

Running Head: DIFFERENCES IN 'ACTIVE' AND 'PRE-ACTIVE' LABOR GROUPS

DIFFERENCES IN INFLAMMATION, INTERVENTION RATES, AND BIRTH
OUTCOMES IN 'ACTIVE' AND 'PRE-ACTIVE' LABOR ADMISSION GROUPS

UNDERGRADUATE HONORS THESIS

Presented in Partial Fulfillment of the Requirements for the
College of Nursing Honors Program, The Ohio State University

By

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The Ohio State University
2011

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I. INTRODUCTION

Identifying when a nulliparous woman enters active labor is difficult because labor does not readily lend itself to measurement and evaluating its progression is based upon crude estimates of cervical dilatation. There have been many attempts to define active labor onset. Active labor is commonly defined to begin at 3-5 cm + regular uterine contractions (Battista & Wing, 2007; Cunningham, Leveno, Bloom, Hauth, Rouse, Spong, 2010; Varney et al., 2004), however, a substantial number of nulliparous women admitted according to these criteria do not progress at dilatation rates indicative of active labor (Peisner & Rosen, 1986). Therefore, many women presumed to be in active labor may, in fact, not be. 'Pre-active' labor admissions become troubling for nulliparous women when they are still held to the labor progression standards of women in active labor. The likely result is increased intervention rates such as more cervical examinations, amniotomy, and oxytocin augmentation rates. Labor outcomes may also be poorer among women admitted prior to active labor.

Evidence suggests that inflammation is a driving force in the progression of labor. Inflammatory markers are present in increasing quantities in the uteri of laboring women as well as in their peripheral blood (Norman, Bollapragada, Yuan, & Nelson, 2007; Osman et al., 2003; Thomson et al., 1999; Tornblom et al., 2005). When nulliparous women are admitted for spontaneous labor onset prior to active labor and followed by interventions aimed at accelerating labor (e.g., oxytocin augmentation), the acute, feed-forward, inflammatory processes that drive labor may be interrupted. This may disrupt the optimal manifestation of physiological processes important to efficient labor progression and contribute to less than optimal birth outcomes.

The purpose of this study was to determine what percentage of low-risk, nulliparous women were admitted prior to active phase onset and to compare 'pre-active' and 'active' labor

groups on differences in specific inflammatory markers, rates of labor interventions, and rates of labor outcomes.

II. REVIEW OF LITERATURE

Labor is “the presence of uterine contractions of sufficient frequency, duration, and intensity to cause demonstrable effacement and dilation of the cervix” (ACOG, 2003). It is a continuum that culminates in birth. For clinical and academic purposes, the labor continuum is divided into several stages and phases (see Figure 1). The *first stage of labor* encompasses the time from the onset of regular, painful uterine contractions, through complete cervical dilatation. The *first stage* is further divided into two phases, i.e., *latent* and *active*. The *latent phase* is defined as the onset of regular, painful uterine contractions (O'Driscoll, Foley, & MacDonald, 1984) and extends to the point when cervical dilation becomes more rapid. The *active phase* begins when cervical dilation becomes more rapid and ends with complete cervical dilatation (ACOG, 2003; Cunningham et al., 2010; Friedman, 1954, 1955, 1978; Varney, Kriebs, & Gegor, 2004). The *active phase* has been suggested to reliably begin between 3 cm and 5 cm, in the presence of uterine contractions (Battista & Wing, 2007; Cunningham et al., 2010; Varney et al., 2004). This is, generally, when women in the U.S. are admitted to labor units.

Correctly establishing that a parturient is in 'active' labor is of utmost importance because it serves as the basis for identifying slow cervical dilation that might require accelerative intervention. Unfortunately, truly active labor can never be diagnosed prospectively; rather, active labor can only be determined retrospectively based on an assessment of adequate cervical change over time (cm/hr). For example, a woman admitted for labor at 4 cm dilatation is typically only known to be *actively* or *not actively* dilating hours later based on subsequent cervical examinations. The reality in clinical practice is that laboring women are typically admitted to labor units under criteria commonly associated with 'active' phase labor, e.g., 3-5 cm + regular uterine contractions. However, these criteria do not validly describe active labor onset for an appreciable percentage of laboring women. Peisner and Rosen (1986) report that 75%, 50%, and 25% of regularly contracting, low-risk, nulliparous women admitted for spontaneous labor (n = 1060) *do not* dilate at rates indicative of active labor at 3, 4, and 5 cm,

