Review

Maternal Physiologic Parameters in Relationship to Systemic Inflammatory Response Syndrome Criteria

A Systematic Review and Meta-analysis

Melissa E. Bauer, DO, Samuel T. Bauer, MD, Baskar Rajala, MBBS, Mark P. MacEachern, MLIS, Linda S. Polley, MD, David Childers, MA, and David M. Aronoff, MD

OBJECTIVE: To establish the normal maternal range in healthy pregnant women for each component of the systemic inflammatory response syndrome (SIRS) criteria and compare these ranges with existing SIRS criteria.

DATA SOURCES: PubMed, Embase, and ClinicalTrials.gov databases were searched to identify studies of healthy parturients from the first trimester through 12 weeks postpartum that reported maternal temperature, respiratory rate, $PaCO_2$, heart rate, white blood cell count data, or a combination of these.

METHODS OF STUDY SELECTION: Data were extracted from studies providing maternal values for components of SIRS criteria. The mean, standard deviation, and two standard deviations from the mean for all criteria parameters published in the literature were reported.

TABULATION, INTEGRATION, AND RESULTS: Eighty-seven studies met inclusion criteria and included 8,834 patients and 15,237 data points: temperature (10 studies and 2,367 patients), respiratory rate (nine studies and 312 patients), $PaCO_2$ (12 studies and 441 patients), heart rate (39 studies and 1,374 patients), and white blood cell count (23 studies and 4,553 patients). Overlap with SIRS criteria occurred in healthy pregnant women during the second trimester, third trimester, and labor for each of the SIRS criteria except temperature. Every mean value for $PaCO_2$ during pregnancy (and up to 48 hours postpartum) was below 32 mm Hg. Two standard deviations above the mean for temperature, respiratory rate, and heart rate were 38.1°C, 25 breaths per minute, and 107 beats per minute, respectively.

CONCLUSION: Current SIRS criteria often overlap with normal physiologic parameters during pregnancy and the immediate postpartum period; thus, alternative criteria must be developed to diagnose maternal sepsis.

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From the Department of Anesthesiology, Division of Obstetric Anesthesiology, and the Taubman Health Sciences Library, University of Michigan Health System, and the Center for Statistical Consultation & Research, University of Michigan, Ann Arbor, and the Department of Obstetrics and Gynecology, Division of Maternal Fetal Medicine, Oakland University William Beaumont School of Medicine, Royal Oak, Michigan; and the Department of Medicine, Division of Infectious Diseases, Vanderbilt University Medical Center, Nashville, Tennessee.

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Corresponding author: Melissa E. Bauer, DO, 1500 East Medical Center Drive, SPC 5278, Neuroscience Hospital, L3627, Ann Arbor, MI 48109-5278; e-mail: mbalun@med.umich.edu.

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In the United Kingdom, sepsis was the leading cause of maternal direct death for the triennium 2006–2008.[1] Maternal severe sepsis and sepsis-related deaths in the peripartum period have doubled in the United States during the years 1998–2008.[2] Delay in diagnosis and treatment of sepsis has been shown to increase mortality in the general population and inquiry into maternal sepsis-related deaths revealed that delay in diagnosis and treatment contributed to maternal deaths.[1,3]

