAS BEEN FOCUSED IN WOMEN'S HEALTH, POSTMASTECTOMY PAIN RESEARCH IS HIGHLIGHTED. WE KEPT THIS SECTION BECAUSE IT DESCRIBES THE

**MANAGEMENT AND RISK OF ACUTE AND PERSISTENT PAIN AFTER BREAST CANCER SURGERY, WHICH IS OF HIGH PREVALENCE SURGERY AMONG FEMALES.
CHANGES IN THE TEXT: PAGE 15- 18, LINE 285-363**

322: (SECTION 3): THIS IS A TOPIC THAT COULD FILL A TEXTBOOK AND DOES NOT SEEM CONSISTENT WITH THE PRECEDING SECTION.

REPLY: WE ELIMINATED THIS SECTION AND INSTEAD INCLUDED A SECTION ON: “SEX DIFFERENCES IN RESPONSE TO THE SIDE EFFECTS OF OPIOID MEDICATIONS: POSSIBLE MECHANISMS”

CHANGES IN THE TEXT: PAGE 10, LINE 179-180

OVERALL COMMENTS:

THIS REVIEW ARTICLE SHOWS A LARGE AMOUNT OF EFFORT ON THE PART OF AUTHORS; HOWEVER IT CONTAINS 3-4 MAJOR TOPICS THAT COULD EACH CONSTITUTE A PAPER (IF NOT A BOOK!):

- **RECENT LITERATURE ON SEX DIFFERENCES IN PAIN PERCEPTION**
- **UPDATES ON PERIOPERATIVE ANESTHETIC AND PAIN MANAGEMENT FOR MASTECTOMY**
- **UPDATES ON PAIN MANAGEMENT IN LABOR AND DELIVERY**
- **UPDATES ON PRE-ECLAMPSIA AS PERTAINS TO ANESTHETIC MANAGEMENT**

I WOULD MAKE THE FOLLOWING RECOMMENDATIONS:

1. LIMIT THE SCOPE OF THE SUBJECT MATTER, IF THE AUTHORS WISH TO FOCUS ON SEX-RELATED DIFFERENCES PERTAINS TO ANESTHETIC MANAGEMENT, THE REVIEW FOUND EARLIER IN THE PAPER PERTAINING TO THIS TOPIC WOULD MEET THIS. THERE IS AN EMPHASIS THROUGHOUT LINKING POTENTIAL SEX-RELATED DIFFERENCES IN RESPONSIVENESS TO OPIOIDS. THEREFORE, FOCUSING ON OPIOID-SPARING APPROACHES TO ANALGESIA COULD PROVIDE A WAY FOR THE AUTHORS TO UTILIZE THE WORK THEY HAVE DONE UNDER A MORE PARSIMONIOUS HEADING FOR THE TOPICS ADDRESSED. ALTERNATIVELY, THIS CONTENT REPRESENTS 3-4 PAPERS (AND HONESTLY THE SECTION ON UPDATES IN LABOR ANALGESIA LIKELY RECEIVED SHORT SHRIFT GIVEN THE ENORMITY OF THAT TOPIC).

REPLY: WE APPRECIATE THE RECOMMENDATION OF THE REVIEWER AND APPRECIATE THAT THE SCOPE OF THE ORIGINAL DRAFT MAY APPEAR BROAD. WE REVISED THE ENTIRE MANUSCRIPT TO CLARIFY THAT THE GOAL OF THE REVIEW WAS TO PROVIDE AN OVERVIEW OF THE MOST RELEVANT TOPICS IN TRANSLATIONAL ANESTHESIOLOGY RESEARCH RECENTLY, FOCUSED ON IMPORTANT FEMALE’S HEALTH ISSUES. WE FOCUSED ON IMPROVING SECTION TRANSITIONS, AND ON SPENDING EQUAL WEIGHT ON SECTIONS.

CHANGES IN THE TEXT: THROUGHOUT THE WHOLE MANUSCRIPT.

2. BETTER DESCRIBE THE PROCESS FOR INCLUSION AND EXCLUSION OF PAPERS. SPECIFY HOW MANY WERE ACTUALLY UTILIZED IN THE REVIEW (IT IS IMPLAUSIBLE THAT OVER 7000 MANUSCRIPTS WERE UTILIZED TO PREPARE THIS REVIEW).

REPLY: WE UPDATED TABLE S1 WITH DETAILS OF THE SEARCH.