respectively. More recent studies also indicate that the transition from latent to active labor may not be identifiable (Suzuki, Horiuchi, & Ohtsu, 2010; Zhang, Troendle, & Yancey, 2002; Zhang et al., 2010; Zhang et al., 2010). For example, Zhang et al. (2010) evaluated contemporary labor data and found no clearly identifiable inflection point in the average labor curve of nulliparous women ($n = 27,170$). This undistinguishable transition makes it much more difficult to correctly identify nulliparous women in active labor. The clinical dilemma is that many women may be inadvertently admitted prior to progressive labor yet held to dilation expectations of active labor. For these women, active labor will be perceived to be longer and rates of dilation will seemingly be slower.

The timing of admission for childbirth influences the outcomes of labor. When made in error, diagnoses of 'active' labor lead to the overuse of risk-bearing interventions aimed at accelerating dilation and as well as to poorer birth outcomes. For example, low-risk, nulliparous women admitted too early are approximately twice as likely to be augmented with oxytocin (Bailit, Dierker, Blanchard, & Mercer, 2005; Holmes, Oppenheimer, & Wen, 2001; McNiven, Williams, Hodnett, Kaufman, & Hannah, 1998). This is concerning because oxytocin is the drug most commonly associated with preventable adverse perinatal outcomes (Clark, Simpson, Knox, & Garite, 2009). Moreover, early oxytocin may derail important acute, labor-associated inflammatory processes. Additionally, women admitted early spend more time in the labor unit (weighted mean difference = 5.20 hrs; $p = 0.001$), are more likely to request epidurals [OR 0.40 (95% CI: 0.18-0.90); $p = 0.023$], and report lower levels of sense of control during labor (McNiven et al., 1998).

Regarding cesarean risk, admission of women to labor units after the spontaneous onset of labor contractions but prior to 'active' labor onset increases low-risk, nulliparous cesarean rates by 2.1- to 2.7-fold (see Table 1) (Bailit et al., 2005; Holmes et al., 2001; Impey, Hobson, & O'Herlihy, 2000; Main et al., 2006; Mikolajczyk, Zhang, Chan, & Grewal, 2008; Rahnama, Ziaei, & Faghihzadeh, 2006). Moreover, cesarean rates for slow labor progress (i.e., dystocia) were

significantly higher in the early admission groups in both studies that reported specific surgical indications ($p < 0.001$) (Bailit et al., 2005; Rahnama et al., 2006). These findings corroborate those from a large, multi-institutional study (20 birthing units) of term, nulliparas carrying singleton, vertex fetuses ($n = 41,416$) wherein the cesarean delivery rate was found to be significantly associated with labor admissions occurring at < 3 cm dilatation ($r = 0.62$; $r^2 = 0.38$; $p < 0.0001$) (Main et al., 2006). Furthermore, a recent study reported that before 4 cm dilatation, the earlier a woman was admitted for labor is *linearly* related to her risk of cesarean delivery (Mikolajczyk et al., 2008). These findings regarding cesarean risk are telling, considering that cesarean rates among low-risk, nulliparous women are reportedly reliable indicators of obstetrical care quality, with higher rates indicating poorer care (Cleary et al., 1996; Main, Bloomfield, & Hunt G, 2004; Main et al., 2006).

Increasing evidence suggests that the labor continuum is mediated by acute inflammatory events that begin just prior to labor onset. It has been demonstrated that inflammatory cells, leukocytes in particular, infiltrate the myometrium of the uterus and cervix during the labor process, and are responsible for initiating and propagating cervical ripening and uterine contractions. In a study by Thomson et al. (1999), it was revealed that myometrial biopsies from women in labor (cervical dilatation >4 cm and <9 cm) at term showed a marked inflammatory infiltrate in 17 of 18 specimens of muscle connective tissue, unlike the biopsies from women who were not in labor. Additionally, under closer analysis of individual cell types using immunocytochemistry, it was found that there were significantly more inflammatory cells present in laboring versus non-laboring myometrial biopsies ($p = 0.0001$), particularly in the lower uterine segment (Thomson et al., 1999). Osman et al. (2003) obtained biopsies from women who delivered at term by lower segment caesarean section, either during spontaneous labor or prior to the onset of labor, to examine for inflammatory cell content. Women were considered to be in spontaneous labor if cervical dilatation was between 4 and 8 cm. In the cervix, the total leukocyte, macrophage, and neutrophil densities were all found to be

significantly greater in laboring versus non-laboring women ($p < 0.04$, $p < 0.02$, $p < 0.001$ respectively).