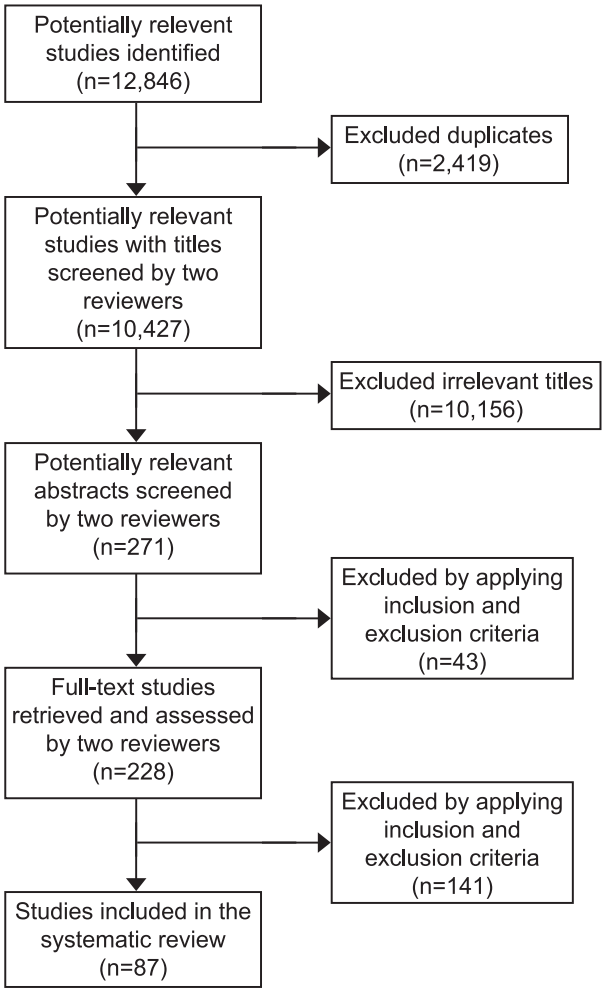

Fig. 1. Flowchart for study selection.
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The physiologic changes of pregnancy likely contribute to delayed recognition of sepsis. The American College of Chest Physicians and Society of Critical Care Medicine define the diagnosis of sepsis as a systemic inflammatory response syndrome (SIRS) secondary to infection. Two of the following four criteria must be present to meet SIRS criteria: temperature greater than 38°C or less than 36°C; respiratory rate greater than 20 breaths per minute or $PaCO_2$ less than 32 mm Hg; heart rate greater than 90 beats per minute (bpm); or white blood cell count greater than 12×10^9/L or less than 4×10^9/L, or bands greater than 10%.[4] Over time, empirically derived SIRS criteria for the general population have been applied to the obstetric population. In a study evaluating patients with chorioamnionitis, although more than 80% met SIRS criteria, fewer than 0.5% had clinical decompensation from sepsis indicating poor test prediction.[5] However, the literature lacks evidence-based criteria for SIRS that specifically adjust for the physiologic changes of pregnancy. Consequently, obstetric patients may meet criteria for SIRS simply as a result of normal maternal physiology.

A substantial body of literature reports normal values during each stage of pregnancy, albeit with small numbers in each study. This study aimed to systematically review the literature to establish the normal maternal range in healthy pregnant women for each component of the SIRS criteria and compare these ranges with existing SIRS criteria.

SOURCES

PubMed and Embase databases were searched to identify observational, randomized controlled trials, case–control, longitudinal, and cross-sectional studies that reported temperature, respiratory rate, $PaCO_2$, heart rate, and white blood cell count in relation to pregnancy published between and including the years 1950–2012. The search was completed on June 5, 2013. The full search details may be found in Appendices 1 and 2, available online at http://links.lww.com/AOG/A542. Additionally, ClinicalTrials.gov was searched to identify published trials that included our variables of interest through June 2013. All searches used a combination of controlled terms (MeSH or EMTREE) and title or title and abstract text words. The search included sentinel articles that were identified by the first author in a previous literature search.

STUDY SELECTION

Relevant publications were reviewed independently by two reviewers. All bibliographies of selected articles and articles citing the selected articles were also screened for inclusion. After relevant articles were identified, data were extracted by one author and checked by a second author. Any discrepancies were resolved through discussion. Articles that contained information for more than one SIRS category were included for each category for which appropriate information was reported. Data were extracted from each study for each observation during the periods of interest.

The authors of included publications were contacted for additional information for any article within the past 10 years, which included values or graphs without a mean, standard error, or standard deviation (SD) from the mean. If available, this clarifying information was included in the review.