CHANGES IN THE TEXT: PLEASE REFER TO SUPPLEMENTARY MATERIAL TABLE S1

3. IF THE AUTHORS WISH TO MAINTAIN THE FOCUS ON SEX-RELATED DIFFERENCES, BETTER DISAGGREGATE THE DISTINCTION BETWEEN SEX AND GENDER (IF THIS

DISTINCTION IS EVEN NECESSARY). THE DEFINITION OF GENDER PROVIDED IS CONSISTENT WITH THAT BROADLY UTILIZED, HOWEVER IT WAS A DISTINCTION MADE THAT NEVER HAD RELEVANCE FOR THE CONTENT THAT FOLLOWED. FURTHERMORE, THE USE OF THE TERM "WOMEN" UNDER THE DEFINITION THE AUTHORS PROVIDED FOR SEX IS NOT CONSISTENT WITH MANY CURRENTLY USED IN GENDER/SEX LITERATURE.

REPLY: WE INCLUDED ONLY "FEMALE" AND "SEX".

CHANGES IN THE TEXT: THROUGHOUT THE WHOLE MANUSCRIPT.

Reviewer B Comments:

THIS NARRATIVE REVIEW, BASED ON RECENT LITERATURE EVIDENCE, PROVIDED UPDATES IN SELECTIVE TOPICS IN TRANSLATION RESEARCH AND CLINICAL PRACTICE RELEVANT TO ANESTHETIC CARES OF PATIENTS WITH BREAST CANCER, AS WELL AS THE OBSTETRIC PATIENTS WHO HAVE OR ARE AT RISKS OF PREECLAMPSIA, PREGNANCY RELATED CEREBROVASCULAR AND CARDIOVASCULAR DISEASES. THIS IS THE EXTENSION OF A REVIEW PUBLISHED BY THE SAME GROUP RECENTLY. HERE ARE SOME THOUGHTS AND CONCERNS:

1. THE TITLE, "TRANSLATIONAL MEDICINE UPDATES IN OBSTETRIC & WOMEN'S ANESTHESIOLOGY", IS NOT ACCURATE, WHILE THE TERM "OBSTETRIC ANESTHESIOLOGY" IS ACCEPTABLE, WHAT DOES "WOMEN'S ANESTHESIOLOGY" INDICATE?

REPLY: WE CHANGED THE TITLE TO "TRANSLATIONAL RESEARCH UPDATES IN FEMALE HEALTH ANESTHESIOLOGY: A NARRATIVE REVIEW"

CHANGES IN THE TEXT: PAGE 1, LINE 1-2

2. THE RUNNING TITLE, "ANESTHESIOLOGY UPDATES IN OBSTETRIC AND WOMEN'S HEALTH", DOES NOT REFLECT THE REAL CONTENT OF THIS MANUSCRIPT, HERE "TRANSLATIONAL MEDICINE UPDATES" IS REPLACED BY "ANESTHESIOLOGY UPDATES", APPARENTLY THESE ARE VERY DIFFERENT CONCEPTS; IN ADDITION, THIS REVIEW IS NOT AN UPDATE FOR WOMEN'S HEALTH, RATHER, IT FOCUSES ON THE ANESTHETIC CARES OF PATIENTS WITH BREAST CANCER AND THE IMPLICATIONS OF SEX DIFFERENCES IN THE MANAGERMENTS OF CLINICAL ANESTHESIA AND ANALGESIA.

REPLY: WE CHANGED THE RUNNING TITLE TO "TRANSLATIONAL UPDATES IN FEMALE HEALTH ANESTHESIOLOGY"

CHANGES IN THE TEXT: PAGE 1, LINE 15

3. THE ABSTRACT HAS MORE THAN THE WORDS LIMIT, THE STRUCTURE IS NOT STANDARDIZED. THE ABSTRACT AND THE MAIN BODY SHOULD BE MORE CONCISE.

REPLY: WE EDITED THE ABSTRACT TO CONFORM TO THE JOURNAL GUIDELINES (TOTAL: 325 WORDS)

CHANGES IN THE TEXT: PAGE 2-3, LINE 24-55

4. THE KEY WORDS SHALL BE VERY PRECISE, "PAIN DIFFERENCES", "OPIOID-SIDE EFFECTS", "CARDIO-OBSTETRICS" ARE NOT CORRECT TERMS.

REPLY: WE REPLACED THE KEYWORD TO "CARDIOVASCULAR", "REVIEW" AND "SEX-DIFFERENCES"

CHANGES IN THE TEXT: PAGE 3, LINE 55

5. THE AUTHORS DID EXPLAIN THE DIFFERENCE BETWEEN THE TERMS OF SEX DIFFERENCES AND GENDER DIFFERENCES, HOWEVER, IN THE ABSTRACT AND MAIN BODY, THESE TWO TERMS WERE MIXED, THERE WAS NO DISCUSSION OF

“GENDER DIFFERENCES”, THEREFORE THIS TERM SHOULD NOT BE USED TO AVOID CONFUSION.