Acute inflammatory events are also evident in the peripheral blood of women in active labor that are not seen before the onset of labor. Törnblom et al. (2005) compared venous white blood cell counts between laboring and non-laboring women. Leukocyte counts were found to be non-significantly higher in term, laboring women ($n=14$) (median $15.65 \times 10^3/\text{ul}$) than in non-laboring women ($n=11$) (median $10.0 \times 10^3/\text{ul}$) ($p > 0.05$). Similarly, preliminary studies by Norman, Bollapragada, Yuan, & Nelson (2007) revealed that chemotaxis of peripheral blood leukocytes is greater in women whom are in labor compared to those not in labor. Although neither of these studies reached statistical significance, likely due to small sample sizes, the trends toward significance provide a rationale for investigating if leukocyte concentrations assist in predicting active labor.

In summary, it is possible that criteria prospectively applied as evidence of active phase onset are not reliable. Therefore, many laboring women may be admitted prior to active labor onset. This is problematic because admissions for spontaneous labor onset occurring *prior to* 'active' labor followed by interventions to accelerate labor (e.g., oxytocin use) may interrupt acute, feed-forward inflammatory processes necessary for the optimal progression of labor. This may compromise important labor outcomes.

III. METHODS

This secondary analysis intended to accomplish the three following specific aims: (1) to determine what percentage of low-risk, nulliparous women are admitted prior to active phase onset using criteria commonly applied as prospective evidence of active phase onset; (2) to compare specific inflammatory markers (i.e. WBCs, admission temperature) between those admitted in 'active' versus 'pre-active' labor; (3) Compare women admitted in 'active' versus 'pre-active' labor on rates of labor interventions (e.g. cervical examinations, amniotomy, oxytocin augmentation) and labor outcomes (e.g. duration of in-hospital labor time, neonatal Apgar scores, mode of delivery).

It was hypothesized that greater than 25% of low-risk women with spontaneous labor onset were admitted prior to 'active' labor onset. Furthermore, those admitted in 'pre-active' would have lesser inflammatory preparedness for labor and would receive more labor interventions and have more adverse labor outcomes as compared to those admitted in 'active' labor.

Conceptual Framework

The conceptual framework guiding the proposed study asserts that when providers admit parturients to the labor unit during active dilation, physiological phenomenon important to successful parturition will have had more time to more fully manifest leading to more efficient labor, less labor intervention, and more optimal labor outcomes. Conversely, admittances prior to active dilation will be measurably less prepared for labor with more adverse outcomes (See Figure 2).

Design

This study used a prospective, comparative design in which women admitted for labor in 'pre-active' labor (i.e., <0.5 cm/hr for the first 4 hours post-admission) were compared to those

admitted in active labor (i.e., ≥ 0.5 cm/hr for the first 4 hours post-admission) on the following parameters: inflammatory biomarkers [i.e., white blood cells (WBCs); temperature at admission]; labor process interventions (i.e., number of cervical examinations during labor; frequency of oxytocin augmentation; frequency of amniotomy); and labor outcomes [i.e., 'in-hospital' labor duration, Apgar scores, mode of delivery (underpowered variable)].

Participants

This was a study of 93 nulliparous women of low obstetric risk (no significant medical history, absence of major complication of pregnancy, e.g., pre-eclampsia or diabetes) admitted for spontaneous labor onset under criteria commonly associated with active labor onset, i.e., 3 cm to 5 cm cervical dilatation in the presence of regular uterine contractions (≥ 2 in a 10 minute window). Additional inclusion criteria were 18-39 years of age, 37- 42 weeks gestation (259-294 days), singleton gestation, cephalic presentation, no identified fetal anomalies or growth issues, anticipated vaginal delivery, maternal weight < 250 lbs (< 114 kg) at study entry, afebrile at study entry, and able to read and speak English. Augmentation of labor was permitted after the labor admission although women undergoing labor inductions were not permitted study entry. Care during labor was at the discretion of the labor care provider.