Inclusion criteria included: any study of a parturient with an uncomplicated singleton gestation from the first trimester through 12 weeks postpartum that reported maternal temperature, respiratory rate, $PaCO_2$, heart rate, white blood cell count data, or a combination of

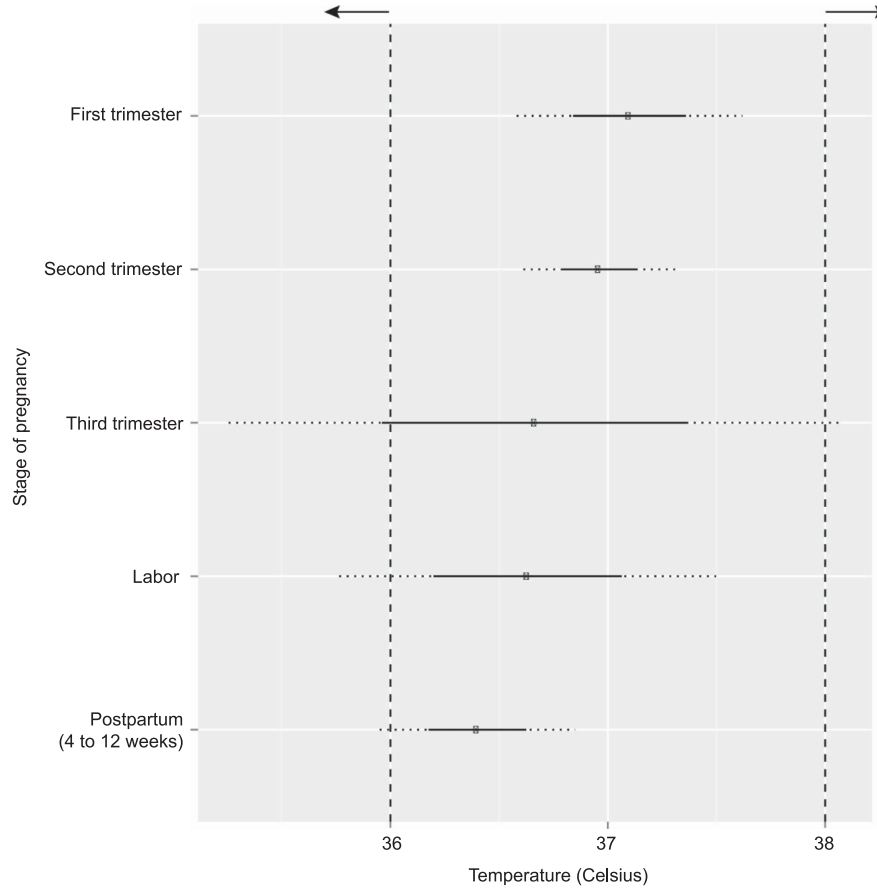

Fig. 2. Normal temperature variation during pregnancy and postpartum. Mean is indicated by the *center* of each forest plot, 1 standard deviation (SD) is indicated by a *solid line,* and a *dotted line* indicates 2 SDs from the mean. *Vertical dotted lines* indicate systemic inflammatory response syndrome criteria for each parameter.
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these. Values in randomized controlled trials were extracted from control groups and before treatment in interventional studies. Exclusion criteria included: case reports, case series, correspondence, systematic reviews, reviews, editorials, non-English language, inability to establish or demonstrate gestational age, indeterminate number of weeks postpartum, values displayed only in graphical form without numeric values listed for mean, SD from the mean, standard error, or both, $PaCO_2$ values not from arterial samples, and white blood cell count values not specified when drawn during labor. Heart rate values did not include values during active pushing and were collected for any patient position. White blood cell count increased with length of labor and cervical dilation[6,7] and was separated into two groups: white blood cell count at admission or early labor (less than 4 cm or 6 hours of labor) and late labor (greater than 4 cm or 6 hours of labor). Postpartum values for patients with a cesarean delivery were excluded as a result of a possible confounding effect on the white blood cell count in the postpartum period.[8,9] Postpartum patients were separated into two groups: the first 48 hours postpartum and 4–12 weeks postpartum (representing baseline nonpregnant values).

The inverse-weighting technique was used to obtain an aggregate measure of the mean response where the weight of an individual study mean was inversely proportional to the sampling variance of the mean in that individual study. Standard deviations were computed by pooling variances across studies. The pooled variance was computed as the weighted average of the individual study variances where the weight of an individual study was that study's sample size. All analyses were performed separately for each outcome measure (white blood cell count, temperature, etc) and for each time period (first trimester, second trimester, etc) using R 2.14.1.

