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Differences in Inflammatory Markers between Nulliparous Women Admitted to Hospitals in Preactive vs Active Labor

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Differences in Inflammatory Markers Between Nulliparous Women Admitted to Hospitals in Preactive Vs Active Labor

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Objective: To determine whether labor-associated inflammatory markers differ between low-risk, nulliparous women in preactive vs active labor at hospital admission and over time.

Study Design: Prospective comparative study of low-risk, nulliparous women with spontaneous labor onset at term (n = 118) sampled from 2 large Midwestern hospitals. Circulating concentrations of inflammatory markers were measured at admission and again 2 and 4 hours later: namely, neutrophil, and monocyte counts; and serum inflammatory cytokines (interleukin -1β, interleukin-6, tumor necrosis factor-α, interleukin-10) and chemokines (interleukin-8). Biomarker concentrations and their patterns of change over time were compared between preactive (n = 63) and active (n = 55) labor admission groups using Mann-Whitney *U* tests.

Results: Concentrations of interleukin-6 and interleukin-10 in the active labor admission group were significantly higher than concentrations in the preactive labor admission group at all 3 time points. Neutrophil levels were significantly higher in the active group at 2 and 4 hours after admission. The rate of increase in neutrophils and interleukin-10 between admission and 2 hours later was faster in the active group ($P < .001$ and $P = .003$, respectively).

Conclusion: Circulating concentrations of several inflammatory biomarkers are higher and their rate of change over time since admission is faster among low-risk, nulliparous women admitted to hospitals in active labor, as compared with those admitted in preactive labor. More research is needed to determine if progressive changes in inflammatory biomarkers might be a useful adjunct to improving the assessment of labor progression and determining the optimal timing of labor admission.

Key words: cytokines; inflammation; interleukins; labor onset; nulliparity

Inflammatory events not seen before labor onset can be observed during parturition in the cervix, myometrium, and fetal membranes.[1], [2], [3], [4] and [5] Coincident with these events, maternal peripheral leukocytes (primarily neutrophils and monocytes) infiltrate the reproductive tissues, even in the absence of infection.[6], [7], [8], [9] and [10] These leukocytes are a major source of proinflammatory peptides in uterine and cervical tissues during labor, although the reproductive tissues also synthesize cytokines/chemokines (eg, interleukin [IL]-8)

that may attract additional leukocytes through chemotaxis.[8 and 11] The proinflammatory peptides most implicated in labor progression are IL-1β, IL-6, IL-8, and tumor necrosis factor (TNF)-α, which contribute to recruitment and activation of additional leukocytes, augmentation of prostaglandin production, cervical ripening and dilation, membrane rupture, and uterine contractions.[2, 6, 12, 13, 14, 15 and 16] Thus, a positive feedback loop of cytokine production by activated leukocytes in maternal and fetal tissues is at least permissive, and perhaps essential, to labor onset and progression.

Activation of the inflammatory response likely explains the marked leukocytosis commonly found in the maternal blood during physiologic labor. Serum concentrations of IL-1β,[17, 18 and 19] IL-6,[17, 18, 20, 21, 22, 23 and 24] IL-8,[17, 20 and 23] and TNF-α[25 and 26] are also significantly higher during labor than levels found *before* labor onset. Hebisch and colleagues [23] reported that IL-6 concentrations during latent labor were significantly lower than concentrations associated with established and advanced labor. Moreover, serum IL-6 and IL-8 levels were positively related to cervical dilatation,[23] and IL-6 was significantly higher with stronger and more frequent contractions, [27 and 28] which are more likely to occur during active labor. Production of antiinflammatory cytokines such as IL-10 (which is produced by almost every immune cell[29] and within reproductive tissues [30, 31, 32 and 33]) is enhanced by proinflammatory stimuli; thus, increases in serum concentrations of IL-10 are also expected with advancing labor. These findings suggest that women in earlier vs more advanced labor may be at distinctly different points in the inflammatory pathway. A better understanding of the physiologic differences between women in preactive vs active labor is important to improving birth outcomes in light of the higher rates of oxytocin augmentation and cesarean delivery rates seen in nulliparous women admitted to hospitals before active labor begins. [34, 35, 36, 37, 38 and 39] Knowledge of the progression of inflammatory processes known to be associated with efficient labor progress will advance our understanding of labor physiology and may eventually inform admission decisions and evaluation of labor progress.

