PHYSIOLOGICAL FACTORS INFLUENCING LABOR LENGTH

DISSERTATION

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By

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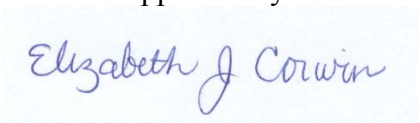

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ABSTRACT

The total cesarean rate in the United States (U.S.) in 2006 was 466% greater than in 1970. The Centers for Disease Control and Prevention (CDC) reported that in 2006, 31.1% of all U.S. deliveries were accomplished via cesarean. Among term, low-risk women giving birth for the first time and with a vertex presenting fetus, a cesarean rate of 25% was reported by the CDC in 2005. These cesarean rates are now higher than ever before and farther from national objectives.

While in some cases necessary for the health of the mother and/or neonate, cesareans are major surgical procedures that carry multiple short- and long-term maternal risks and risk of respiratory morbidity for the neonate. It has been recently suggested that a cesarean rate between 5-10% seems to achieve the best outcomes, whereas a rate higher than 15% seems to result in more harm than good. This suggestion reaffirms the conclusion reached by the World Health Organization over twenty years ago that no region in the world is justified in having a cesarean rate above 10-15%. Although it is difficult to put an accurate figure on the financial impact of current cesarean rates, it is estimated that costs for a cesarean are, on average, $2180 more than for a vaginal delivery. Based on 2006 statistics, simply decreasing the current cesarean rate of 31.1% to 30.1% would save approximately $93 million per

year while decreasing the total U.S. cesarean rate to 15% would save approximately $1.5 billion per year. With the dual benefit of decreasing morbidities and cost achievable through decreasing cesarean rates, understanding factors that may contribute to cesareans must be a research priority.

Dystocia, characterized by "slow, abnormal progression of labor", is the most common indication for cesareans among nulliparous women accounting for nearly 50% of all cesareans performed in this population. Because dystocia is the original indication for most repeat cesareans, it follows that the majority of cesareans in the U.S. are related to the diagnosis of dystocia. Thus, when attempting to identify contributors to, or strategies for lowering, cesarean rates, it is most appropriate to focus on contributors to dystocia in low-risk nulliparous women. In clinical practice, dystocia is generally defined as a delay in cervical dilation progression beyond which accelerative interventions, e.g., oxytocin administration, are considered justifiable. Rates of uterine contraction augmentation in contemporary obstetrical practice suggest that the clinical expectations of nulliparous labor have surpassed normalcy. It must be considered that current definitions of dystocia, in terms of cervical dilation rates, may be inappropriately defined.

Three manuscripts are presented in this dissertation document. The first manuscript presents a systematic review aimed at identifying the norms and limits of *active phase labor length* and *active phase cervical dilation rates* in low-risk, nulliparous women with spontaneous labor onset in order to better define labor

expectations. Studies included in this review were limited to those sampling nulliparous women. Inclusion criteria were as follows: singleton fetus; cephalic presentation or no indication of alternative presentations; low-risk (no identified major complications of pregnancy); ≥ 36 weeks' gestation; spontaneous active labor onset (no inductions); cervical dilatation of 3-5 cm at study enrollment; labor length from 3-5 cm through complete cervical dilatation (approximated at 10 cm when necessary) must have been presented or calculable from study data. Fourteen studies met all inclusion criteria. Among participants in the studies reporting a mean active phase labor length (n = 2990), the weighted mean active phase length was 6.45 ± 1.68 hours while the weighted mean rate of cervical dilation, based on linear cohort calculations, was 1.01 ± 0.27 cm/hour. The weighted active phase length at the mean + 2 standard deviations was 13.61 ± 3.51 hours while the cervical dilation rate was 0.48 ± 0.13 cm/hour. In studies using a median measure of active phase length, subjects (n = 718) had an average weighted median active phase length of 4.91 ± 1.01 hours. It is concluded that active phase labor among low-risk, nulliparous women with a spontaneous labor onset is longer and has a wider range of *normal* than is generally appreciated. Likewise, overall linear rates of cervical dilation in the active phase are not as steeply sloped as traditionally believed. Accordingly, many nulliparous active phase labors in contemporary practice are likely being misclassified as slowly-progressing. Revisions of existing expectations of active phase labor progress are

warranted and efforts to do so must supersede efforts to change labor to fit existing expectations.