REPLY: WE ONLY INCLUDED THE "SEX" TERM.

CHANGES IN THE TEXT: THROUGHOUT THE WHOLE MANUSCRIPT.

6. THE AUTHORS SEARCHED PUBMED ONLY, IS THERE ANY REASON WHY MEDLINE, EMBASE, GOOGLE SCHOLAR... WERE NOT MENTIONED? THE FREE-PHRASE SEARCH OF PUBMED DOES PROVIDE GREAT CONVENIENCE FOR LITERATURE SEARCH, HOWEVER ON THE FLIP SIDE, IT MAY RISK MISSING IMPORTANT PUBLICATIONS.

REPLY: FOR THIS NARRATIVE REVIEW, WE FOCUSED ONLY ON PUBMED DUE TO CONVENIENCE.

CHANGES IN THE TEXT: PAGE 6, LINE 89-93

7. THE INCLUSION AND EXCLUSION CRITERIA ARE NOT CLEAR, TABLE 1 INDICATES THAT “FULL-TEXT ARTICLES RELEVANT TO ANESTHESIA IMPLICATIONS FOR WOMEN”, SOME CRITICAL INFORMATION WAS MISSING, STUDY TYPE, LANGUAGE, RESTRICTIONS WERE REQUIRED BUT IGNORED, PLEASE CLARIFY WHAT “ARTICLES RELEVANT TO ANESTHESIA IMPLICATIONS FOR WOMEN” INDICATE.

REPLY: WE UPDATED TABLE S1 WITH DETAILS OF THE SEARCH.

CHANGES IN THE TEXT: PLEASE REFER TO SUPPLEMENTARY MATERIAL TABLE S1

8. TABLE S1 SUMMARIZED THE PUBMED SEARCH, SEEMS LIKE ONLY “AND” OR “,” WERE USED TO CONNECT THE SEARCH PHRASES, “OR” AND “NOT” WERE NOT APPLIED, IS THIS CORRECT? I DID THE SEARCH USING THE SEARCH STRATEGY, THE RESULTS WERE QUITE DIFFERENT FROM THE ONES POSTED, FOR EXAMPLE, THE SEARCH USING TERMS “BREAST CANCER ANESTHESIA, BREAST SURGERY ANALGESIA” HAD 396 HITS, NOT 2484; “OPIOID ANALGESIA AND SIDE EFFECT, OPIOID INDUCED RESPIRATORY DEPRESSION, OPIOID INDUCED PRURITUS” GENERATED 66 HITS INSTEAD OF 603 (THE YEARS ARE FROM 1987 TO 2022). PLEASE CLARIFY.

REPLY: WE UPDATED TABLE S1 WITH DETAILS OF THE SEARCH.

CHANGES IN THE TEXT: PLEASE REFER TO SUPPLEMENTARY MATERIAL TABLE S1

9. A FLOWCHART FOR THE LITERATURE SEARCH AND ENROLLMENT COULD BE VERY HELPFUL FOR EXPLAINING HOW THE LITERATURE EVIDENCE WERE OBTAINED.

REPLY: WE UPDATED TABLE S1 WITH DETAILS OF THE SEARCH.

CHANGES IN THE TEXT: PLEASE REFER TO SUPPLEMENTARY MATERIAL TABLE S1

10. IN THE DISCUSSION SECTION, THE AUTHORS: (1). SUMMARIZED RECENT EVIDENCE OF SEX DIFFERENCES IN PAIN PERCEPTION AND MANagements AND POTENTIAL MECHANISMS INCLUDING THE IMPORTANCE OF GENETIC FACTORS IN ANESTHESIA AND ANALGESIA, (2). DISCUSSED THE POTENTIAL ADVANTAGE OF PERIPHERAL NERVE BLOCK AND TOTAL INTRAVENOUS ANESTHESIA ON PREVENTING BREAST CANCER METASTASIS; LISTED EVIDENCE OF MANAGING ACUTE AND CHRONIC PAIN INCURRED BY SURGERY AND CHEMOTHERAPY WITH MULTIMODAL PAIN THERAPY WITH REGIONAL BOCK, NARCOTICS, AND NON-NARCOTICS. (3). THE PATHOPHYSIOLOGY AND MECHANISMS OF PRURITUS AND OPIOID INDUCED RESPIRATORY DEPRESSION FROM NEURAXIAL AND PARENTERAL OPIOIDS, THE ROLE OF GABANERGIC NEURONS IN SPINAL CORD AND BRAIN STEM, THE POTENTIAL INTERVENTIONS. (4) LISTED SEVERAL BIOMARKERS IN PATIENTS WITH