In this study, we examined neutrophil and monocyte counts and serum cytokine/chemokine (IL-1β, IL-6, IL-8, TNF-α, and IL-10) concentrations in low-risk, nulliparous women at term admitted to the

American Journal of Obstetrics and Gynecology, Vol 212, No. 1 (January 2015): pg. 68.e1-68.e8. DOI.

hospital following the onset of spontaneous contractions. Our primary aim was to evaluate differences in these biomarkers at admission and at 2 and 4 hours after admission between women later determined to be admitted in preactive or active labor. We hypothesized that women admitted in active labor would have greater concentrations of inflammatory biomarkers than women admitted in preactive labor, indicating a more advanced stage of the inflammatory pathway driving labor progress. Our secondary aim was to evaluate patterns of biomarker changes over time between the preactive and active labor admission groups.

Materials and Methods

We performed a prospective comparative study at 2 large Midwestern hospitals in the United States. Institutional Review Board approval was granted, and written informed consents were obtained from all participants. Recruitment took place from March 2011 to December 2012 and was conducted by research team members in the labor and delivery triage unit or in the labor room soon after admission. All eligible women were approached for participation when a research team member was present on the unit. Approximately 70% of approached women accepted participation; we confirmed that study acceptance rates did not differ between those admitted in preactive vs active labor. The predominant rationale for declining participation was to avoid blood draws required by the study protocol.

Participants (n = 118) were nulliparous women carrying a single, cephalic presenting fetus at term (37-42 weeks' gestation) admitted by their providers for spontaneous labor onset and an anticipated vaginal delivery. Eligible women were experiencing 2 or more uterine contractions every 10 minutes as objectively determined by external monitoring or palpation at admission, were dilated no more than 6 cm at admission, and had fetal membranes that were either intact or ruptured for not more than 4 hours before admission. Additional eligibility criteria included maternal age of 18-39 years, no significant medical history, absence of major pregnancy complications (eg, preeclampsia, diabetes, oligohydramnios), absence of identified fetal complications (eg, anomalies, nonreassuring status, intrauterine growth restriction), afebrile at study entry, lack of antibiotic or

American Journal of Obstetrics and Gynecology, Vol 212, No. 1 (January 2015): pg. 68.e1-68.e8. DOI.

antiinflammatory medication use in the past 6 weeks, and ability to read and speak English. Women with preexisting conditions known to be associated with chronic, low-grade inflammation were excluded (eg, asthma, autoimmune diseases, cardiovascular disease, metabolic syndrome, type 2 diabetes, atherosclerosis, acid reflux, chronic obstructive pulmonary disease, chronic pain). Women undergoing inductions of labor were not eligible. Care during labor was at the discretion of the providers.

All digital cervical examinations by labor care providers during the course of labor were retrieved from the labor record, and the average dilation slope for the first 4 hours postadmission was determined. Because cervical examinations are rarely performed at exactly 4 hours after the admission examination, slope calculations based on the examinations immediately before and after the 4-hour time point were used to approximate dilatation at the 4-hour postadmission time point. The average dilation slope (cm/hour) for the first 4 hours postadmission was then calculated. Finally, each participant's labor admission was retrospectively classified as either preactive labor or active labor based on the rate of cervical change during the first 4 hours after admission using a priori criteria: a labor admission was classified as preactive when average dilation was <0.5 cm/hour for the first 4 hours postadmission or as active when average dilation was ≥0.5 cm/hour. This differentiation cut point was based on contemporary labor progression research,[40] and [41] which is now formally supported by the American College of Obstetricians and Gynecologists and the Society for Maternal-Fetal Medicine in their joint obstetric care consensus on the safe prevention of the primary cesarean delivery.[42] Demographic data were collected from each participant via interview; labor process, and outcome data were extracted from electronic health care records following birth.