RESULTS

The study selection process is described in Figure 1. The PubMed and Embase database searches yielded a total of 10,427 unique, potentially relevant studies from which 271 abstracts were selected based on inclusion criteria for further review. After abstract evaluation, 228 articles were selected for full text evaluation for inclusion. This yielded 87 articles that met criteria for data extraction. No additional studies were identified through a citation, bibliography, or

ClinicalTrials.gov search. From the selected 87 studies, there were 8,834 patients and 15,237 observations. Combined studies for temperature included 2,367 patients with 2,427 observations from 10 studies, respiratory rate included 312 patients with 887 observations from nine studies, $PaCO_2$ included 441 patients and 549 observations from 12 studies, heart rate included 1,374 patients with 3,196 observations from 39 studies, and white blood cell count included 4,553 patients with 8,178 observations from 23 studies. Six articles met criteria for more than one component of the SIRS criteria.

Results are displayed in Figures 2–5. Overlap with SIRS criteria occurred in healthy pregnant women during the second trimester, third trimester, and labor for each of the SIRS criteria except temperature. Every mean value during all trimesters, labor, and postpartum up to 48 hours for $PaCO_2$ was below 32 mm Hg. During early labor, late labor, and up to 48 hours postpartum, 2 SDs from the mean for white blood cell count was 17.5, 18.1, and 23.1×10^9/L, respectively. Two SDs from the mean for temperature, respiratory rate, and heart rate were 38.1°C, 25 breaths per minute, and 107 bpm, respectively.

Detailed information for each included study is listed in Appendices 3–7, available online at http://links.lww.com/AOG/A542.

CONCLUSION

This systematic review demonstrates that the normal range for physiologic and laboratory parameters during pregnancy and immediately postpartum substantially overlaps with SIRS criteria. For example, values for respiratory rate, $PaCO_2$, heart rate, and white blood cell count during normal pregnancy meet criteria for SIRS, thus reducing the specificity and use of those indices for diagnosing sepsis in pregnant and postpartum women.

Temperature values for healthy pregnant and postpartum women within 1 SD from the mean did not include values greater than 38°C. The highest second SD from the mean for temperature was during the third trimester at 38.1°C. There were only four eligible studies (89 observations) in this time period. These findings are consistent with the definition of puerperal fever as greater than 38°C,[10] suggesting that fever greater than 38°C persisting more than 1 hour warrants evaluation and appropriate intervention. Fever is generally present in 95–100% of cases of clinical chorioamnionitis or other uterine infections.[11]

This current study demonstrates that the SIRS criterion of $PaCO_2$ less than 32 mm Hg is not valid in pregnant or immediately postpartum women. $PaCO_2$ was less than 32 mm Hg for all stages of pregnancy up to 48 hours postpartum reflecting normal maternal physiology. The nadir value for $PaCO_2$ was during