Sample Size Justification

To test for differences between pre-active and active labor admission groups, Student's t tests and Chi-square analyses were performed, as appropriate. For t test analyses, 45 subjects per group were required when considering a medium-large effect size (0.60), alpha (α) of 0.05, and power of 0.80 (Cohen, 1988). For Chi-square analyses, 87 subjects were required when considering a medium effect size (0.60), alpha (α) of 0.05, and power of 0.80 (Cohen, 1988). Thus, a total minimum sample size of 90 women with complete data was the goal for the initial

prospective study. Ultimately, 93 subjects were enrolled.

Setting

This study was conducted at a suburban, academic, Midwestern medical care center in which nearly 5000 women deliver annually. Recruitment occurred between 4/2007 and 2/2008.

Human Subjects

Institutional Review Board (IRB) approval was obtained by the investigators of the primary study. Written, informed and HIPAA consents were obtained from all women.

Procedure

Low-risk, nulliparous women who were admitted for spontaneous labor onset under criteria commonly associated with active labor onset, i.e., 3 cm to 5 cm cervical dilatation in the presence of regular uterine contractions, were approached for consent. Recruitment primarily occurred in the labor and delivery triage unit or in the labor room as soon after admission as possible. In the primary study, maternal WBC concentrations were measured in maternal sera as near to the time of labor admission as logistically possible with most sampling occurring concurrently with intravenous line placement, a standard order in the facility. Samples not collected during intravenous site placement were collected via either a 20- or 22-gauge needle from the antecubital vein or below in the uncannulated arm. Each sample was collected into an ethylenediaminetetraacetic acid (EDTA)-containing tubes. Hemolyzed samples were redrawn at the admission time point if labor had not progressed beyond the aforementioned labor onset criteria. Tympanic temperature was measured at the admission time point.

Variables

Classification of Labor

Active versus non-active cervical dilation can only be determined retrospectively, never prospectively; thus, labor classification for this study must also be determined retrospectively. To accomplish this, *all* digital cervical exams performed by labor care providers during the course of labor were transcribed *post hoc* from the labor record onto study data collection forms exclusively by the PI. *A priori* criteria, based on established criteria (Society of Obstetricians and Gynaecologists of Canada, 1995) and several reports (Neal et al., 2010; Neal, Lowe, Patrick, Cabbage, & Corwin, 2010; Suzuki et al., 2010; World Health Organization, 1994; Zhang et al., 2002; Zhang et al., 2010) were used to categorize each labor admission based on *average* cervical dilation occurring over the first 4 hrs after the digital cervical exam on which the admission was based, i.e., < 0.5 cm/hr or ≥ 0.5 cm/hr. Dilation rates were reported to the tenths position with upward rounding if the digit in the hundredths position was ≥ 5 , e.g., a dilation rate of 0.45 cm/hr would round to 0.5 cm/hr and the labor classified in the ≥ 0.5 cm/hr group. Since cervical exams were rarely performed at exactly 4 hrs after the admission exam, slope calculations based on the exams immediately *prior to* and *after* the 4 hr time point were used to approximate dilatation at the 4 hr post-admission time point. The average dilation slope could then be calculated for the first 4 hrs post-admission and the labor classified. This technique addresses the curvilinear nature of labor dilation. Using example data, Table 2 shows the data of a parturient who would be categorized in the ≥ 0.5 cm/hr group and the calculations on which the decision was based. All labors were classified by the study PI (JN) who was blinded to laboratory results when determining dilation rates. Of note, cervical exams are accurate to ± 1 cm from actual dilatation in 90% of cases (Buchmann & Libhaber, 2007; Huhn & Brost, 2004; Phelps et al., 1995; Tuffnell, Bryce, Johnson, & Lilford, 1989).

Consideration was given to the fact that the dilation rates used to discriminate pre-active and active may not adequately discriminate groups; thus, we also planned group comparisons between the quartiles of cervical dilation rates for the first 4 hours after admission.

White blood cells (WBC)

Concentrations were measured at admission in the hospital labs using a Beckman Coulter® LH 750 (Beckman Coulter, Inc., Fullerton, CA), an automated quantitative hematology analyzer that uses a refined electronic particle counting principle to quantify leukocytes. Ethylenediaminetetraacetic acid (EDTA)-containing tubes were used for all collections.