Maternal blood was drawn at admission and 2 and 4 hours later. Blood at admission was sampled within 90 minutes of the cervical examination on which the labor admission was based; the median time to initial blood sampling was 33 minutes. Blood for neutrophil and monocyte counts was collected into ethylenediaminetetraacetic acid–containing tubes and quantified using a Sysmex XE-2100 within 30 minutes of blood collection (Sysmex America, Inc., Lincolnshire, IL). Blood for serum cytokine/chemokine determinations was collected into

American Journal of Obstetrics and Gynecology, Vol 212, No. 1 (January 2015): pg. 68.e1-68.e8. DOI.

serum separator tubes. These samples were allowed to clot for up to 30 minutes followed by centrifugation at 4° C for 10 minutes at 3000 rpm. Serum was then stored as 1.5 mL aliquots at −70° C. All serum samples from a single participant were analyzed simultaneously in duplicate. Cytokines/chemokines were assayed using Human Proinflammatory 7-Plex II Ultra-Sensitive kits measuring IL-1β, IL-6, IL-8, TNF-α, and IL-10 (Meso Scale Discovery, Rockville, MD) according to manufacturer's instructions. Assay sensitivity varies by cytokine: IL-1β = 0.58 pg/mL; IL-6 = 0.18 pg/mL; IL-8 = 0.10 pg/mL; TNF-α = 0.28 pg/mL; and IL-10 = 0.57 pg/mL.

Statistical analyses were performed using SPSS Statistics 21 (IBM Corporation, Armonk, NY) and SAS version 9.3 (SAS Institute Inc., Cary, NC). Maternal demographic characteristics and labor outcomes were compared by Mann-Whitney *U* tests for continuous variables and Fisher exact tests for categorical variables. Median neutrophil, monocyte, and cytokine/chemokine concentrations and their patterns of change over time (slope) were compared between the preactive and active labor admission groups using Mann-Whitney *U* tests with Holm's sequential Bonferroni correction. [43] Alpha level was set at .05; with Holm's approach, *P* values considered significant were sequentially determined to account for multiple testing.

Results

Maternal demographic characteristics and labor outcomes are summarized in Table 1. Of the 118 low-risk nulliparous women, 63 (53.4%) were admitted in preactive labor and 55 (46.6%) in active labor. Women in the preactive group were more racially diverse. Groups had similar dilatations at admission, although women in the preactive group had less cervical effacement. Women admitted in preactive labor received oxytocin more often than the active labor admission group (88.9% vs 43.6%, $P < .001$) and had a higher cesarean rate (17.5% vs 5.5%, $P = .040$). In-hospital labor duration was longer in the preactive admission group (12.3 vs 8.0 hours, $P < .001$).

Table 1. Characteristics and labor outcomes of nulliparous women admitted in preactive or active labor (n = 118)[a]