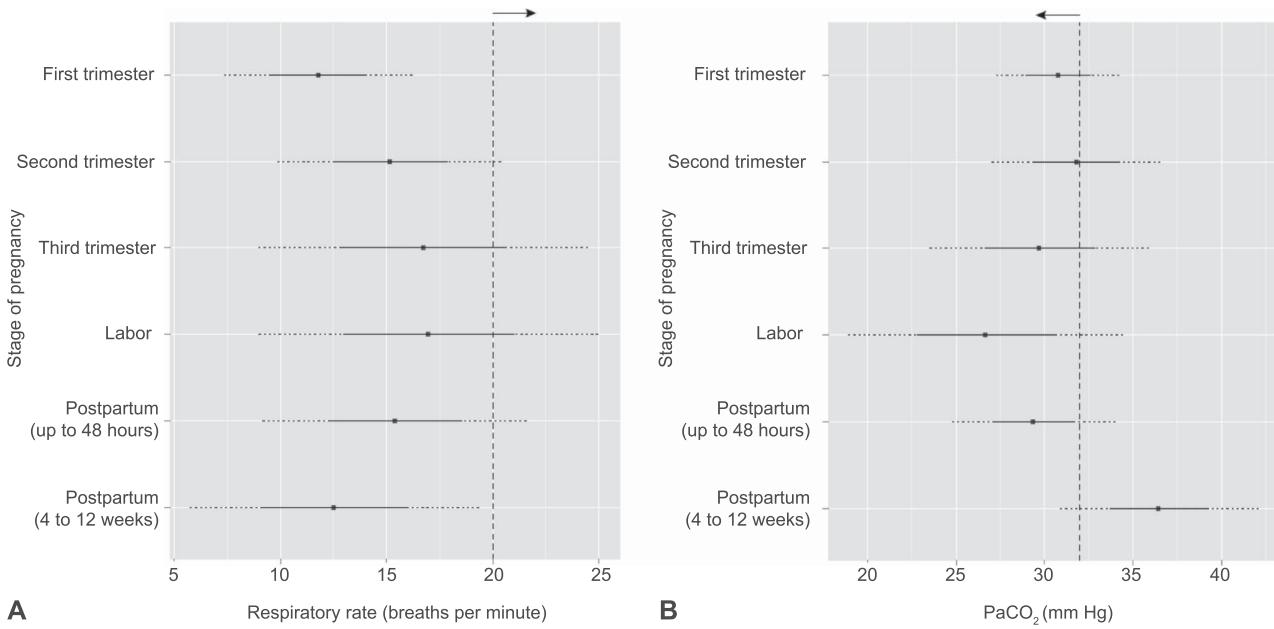

Fig. 3. Normal respiratory rate (**A**) and $PaCO_2$ (**B**) variation during pregnancy and postpartum. Mean is indicated by the *center* of each forest plot, 1 standard deviation (SD) is indicated by a *solid line,* and a *dotted line* indicates 2 SDs from the mean. *Vertical dotted lines* indicate systemic inflammatory response syndrome criteria for each parameter.

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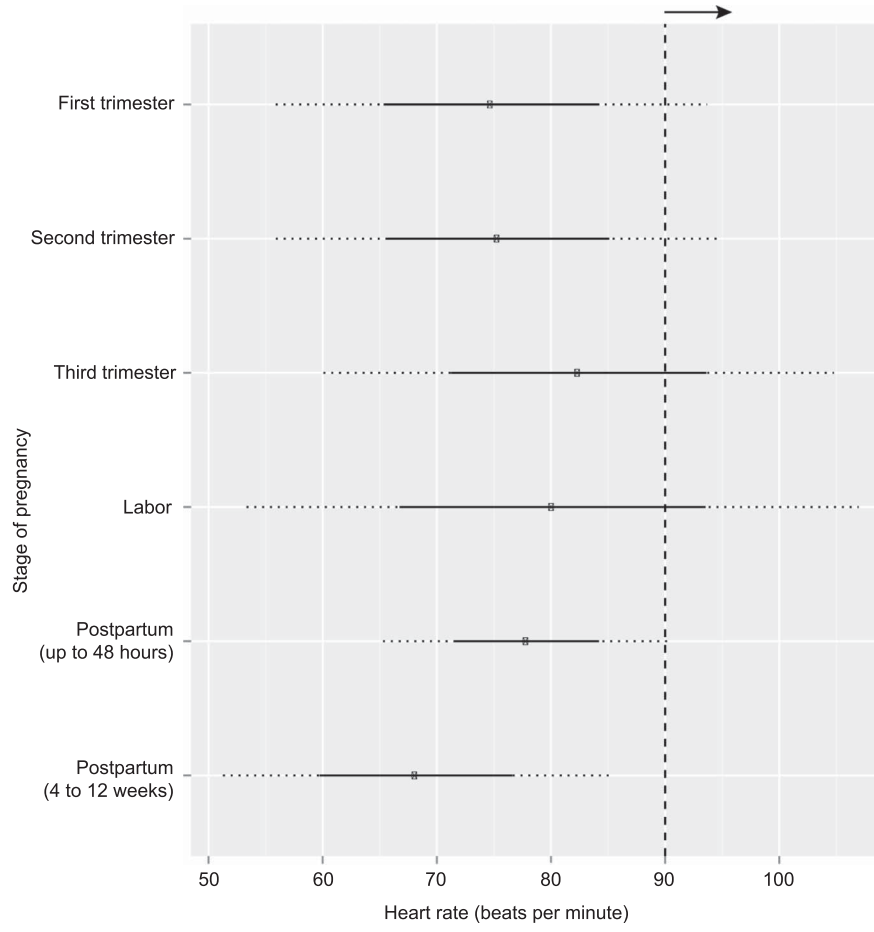