Body Temperature

At admission, temperature was measured by a GENIUS™ Model 3000A Tympanic Thermometer (Covidien, Mansfield, MA) which uses the Peak Select System™, an infrared technology that records and analyzes 32 separate measurements and selects the highest, most accurate temperature in < 2 seconds [accuracy +/- 0.1°C (36.7 - 38.9)]. The tympanic membrane yields an excellent approximation of core temperature because it shares blood supply with the hypothalamus, the body's thermostat. Use of tympanic thermometry avoids the possibility of maternal oral intake during labor, e.g. water and/or ice chips, confounding temperature measures.

Demographics

The following data were collected from each subject's medical record and/or via interview by the PI:

General Information: Age; race; ethnicity; gravidity; pre-pregnancy weight; height; marital status; alcohol, tobacco, and/or illicit drug use; current and recent medications; medical history.

Labor Admission Information: Date and time of admission; weight; BMI at admission (kg/m^2); gestational age at admission; cervical examination findings at labor admission (i.e., dilatation, effacement, position, consistency, fetal station).

Labor Process Information: Findings of all cervical examinations during labor; type of amniotic membrane rupture, i.e., spontaneous or artificial (all subjects have intact membranes at admission); time of membrane rupture in relation to admission; cervical dilatation at time of membrane rupture; duration of membrane rupture prior to delivery; consistency of amniotic fluid (clear, meconium stained); oxytocin augmentation in labor (yes/no); time of oxytocin implementation in relation to admission (if applicable); cervical dilatation at time of oxytocin implementation (if applicable); analgesia use [type(s), amount(s), time(s)]; epidural use (yes/no); cervical dilatation at time of epidural implementation (if applicable); date and time of delivery.

Labor Outcome Information: Mode of delivery, i.e., vaginal or cesarean (indication if cesarean); [2] Apgar scores; [3] maximum maternal temperature during labor, i.e., $< 100.4^{\circ}\text{F}$ or $\geq 100.4^{\circ}\text{F}$; [4] neonatal disposition, i.e., newborn nursery or NICU.

Neonatal Information: Weight; length; sex.

Data Analysis

For data analyses, demographic variables were expressed as mean (SD) if continuous and as n (%) if categorical. For the first specific aim, simple frequencies were used to determine what percentage of low-risk, nulliparous women were admitted prior to active phase onset using criteria commonly applied as prospective evidence of active phase onset. For the second specific aim, student's t tests were used to compare specific inflammatory markers (i.e. WBCs, admission temperature) between those admitted in 'active' versus 'pre-active' labor. In addition, correlational testing between continuous variables and dilation rates in active and pre-active were performed. For the third specific aim, student's t tests and Chi-square analyses were performed to compare women admitted in 'active' versus 'pre-active' labor on rates of labor

interventions (e.g., cervical examinations, amniotomy, oxytocin augmentation) and labor outcomes (e.g., duration of in-hospital labor time, neonatal Apgar scores, mode of delivery). Kolmogorov-Smirnov tests were performed on appropriate variables with normality being assumed when $p > 0.05$. For variables not normally distributed, appropriate non-parametric statistics were employed in lieu of the aforementioned statistics. P-values < 0.05 were considered significant. Statistical analyses were made via PASW Statistics 18 (SPSS Inc., Chicago, IL).

IV. RESULTS

Subject Characteristics

Ninety-three low-risk, parturients were enrolled in the study and there was no attrition. Demographics of the sample are shown in Table 3. The majority of the sample self-classified as non-Hispanic whites. The mean cervical dilatation at admission was 3.55 (0.52) cm. Of the 93 subjects, 94.6% (n = 88) received an epidural, 64.5% (n = 60) received oxytocin augmentation, and 63.4% (n = 59) received an amniotomy. Vaginal birth was achieved by 89.2% (n = 83) of the subjects. Among all women delivering vaginally, in-hospital labor duration from admission to delivery was 8.9 (3.7) hours.

Specific Aim 1

Of the 93 subjects, 50.5% (n = 47) of women were admitted in active labor, while 49.5% (n = 46) of women were admitted in pre-active labor.