Description	Preactive labor (n = 63)	Active labor (n = 55)	*P* value
Maternal age, y	26.0 (20.4–32.6)	28.0 (21.0–33.4)	.243
Gestational age at admission, wk	39.6 (37.9–40.6)	39.6 (38.2–40.6)	.413
Race			
White	47 (74.6%)	49 (89.1%)	< .05
Black	13 (20.6%)	2 (3.6%)	
Other	6 (4.8%)	4 (7.3%)	
Body mass index at admission, kg/m^2	30.7 (25.0–38.2)	28.9 (24.1–36.8)	.109
Cervical dilatation at admission, cm	3.0 (1.0–4.5)	3.0 (1.5–4.7)	.123
Cervical effacement at admission[c]			
50-75%	19 (30.2%)	1 (1.8%)	< .001
≥80%	44 (69.8%)	54 (98.2%)	
Fetal station at admission	−2 (−2 to −1)	−2 (−2 to −0.6)	.227
Membrane status at admission			
Intact	36 (57.1%)	39 (70.9%)	.130
Ruptured	27 (42.9%)	16 (29.1%)	
Number of cervical examinations during labor	8 (5–11)	6 (3.6–9)	< .001
Rupture of membranes			
Spontaneous	30 (47.6%)	25 (45.5%)	.480[b]
Amniotomy	33 (52.4%)	30 (54.5%)	
Oxytocin augmentation			
No	7 (11.1%)	31 (56.4%)	< .001[b]
Yes	56 (88.9%)	24 (43.6%)	
Narcotic analgesia used	13 (20.6%)	5 (9.1%)	.123
Epidural analgesia used	62 (98.4%)	51 (92.7%)	.183
Mode of birth			
Vaginal[d]	52 (82.5%)	52 (94.5%)	.040[b]
Cesarean	11 (17.5%)	3 (5.5%)	
Indication for cesarean, n			
Dystocia (1st stage)	6	0	< .05
Arrest of fetal descent (2nd stage)	1	1	> .999
Nonreassuring fetal well-being	4	2	.684
Time from admission to complete dilation, h	10.9 (7.3–17.2)	6.0 (3.7–10.8)	< .001
Second stage duration, min	79 (30–167)	83 (30–198)	.859
In-hospital labor duration, h	12.3 (8.3–19.3)	8.0 (4.6–12.1)	< .001
Maximum temperature during labor >100.4° F	5 (7.9%)	3 (5.5%)	.722
Infant sex			
Female	31 (49.2%)	33 (60.0%)	.270
Male	32 (50.8%)	22 (40.0%)	
Weight (infant), g	3404 (2749–3909)	3386 (2807–3812)	.285
Apgar scores			
<8 at 1 min	9 (14.3%)	3 (5.5%)	.134

American Journal of Obstetrics and Gynecology, Vol 212, No. 1 (January 2015): pg. 68.e1-68.e8. DOI.

Description	Preactive labor (n = 63)	Active labor (n = 55)	*P* value
<8 at 5 min	1 (1.6%)	2 (3.6%)	.600
Neonatal admission to NICU	3 (4.8%)	1 (1.8%)	.622

NICU, neonatal intensive care unit; *ROM*, rupture of membranes.
Neal. Inflammatory markers during preactive and active labor. Am J Obstet Gynecol 2015.
[a]Data are *n* (%) and median (10th, 90th percentile). Mann-Whitney *U* tests performed for continuous level data comparisons because of violations of normality. Fisher exact tests (2-tailed) performed for categorical level data comparisons, unless otherwise specified
[b]Fisher exact test (1-tailed) performed as test of directional hypothesis that women admitted in preactive labor are more prone to the intervention, as compared with women admitted in active labor
[c]Although percent effacement was not an inclusion/exclusion criterion, no woman was <50% effaced at admission
[d]Includes assisted vaginal births (ie, vacuum or forceps), of which there were 6 and 3, respectively, in the preactive and active labor admission groups.

Median concentrations of IL-6 and IL-10 were significantly higher among women admitted in active labor at all 3 sampling points while neutrophil concentrations were higher at 2 and 4 hours after admission with a trend toward significance at the admission time point (Table 2). There were no between group differences in monocyte, IL-1β, IL-8, or TNF-α concentrations at any time point.

Table 2. Comparisons of inflammatory markers between nulliparous women admitted in preactive or active labor (n = 118)

Descriptions	Variable	Preactive labor (n = 63)		Active labor (n = 55)		*P* value
		n	Median (range)	n	Median (range)	
Neutrophils	Admission	61	9.28 (4.07–19.51)	55	10.76 (6.02–20.04)	.030
	+2 hr	54	9.63 (3.83–22.73)	51	12.00 (7.23–23.11)	< .001[a]
	+4 hr	49	10.54 (4.69–23.15)	46	12.91 (7.82–23.31)	< .001[a]
Monocytes	Admission	61	0.75 (0.30–2.31)	55	0.72 (0.38–1.82)	.866
	+2 hr	54	0.71 (0.12–1.35)	51	0.69 (0.22–1.63)	.850
	+4 hr	49	0.70 (0.34–1.26)	46	0.64 (0.34–1.38)	.826
IL-1β	Admission	63	0.51 (0.00–10.61)	55	0.58 (0.00–3.32)	.352
	+2 hr	58	0.49 (0.00–4.01)	53	0.50 (0.00–3.10)	.906
	+4 hr	56	0.48 (0.00–4.50)	49	0.50 (0.00–2.87)	.916
IL-6	Admission	63	2.9 (0.8–63.9)	55	5.1 (1.4–30.8)	.002[a]
	+2 hr	58	3.6 (1.3–26.7)	53	6.9 (1.9–39.4)	< .001[a]
	+4 hr	56	5.2 (1.7–86.2)	49	9.9 (2.3–46.8)	< .001[a]
IL-8	Admission	63	5.7 (1.2–16.6)	55	5.5 (1.8–96.5)	.728
	+2 hr	58	5.8 (2.1–17.2)	53	5.7 (2.1–27.7)	.468
	+4 hr	56	6.3 (1.9–14.6)	49	5.3 (1.9–16.3)	.318