Fig. 4. Normal heart rate variation during pregnancy and postpartum. Mean is indicated by the *center* of each forest plot, 1 standard deviation (SD) is indicated by a *solid line,* and a *dotted line* indicates 2 SDs from the mean. *Vertical dotted lines* indicate systemic inflammatory response syndrome criteria for each parameter.

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labor and returned to baseline values during the 4- to 12-week postpartum period.

The highest second SD for respiratory rate occurred during labor and was 25 breaths per minute. Respiratory rate peaks during labor and returns back to baseline during the 4- to 12-week postpartum period. During the third trimester and during labor, a respiratory rate greater than 20 per minute is within 1 SD; however, by 48 hours postpartum, the respiratory rate decreases and returns back to baseline during the 4- to 12-week postpartum period. Although it appears from our data that the respiratory rate increases during gestation and labor, there is overlap between the SDs likely related to heterogeneity between studies and patients. However, our data may be limited by the small number of studies (nine) and patients (312).[12–20] A respiratory rate greater than 20 per minute indicates hyperventilation and a possible acidotic state in nonpregnant patients and tachypnea on arrival to the hospital has been found to significantly correlate with severity of sepsis in the general population.[21] Future research is required to determine whether and to what degree hyperventilation is an early marker of sepsis in pregnancy and the immediate postpartum period. Maternal heart rate values greater than 90 beats per minute were within 2 SDs for the time periods starting in the first trimester through 48 hours postpartum. Although there were 1,374 patients sampled, there was a wide range of heart rate means reported across all studies. As a result of the physiologic increase in heart rate of pregnant women, a higher threshold for heart rate may be needed to identify sepsis. A heart rate of 107 bpm was 2 SDs above the mean and lends support to the recommendations of Barton and Sibai[22] who advised a sepsis evaluation at greater than 110 bpm in pregnant women.

There are a number of limitations with respect to this study. First, there was a relative scarcity of temperature data. Our study contained only a baseline temperature at admission for labor or induction. However, temperature increases with labor and epidural analgesia.

A further limitation involves the difficulty of establishing a mean white blood cell count as a result of normal variation during labor. It has been shown that white blood cell count increases with length of time