Specific Aim 2

Maternal admission temperature and WBC counts were compared between those admitted in active versus pre-active labor. The temperature variable was determined to not be normally distributed via Kolmogorov-Smirnov testing ($p < 0.05$) thus non-parametric statistics were used to test for group differences, i.e., Mann-Whitney U. No statistically significant difference was found between pre-active and 'active' admission groups ($p > 0.05$). However, body temperature at admission was positively related to the rate of cervical dilation over the first 4 hrs post-admission in women determined to have been actively dilating ($r = 0.325$, $p = 0.026$). However, when combining the active and pre-active groups, this significance dissipated.

When comparing the two groups on WBC counts, those admitted in pre-active labor (n = 46) had a mean of $12.26 \pm 3.53 \times 10^3/\mu\text{L}$ and those admitted in 'active' labor (n = 47) had a mean of $12.87 \pm 2.86 \times 10^3/\mu\text{L}$ ($t = 0.919$; $p = 0.361$). Furthermore, when these groups were

further broken down into quartiles (cervical dilation rate ≤ 0.25 cm/hr, middle quartile, and ≥ 1.0 cm/hr) a greater, yet non-significant, difference was noted. Specifically, women dilating most efficiently for the first 4 hrs after admission for spontaneous labor (≥ 1.0 cm/hr) ($n = 24$) had higher leukocyte counts ($13.38 \pm 2.44 \times 10^3/\mu\text{l}$) compared to those dilating most slowly (< 0.25 cm/hr) ($n = 20$) ($11.95 \pm 3.32 \times 10^3/\mu\text{l}$) ($t = 1.644$; $p = 0.108$).

Specific Aim 3

Women admitted in active versus pre-active labor had similar cervical dilatations at admission [3.57 ± 0.55 and 3.53 ± 0.49 , respectively; Mann-Whitney U, $p = 0.794$]. Despite this, they differed significantly on labor process and labor outcome variables.

All labor process variables significantly differed between the active and pre-active labor admission groups. The pre-active labor admission group had a greater mean number of cervical examinations than the active labor admission group (7.91 ± 2.64 versus 5.72 ± 1.63 examinations respectively; $t = 4.828$; $p < 0.001$). Oxytocin augmentation rates were 48.9% ($n = 23$ of 47) among women admitted in active labor and 80.4% for those admitted in pre-active labor ($\chi^2=10.075$; $p=0.002$). At <6 cm dilatation, rates of oxytocin use between these groups were 26.1% and 62.2%, respectively ($\chi^2=12.057$; $p=0.001$). Amniotomy is an intervention eventually used in all hospital-attended labors during which spontaneous rupture of membranes does not occur, thus, overall group comparison lack meaning although the timing of amniotomy can be telling. In the present study, rates of amniotomy occurring at <6 cm dilatation in the active and pre-active labor admission groups were 41.3% and 51.1%, respectively ($\chi^2=4.125$; $p=0.042$).

Regarding labor outcome variables, women admitted in pre-active labor and delivering vaginally ($n=40$) had an in-hospital labor duration of 10.95 ± 3.67 hours while those admitted in active labor ($n=43$) had a duration of 6.97 ± 2.43 hours ($t=5.858$, $p<0.001$). Among cesarean deliveries ($n=10$), six were performed in the first-stage of labor (slow labor progression=3; non-

reassuring fetal heart patterns=3) and four in the second-stage for arrest of fetal descent.

Interestingly, all three cesareans performed in the active phase for slow labor progression followed a pre-active labor admission although this variable was significantly underpowered.

No significant differences in neonatal Apgar scores were found.

V. DISCUSSION

Approximately half of low-risk, nulliparous women with a spontaneous onset of labor are admitted in pre-active labor. These findings, along with those of Peisner and Rosen (1986), indicate that the clinical criteria commonly used as prospective evidence to admit laboring women poorly predict true active labor onset. These findings have significant implications for women admitted to labor units in pre-active labor. Because these women do not dilate at rates associated with active labor, they are perceived to have longer active labor durations. As a consequence, women admitted in pre-active labor are more prone to labor interventions, i.e. cervical examinations, oxytocin augmentation, and amniotomy. The most concerning of these interventions is oxytocin, a high-risk medication and drug most commonly associated with preventable adverse perinatal outcomes (Clark et al., 2009). As shown in the present study and those of Bailit et al. (2005), Holmes, Oppenheimer, & Wen (2001) and McNiven et al. (1998), oxytocin augmentation is performed nearly twice as often in women with a pre-active or early labor admission. This is of concern because oxytocin augmentation can have significant effects on the nulliparous woman and fetus; it can lead to uterine fatigue and fetal distress, and therefore, poorer birth outcomes.