American Journal of Obstetrics and Gynecology, Vol 212, No. 1 (January 2015): pg. 68.e1-68.e8. DOI.

Descriptions	Variable	Preactive labor (n = 63)		Active labor (n = 55)		*P* value
		n	Median (range)	n	Median (range)	
TNF-α	Admission	63	6.8 (1.9–34.7)	55	6.8 (1.9–25.8)	.861
	+2 hr	58	7.2 (2.4–33.3)	53	6.5 (1.8–25.2)	.189
	+4 hr	56	7.7 (2.6–33.4)	49	6.1 (1.6–27.1)	.191
IL-10	Admission	63	3.6 (0.4–78.5)	55	5.2 (0.6–70.5)	.003[a]
	+2 hr	57	3.6 (0.7–27.9)	53	7.3 (1.6–132.8)	< .001[a]
	+4 hr	55	3.4 (0.7–28.6)	49	6.8 (0.7–70.5)	.001[a]

Median (range). Mann-Whitney *U* tests. Leukocytes (absolute) × 1000/μL. Cytokines in pg/mL. The number of research participants sampled for blood at each biomarker collection time point varies because blood was collected only if the woman was still in labor at the sampling time point and because a few sampling time points were inadvertently missed by research team members. Holm's sequential rejective multiple test procedure was applied to sequentially determine significant *P* values, ie, for 21 tests, the most significant *P* value must be smaller than 0.05/21 = 0.0024, the second most significant *P* value must be smaller than 0.05/20 = 0.0025, the third most significant *P* value must be smaller than 0.05/19 = 0.0026, etc.
IL, interleukin; *TNF*, tumor necrosis factor.
Neal. Inflammatory markers during preactive and active labor. Am J Obstet Gynecol 2015.
[a]Significant *P* value after applying Holm's sequential rejective multiple test procedure.

Inflammatory biomarker changes over time compared between the preactive and active labor groups are shown in Figure 1. The magnitude of changes in neutrophil counts and IL-10 concentrations between admission and 2 hours were significantly different between the groups, ie, slopes were more precipitous in the active group. IL-6 slope differences trended toward significance between the groups from admission to admission$_{+2\ hrs}$ and from admission$_{+2\ hrs}$ to admission$_{+4\ hrs}$ and IL-1β slopes trended toward significance from admission to admission$_{+2\ hrs}$. There were no slope differences for monocytes, IL-8, or TNF-α (not shown).

American Journal of Obstetrics and Gynecology, Vol 212, No. 1 (January 2015): pg. 68.e1-68.e8. DOI.