PREECLAMPSIA, THE POTENTIAL DIAGNOSTIC ROLE OF THESE MARKERS IN RISK, PROGNOSTIC PREDICTIONS IN THE ONSET OF PREECLAMPSIA AND THE CEREBRAL EVENTS. (5). MODELS OF RISK STRATIFICATION, BIOMARKERS, AND THE ROLE OF ECHOCARDIOGRAPHY IN PREGNANCY RELATED CARDIOVASCULAR DISEASES. THESE ARE EXCELLENT SUMMARIES IN THE SELECTED FIELD. HOWEVER, THERE ARE IMPORTANT TRENDS AND EMERGING DATA FROM CERTAIN MULTIDISCIPLINE RESEARCH NEED ATTENTION. FOR EXAMPLE:

A. THE FAST GROWING OF RESEARCH IN PRECISION MEDICINE (INDIVIDUALIZED MEDICINE) THAT IS GOING TO RESHAPE AND EVEN DOMINATE THE FUTURE RESEARCH AND CLINICAL PRACTICE. DECISION TO TAILOR ANESTHETIC CARE TO SPECIFIC NEED OF INDIVIDUAL PATIENTS COULD BE THE NEW ROUTINE IN THE FUTURE.

B. THE APPLICATION OF ARTIFICIAL INTELLIGENCE IN PATIENT CARES IS GAINING GREAT MOMENTUM, RESEARCH INVOLVING MACHINE LEARNING IN ANESTHETIC CARE OF OBSTETRIC/GYNECOLOGICAL PATIENTS HAVE PRODUCED INTERESTING DATA OF BETTER ANESTHETIC AND ANALGESIC CARES.

--1. G L. WHAT IS NEW IN OBSTETRIC ANESTHESIA: THE 2021 GERARD W. OSTHEIMER LECTURE. ANESTHESIA AND ANALGESIA. 2022.

--2. TRUONG TM, APFELBAUM JL, SCHIERER E, ET AL. ANESTHESIA PROVIDERS AS STAKEHOLDERS TO ADOPTION OF PHARMACOGENOMIC INFORMATION IN PERIOPERATIVE CARE. PHARMACOGENET GENOMICS. 2022;32(3):79-86.

--3. TRUONG TM, APFELBAUM JL, DANAHEY K, ET AL. PILOT FINDINGS OF PHARMACOGENOMICS IN PERIOPERATIVE CARE: INITIAL RESULTS FROM THE FIRST PHASE OF THE IMPRESS TRIAL. ANESTH ANALG. 2022.

--4. LEE EK, TIAN H, LEE J, ET AL. INVESTIGATING A NEEDLE-BASED EPIDURAL PROCEDURE IN OBSTETRIC ANESTHESIA. AMIA ANNUAL SYMPOSIUM PROCEEDINGS. 2018;2018:720.

--5. JJ IC, J M, Y L, ET AL. MACHINE LEARNING APPROACH TO NEEDLE INSERTION SITE IDENTIFICATION FOR SPINAL ANESTHESIA IN OBESE PATIENTS. BMC ANESTHESIOLOGY. 2021;21(1).

**REPLY: WE APPRECIATE THE COMMENTARY OF THE REVIEWER REGARDING MARCHINE LEARNING. NEW SECTIONS WERE NOT ADDED TO THE MANUSCRIPT AS THIS WAS NOT A SUGGESTED CHANGE.
CHANGES IN THE TEXT: NONE**

Reviewer C Comments:

THE MANUSCRIPT READS WELL AND I ONLY HAVE MINOR COMMENTS:

1. IT MAY BE USEFUL TO HAVE A REFERENCE FOR THE LINE 117 IN THE DISCUSSION WHICH STATES THAT WOMEN ARE UNDERREPRESENTED IN RESEARCH.

REPLY: REPLY: WE INCLUDED THE REFERENCE TO THE PHRASE “MOST FINDINGS ARE SKEWED TOWARD MALE-PREVALENT DISEASES” (6).

CHANGES IN THE TEXT: PAGE 7, LINE 99

2. THE PARAGRAPH ON “THE ROLE OF GENE-ENVIRONMENT AND EPIGENETICS” (LINE 161) CAN BE PRESENTED WITH MORE CLARITY. ESPECIALLY HOW THE INFORMATION ON METHYLATION IN WOMEN WITH INTERSTITIAL CYSTITIS WOULD RELATE TO HYPERMETHYLATION OF OPIOID RECEPTORS AND THE IMPORTANCE OF THIS WHOLE ASPECT TO THE FEMALE GENDER. AT PRESENT, THE PRESENTATION IS A BIT CONFUSING.

**REPLY: THIS SECTION WAS UPDATED AND EDITED.
CHANGES IN THE TEXT: PAGE 9-10, LINE 150-177**