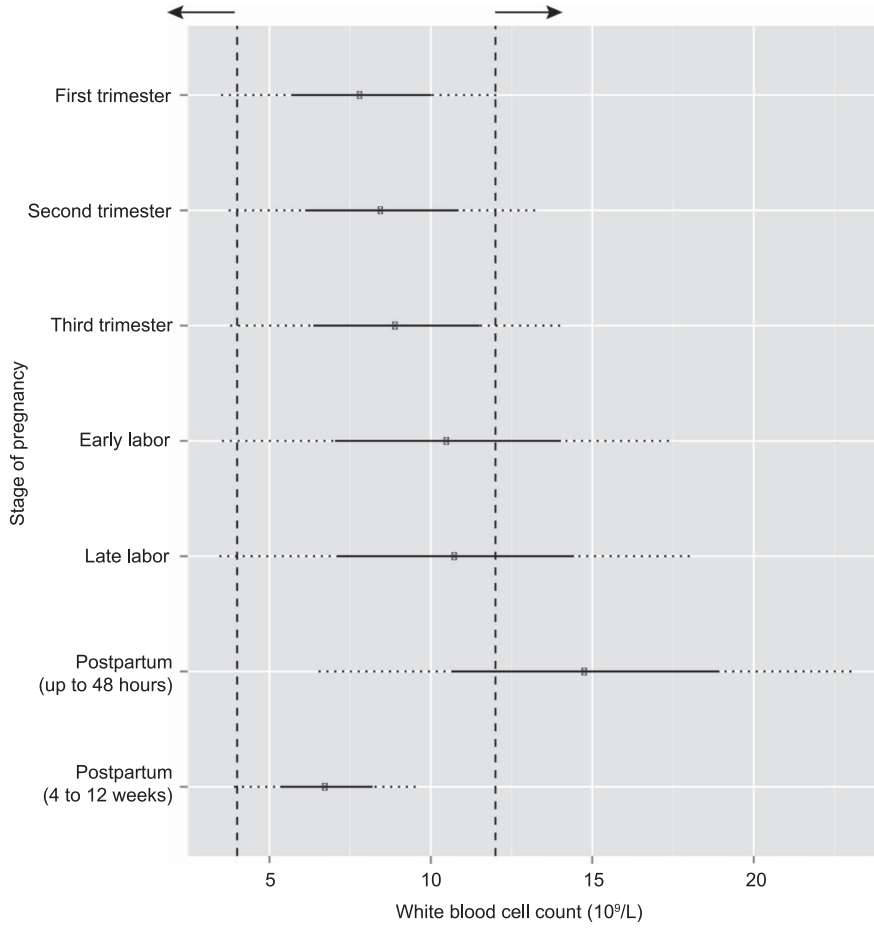

Fig. 5. Normal white blood cell count variation during pregnancy and postpartum. Mean is indicated by the *center* of each forest plot, 1 standard deviation (SD) is indicated by a *solid line*, and a *dotted line* indicates 2 SDs from the mean. *Vertical dotted lines* indicate systemic inflammatory response syndrome criteria for each parameter.
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during labor and increasing cervical dilation.[6,7] However, we were able to determine the mean, SD, and 2 SDs for early labor and late labor from available data. Our study included only postpartum white blood cell counts in women who delivered vaginally, because data on the association between cesarean delivery and postpartum white blood cell count are not consistent.[8,9] Although each patient included was categorized within the original studies as healthy or uncomplicated, we were unable to verify that postobservation complications (such as late-onset infections) did not occur. Thus, we cannot state with certainty that no abnormal pregnancy data were included. However, it is likely that such confounding was uncommon.

Another limitation of this study was that we were able to calculate only mean rather than median values. Outlying values could skew the mean value in the direction of the outliers. However, by including only healthy women, this potential was likely mitigated.

Although this is not a traditional meta-analysis, it is important to address the topics of heterogeneity and bias. A formal assessment of heterogeneity was not conducted across studies because those tests have very low power to detect heterogeneity when the number of studies is small as was the case for some of the assessed parameters. There is potential for heterogeneity between studies as a result of different types of studies and measurement techniques (Appendices 3–7, http://links.lww.com/AOG/A542). However, there is a low likelihood for significant heterogeneity because objective data were measured rather than the effect of a treatment in a traditional meta-analysis. The inverse-variance technique was also used to derive a combined estimate of the mean value for each measure or period minimizing the variance of the weighted average. Regarding bias, each study that met inclusion criteria was included. After the initial studies identifying physiologic changes of pregnancy were published, it is likely that fewer studies were published showing these changes leading to publication bias. However, the later included studies (in which the primary outcome was not evaluating physiologic changes of pregnancy but included the data of

interest) would not likely contribute to bias. Although it is possible, it does not appear likely that a study would be more or less likely to be published just because the mean value of a measure like respiratory rate is higher or lower than expected when that is not the primary outcome.

In conclusion, overlap with SIRS criteria occurred in healthy pregnant women during the second trimester, third trimester, and labor for each of the SIRS criteria except temperature. Current SIRS criteria are inadequate for women during pregnancy and the immediate postpartum period and should be redefined to help identify sepsis in this population. With significant overlap between healthy pregnant patients and SIRS criteria, it may not be possible to use the existing criteria to increase specificity without sacrificing sensitivity. Thus, novel criteria will likely be required to facilitate early diagnosis and prevent pregnancy-associated sepsis-related death.

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