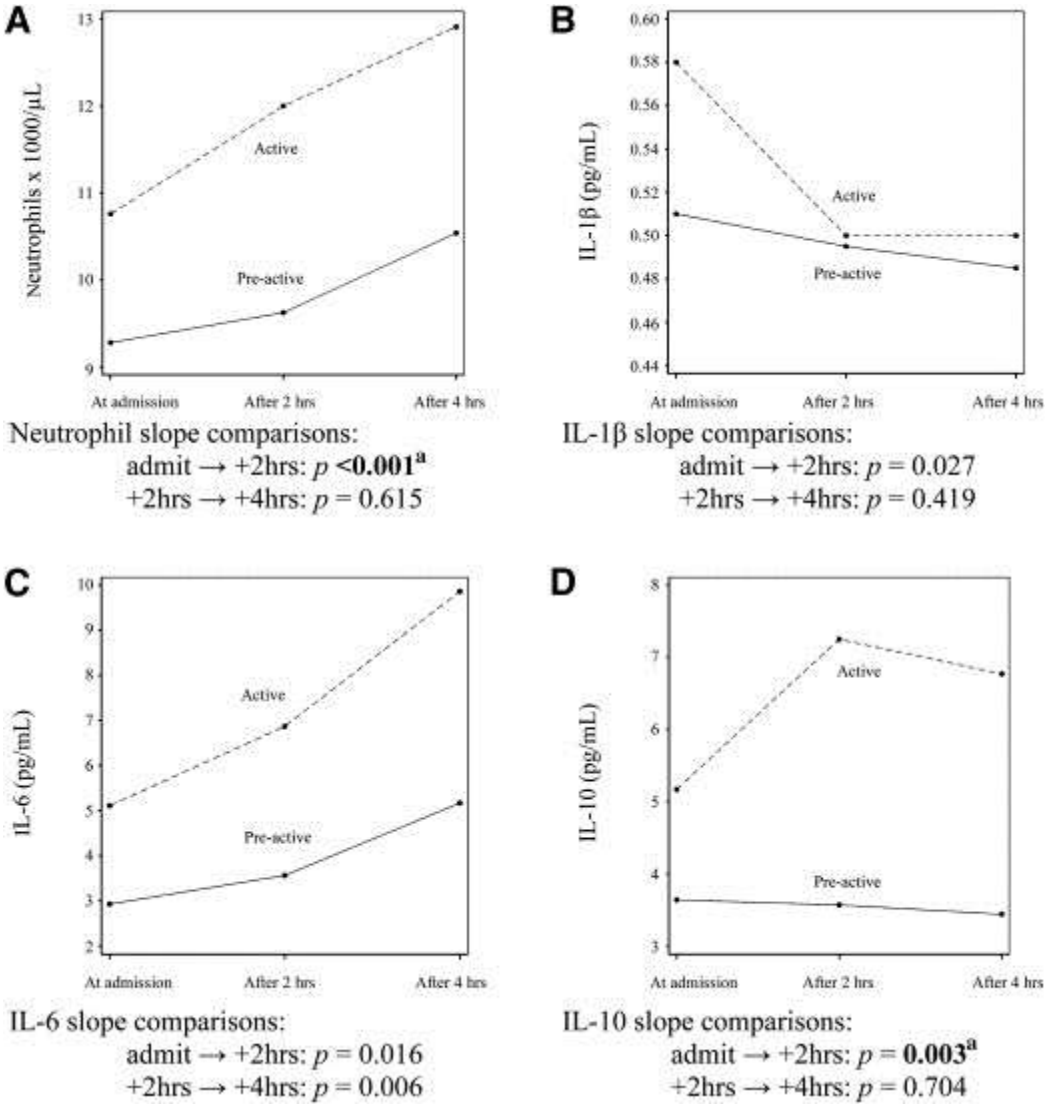

Figure. Comparisons of inflammatory biomarkers in the maternal circulation over time between low-risk nulliparous women admitted in preactive or active labor
Mann-Whitney *U* tests. Analyses based on magnitude of biomarker change (slope) between admission → admission$_{+2\ hrs}$ (ie, biomarker$_{Admission+2\ hrs}$ – biomarker$_{Admission}$) and admission$_{+2\ hrs}$ → admission$_{+4\ hrs}$ (ie, biomarker$_{Admission+4\ hrs}$ – biomarker$_{Admission+2\ hrs}$). Two comparisons (ie, admit → +2 hrs and +2 hrs → +4 hrs) were made between groups for each of the 7 biomarkers measured (monocytes, IL-8, or TNF-α not shown). Holm's sequential rejective multiple test procedure was applied to sequentially determine significant *P* values, ie, for 14 tests, the most significant *P* value must be smaller than 0.05/14 = .0036, the second most significant *P* value must be smaller than 0.05/13 = .0038, the third most significant *P* value must be smaller than 0.05/12 = .0042, etc.
[a] Significant *P* value after applying Holm's sequential rejective multiple test procedure.
Neal. Inflammatory markers during preactive and active labor. Am J Obstet Gynecol 2015.