Furthermore, in regards to cesareans, although underpowered, our findings which align with those of Bailit et al. (2005) and Rahnema et al. (2006) who reported that cesareans performed for slow labor progress occur more frequently in women admitted in the pre-active or early admission groups. Similarly to oxytocin augmentation, cesarean sections come with an increased risk beyond those associated with vaginal birth to mother and fetus. The health risks for the mother include both immediate and long-term risks. Immediate potential complications include anesthesia complications, infection and longer hospital stay or hospital readmission (Liu et al., 2007; National Institutes of Health, 2006) as well as increased risk of death (Harper et al., 2003). Long-term potential complications include future placenta previa, accreta, and abruption (National Institutes of Health, 2006; Kennare, Tucker, Heard, & Chan, 2007; Hemminki &

Merilainen, 1996) as well as ectopic pregnancy (Hemminki et al., 1996), uterine rupture in subsequent labors (National Institutes of Health, 2006; Kennare et al., 2007; Taylor, Simpson, Roberts, Olive, & Henderson-Smart, 2005) and unexplained stillbirth (Kennare et al., 2007; Smith, Pell, & Dobbie, 2003). The increased health risks of neonates born via cesarean section include risk of respiratory morbidities and longer hospitalization (National Institutes of Health, 2006).

While the inflammatory markers evaluated in this study did not significantly differ between pre-active and active labor groups, the trend towards significance suggests that inflammation does play an active role in labor. Others have reported that the quantity of peripherally measured WBCs differ between laboring and non-laboring women. For example, Törnblom et al. (2005) found that peripheral blood WBC counts were increased in laboring women as compared to non-laboring women (n=50), while Norman et al. (2007) reported greater chemotaxis of peripheral blood WBCs in laboring women. Although these studies did not reach statistical significance due to small sample sizes, these findings between laboring women and non-laboring women suggest that differences may also exist in pre-active versus active labor groups; however, a larger sample size may be necessary to demonstrate such differences. Additionally, since WBCs may also be elevated in the presence of infection, even sub-clinical infection, other inflammatory biomarkers that are more specific to the labor process (e.g., TNF- α , IL-1 β , IL-6, IL-8) may be more useful in differentiating pre-active and active labor. This is a potential area of future research.

The present study was limited by a small sample size. This possibly limited our ability to find statistically significant differences in inflammatory biomarkers between the pre-active and active labor groups. The small sample also eliminated our ability to test for between-group differences on particular labor outcomes, e.g., cesareans.

In summary, the clinical criteria commonly applied as evidence of active labor onset does not reliably differentiate pre-active and active labor states among low-risk, nulliparous

women with spontaneous labor onset. Being admitted earlier in labor predisposes women to increased rates of interventions aimed at accelerating labor. This, in turn, may interrupt acute inflammatory processes that are important to efficient labor progression. Increased rates of intervention and/or a derailment of important physiological process may explain the poorer birth outcomes seen in earlier admission groups. Clinicians would benefit from future research aimed at identifying criteria that more reliably describe active labor onset, including possible biomarkers that may reliably predict the onset of active labor. Such criteria may assist clinicians when making admission decisions while simultaneously allowing time for important physiological changes to occur that may facilitate efficient labor progress. The result would likely be decreased interventions during labor and improved birth outcomes.

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APPENDICES

Table 1. Cesarean rate differences based on admission timing in nulliparas with spontaneous labor onset

<i>Study</i>	<i>Country</i>	<i>Dilatation Groups (at admission)</i>	<i>n</i>	<i>Cesarean rate</i>
Bailit et al. (2005)	U.S.	< 4cm	1386	14.2%
		≥ 4cm	1702	6.7%***
Holmes et al. (2001)	Canada	< 4cm	812	10.3%
		≥ 4cm	356	4.2%**
Impey et al. (2000)	Ireland	< 3cm (AML)	421	6.4%
		≥ 3cm (AML)	79	0%*
Rahnama et al. (2006)	Iran	≤ 3cm	466	64.6%
		> 3cm	329	24.3%***

AML = Active management of labor, a multifaceted program including early diagnosis of labor, immediate amniotomy, cervical assessment every 2 hrs, and oxytocin augmentation if cervical dilation is < 1 cm/hr.(Impey et al., 2000)