American Journal of Obstetrics and Gynecology, Vol 212, No. 1 (January 2015): pg. 68.e1-68.e8. DOI.

Comment

Our findings demonstrate physiologic differences in inflammatory markers between women admitted to hospitals in preactive and active labor. We found that neutrophils, IL-6, and IL-10 were in greater concentrations among low-risk, nulliparous women admitted in active labor as compared with women in preactive labor, as measured at independent time points and/or by the magnitude of biomarker change over time during labor. This provides additional evidence that inflammation is involved in the initiation and propagation of term labor with a spontaneous onset, with actively laboring women perhaps being at a more advanced stage in the labor-related inflammatory pathway.

We also found that nulliparous women admitted in active labor received less intervention and were more likely to achieve vaginal birth than laboring women admitted in preactive labor. This finding is supported by prior reports that women admitted earlier (eg, <4 cm dilatation) are approximately twice as likely to be augmented with oxytocin[34, 35, 38 and 39] and delivered via cesarean,[34, 35, 36, 37, 38 and 39] when compared with women admitted later in labor. Unfortunately, true active labor can only be determined retrospectively based on an assessment of cervical dilation over time. The criteria traditionally taken as evidence of active labor onset—dilatation between 3 cm and 5 cm, in the presence of uterine contractions—have not proven to be reliable.[44] Thus, a large percentage of nulliparous women may be admitted to hospitals before active labor onset, as suggested by the findings of our study. While it is possible that women who present earlier in labor may have an inherently higher risk of labor dystocia (ie, slow or difficult labor or delivery) at baseline,[34] this explanation does not adequately explain why more than half of our sample was admitted prior to the onset of active labor. Our preactive and active labor admission groups did not differ on the number of labor evaluation triage visits before admission or cervical dilatation at admission. Clearly, more reliable metrics for determination of active labor onset are needed.

Our finding that the preactive labor admission group had less cervical effacement than the active group at admission, despite

American Journal of Obstetrics and Gynecology, Vol 212, No. 1 (January 2015): pg. 68.e1-68.e8. DOI.

sharing a similar dilatation, warrants discussion. Ninety-eight percent of the women admitted in active labor had cervices that were ≥80% effaced compared with 70% among women in the preactive group ($P < .001$). This alone indicates that degree of cervical effacement must be carefully considered by clinicians making admission decisions because our group and others have found that women in active labor typically have advanced effacement. [34], [39] and [45] In light of the difference in cervical effacement at admission between our study groups, we performed post hoc analyses to determine whether inflammatory biomarker differences between the groups persisted after all women with admission effacement <80% were excluded. For these analyses, the preactive and active groups were comprised of 44 and 54 women, respectively; biomarker concentrations were compared between the groups using Mann-Whitney *U* tests and *P* values < .05 were considered significant. Interestingly, median concentrations of IL-10 remained significantly higher among women admitted in active labor at all 3 sampling points ($P = .005$ at admission; $P < .001$ at admission$_{+2\ hrs}$; $P = .001$ at admission$_{+4\ hrs}$) while IL-6 and neutrophil concentrations remained higher at 2 and 4 hours after admission (for IL-6, $P = .006$ and $P = .015$ at admission$_{+2\ hrs}$ and admission$_{+4\ hrs}$, respectively; for neutrophils, $P = .001$ and $P = .003$ at admission$_{+2\ hrs}$ and admission$_{+4\ hrs}$, respectively). Indeed, of the inflammatory biomarkers that significantly differed between the preactive and active groups before excluding women with effacement <80% at admission, only the difference in IL-6 concentrations at the admission time point was no longer significant after excluding the lessor effaced women ($P = .055$). Thus, although it is reasonable to delay admission for presumed active labor until cervical effacement is complete or near complete, inflammatory biomarker differences between women in preactive and active labor remain evident even when only women with advanced effacement are evaluated.

The American College of Obstetricians and Gynecologists and the Society for Maternal-Fetal Medicine recently endorsed the idea that standards for active phase progress should not be applied before 6 cm dilatation,[42] a consensus based primarily on labor progress work conducted by Zhang and colleagues using Consortium on Safe Labor data.[40] A shortcoming of this approach is that a single dilatation point does not adequately discriminate preactive from active labor for an individual,[39] ie, some women may not be in active labor at 6 cm

American Journal of Obstetrics and Gynecology, Vol 212, No. 1 (January 2015): pg. 68.e1-68.e8. DOI.

whereas many women may be in active labor before 6 cm, as shown in the present study. Moreover, because half of nulliparous women progress from 6 cm to complete dilatation in 3 hours or less,[40] it may not be reasonable to delay admission until 6 cm since doing so may result in a large percentage of women missing their window of opportunity for the care they desire (eg, epidural analgesia and the possibility to acclimate to the birth environment) or undesired out-of-hospital birth. An even greater percentage of multiparous women would be affected by delaying admission until 6 cm since these women generally have more rapid active labors.[40] Therefore, even before 6 cm, clinicians should carefully consider who they admit for labor based on an evaluation of cervical change over time rather than a single integer dilatation point.

Based on additional post hoc findings, consideration should be given to the possibility that many of the women in the preactive labor admission group were only a few hours behind the active group in terms of the physiologic labor pathway. The majority of women admitted in preactive labor in our study achieved dilation rates above 0.5 cm/hour once beyond the first 4 hours after admission (n = 49 of 63). Although this could reflect the more frequent use of oxytocin augmentation in the preactive admission group, an escalation in particular inflammatory biomarker concentrations was also observed in the preactive admission group which, by 4 hours postadmission, reached levels similar to those observed in the active group at admission. Specifically, there were no significant differences between neutrophils or IL-6 when the preactive labor group values at admission$_{+4\ hrs}$ were compared with the active labor group concentrations at admission (neutrophils 10.54 and 10.76 ×1000 cells/μL (P = .999) and IL-6 5.2 and 5.1 pg/mL (P = .333), respectively). Thus, delaying admissions for women in nonprogressive labor may allow time for inflammatory changes important to efficient labor progress to more fully manifest. This may decrease the need for subsequent intervention aimed at accelerating labor progress and improve vaginal birth rates whereas also decreasing the woman's time on the labor unit before progressive labor begins.

Our study included biologic samples collected during labor from a sample of low-risk, nulliparous women with spontaneous labor onset at term. The study had a few limitations that warrant mention. Firstly,

American Journal of Obstetrics and Gynecology, Vol 212, No. 1 (January 2015): pg. 68.e1-68.e8. DOI.

common interventions that may affect rates of dilation (ie, oxytocin, amniotomy, epidural analgesia) were received by many women within the first 4 hours after admission, before labor state was determined (ie, preactive or active). Secondly, although the percentage of women admitted with already ruptured membranes did not differ between the preactive and active groups, eliminating these women would have yielded a cleaner, but less generalizable, sample. Finally, our measurement of cytokine concentrations in the maternal serum may not adequately reflect the cytokine-producing potential of immune cells because of the short half-lives of cytokines and the presence of various inhibitors in human sera. We recommend that this study be repeated in a more racially diverse sample that includes primiparous and multiparous women and, perhaps, with the addition of more frequent blood collection time points. Furthermore, because we speculate that differences and rate of change in biomarkers of inflammation may enhance our ability to accurately diagnose the onset of active labor in the future, we recommend that possible predictive models be developed and rigorously evaluated in subsequent research studies.

In the present study, we found that circulating biomarkers of inflammation differ between women admitted to hospitals in preactive and active labor, suggesting that women in active labor have greater activation of the labor inflammatory pathway contributing to labor progress. Delaying admission of laboring women in preactive labor may allow time for inflammatory events important to efficient labor progress to more fully develop.

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