*p < 0.01; **p = 0.001; ***p < 0.0001

Table 2. Example data with accompanying calculations to be used in categorizing labor

Example labor data

Time	11:30a	12:30p	1:30p	2:00p	2:30p	3:30p	4:30p
Study Hour (x)	0 (x ₀)	1	2	2.5 (x ₁)	3	4 (x)	5 (x ₂)
Dilatation (y)	4 cm (y ₀)	--	--	5 cm (y ₁)	--	(y)	8 cm (y ₂)

Calculations based on example data

Slope from exams <i>prior to</i> and <i>after</i> Study Hour 4	$m = \frac{\Delta y}{\Delta x} = \frac{y_2 - y_1}{x_2 - x_1} = \frac{\Delta cm}{\Delta hr} = \frac{8 - 5 \text{ cm}}{5 - 2.5 \text{ hrs}} = 1.2 \text{ cm/hr}$
Study Hour 4 dilatation	$y = m(x - x_1) + y_1 = 1.2 \text{ cm/hr} (4 - 2.5 \text{ hrs}) + 5 \text{ cm} = 6.8 \text{ cm}$
4 hour dilation slope	$m = \frac{\Delta y}{\Delta x} = \frac{y - y_0}{x - x_0} = \frac{6.8 - 4 \text{ cm}}{4 - 0 \text{ hrs}} = 0.7 \text{ cm/hr}$ ← ≥ 0.5 cm/hr group

Table 3. Demographic Variables (n = 93)

Maternal age (yrs)	25.1 (4.9)	Range: 18-36
Gestational age at delivery (days)	275.9 (7.10)	259-289
Hispanic		
Yes	5 (5.4%)	
No	88 (94.6%)	
Race		
White	68 (73.1%)	
Black	18 (19.4%)	
Other	7 (7.5%)	
Marital status		
Married	42 (45.2%)	
Not married	48 (51.6%)	
Gravidity	1.3 (0.7)	1-5
Weight (maternal) (kg)	80.5 (12.4)	43.2-112.7
Height (maternal) (m)	1.6 (0.06)	1.5-1.8
Body mass index (maternal)	29.8 (4.6)	18-41.7
Cervical dilatation at admission (cm)	3.55 (0.52)	3-5
Cervical effacement at admission		
60-79%	11 (11.8%)	
≥ 80%	82 (88.2%)	
Mode of birth		
Vaginal	83 (89.2%)	
Cesarean	10 (10.8%)	
Amniotomy		
No	34 (36.6%)	
Yes (at < 6 cm)	43 (46.2%)	
Yes (at ≥ 6 cm)	16 (17.2%)	
Oxytocin augmentation		
No	33 (35.5%)	
Yes (at < 6 cm)	41 (44.1%)	
Yes (at ≥ 6 cm)	19 (20.4%)	
Epidural use		
No	5 (5.4%)	
Yes	88 (94.6%)	
In-hospital labor duration (hr)*	8.9 (3.7)	3-21
Weight (infant) (g)	3395 (457)	2329-4722
Length (infant) (cm)	49.6 (2.2)	44-54.5

Mean (SD) for continuous variables; n (%) for categorical variables

* Includes only those delivering vaginally (n = 83)

Figure 1. Labor: Stages and phases.

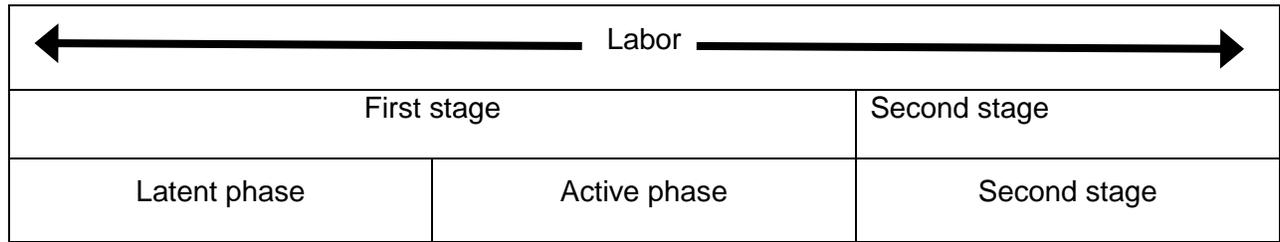


Figure 2. Conceptual Framework