Although the cause(s) of true labor dystocia can rarely be diagnosed with objective certainty, the greatest contributor is inefficient uterine contractions, a diagnosis lacking stringent criteria and with unknown cause(s). Physiological factors potentially contributing to inefficient uterine contractions via a uterine fatigue pathway and eventually culminating in longer labor durations is the focus of the second and third manuscripts. These prospective works describe investigations conducted at a suburban, academic, Midwestern medical care center. Participants were nulliparous women of low obstetric risk with a labor care provider diagnosis of spontaneous labor in the early active-phase of the first stage of labor. Additional inclusion criteria were: 1) 18-39 years of age; 2) singleton gestation; 3) gestational age $\geq$ 37 - $\leq$ 42 weeks; 4) anticipated vaginal delivery; 5) with or without ruptured membranes; 6) cephalic presentation; 7) weight < 250 lbs at study entry; 8) no identified fetal anomalies or growth issues; 9) afebrile at study entry; and 10) able to read and speak English. Participants with augmentation of labor after being diagnosed with active phase labor onset were retained in the study while women undergoing labor inductions were excluded.

Active phase labor duration and total labor duration were the major outcome variables. Based on *a priori* definitions, women were also grouped based on cervical dilation rates occurring over the first 4 hours after a physician/midwife diagnosis of

active labor onset: [1] correctly classified active labor onset was defined as average cervical dilation ≥ 0.5 cm/hour for 4 hours; [2] misclassified active labor onset encompassed labors progressing at < 0.5 cm/hour for 4 hours.

After admission for a diagnosis of active phase labor onset (baseline) and after obtaining informed and HIPAA consents, women were sampled for venous blood and urine specimens. Blood samples were used for hemoglobin (Hb) and lactate dehydrogenase (LDH) total and isoenzyme determinations. Urine samples were used for specific gravity determinations as a measure of maternal hydration. Oxygen saturation (SaO_2) was also measured for 3-5 minutes at baseline and, jointly with Hb, was used to calculate Hb-bound O_2, a measure of maternal oxygenation. Energy substrate measures were determined via blood glucose and β-hydroxybutyric acid fingerstick measurements at baseline. In addition to the physiological variables, measures of maternal pain and anxiety were collected via visual analog scales. At baseline + 4 hours, urine specific gravity, SaO_2, blood glucose, β-hydroxybutyric acid, pain, and anxiety measures were again made if birth had not occurred. At 24-30 hours post-vaginal delivery, LDH measures were repeated as a potential proxy measure of the enzymatic state of uterine muscle existing immediately prior to active phase onset, during active phase labor, and/or at delivery. Demographic data were obtained via interview supplemented via chart review and labor data was obtained via chart review. The study protocol had Institutional Review Board approval.

Ninety-three eligible subjects were enrolled in the study and included in the analysis. There was no attrition. Among all parturients achieving vaginal delivery (n = 83), active phase and total labor durations were 7.44 ± 3.26 and 8.89 ± 3.66 hours, respectively. Among parturients achieving vaginal delivery *and* with a correctly classified active phase labor onset (n = 43), active phase and total labor durations were 5.64 ± 1.85 and 6.97 ± 2.43 hours, respectively. Women with misclassified active phase onsets with eventual vaginal delivery (n = 40) had mean active phase and total labor durations that were 3.74 and 3.98 hours longer, respectively [9.38 ± 3.36 hours and 10.95 ± 3.67 hours], when compared to women with correctly classified active phase onsets ($p < 0.001$).

The second manuscript reports the relationships between labor duration and maternal oxygenation, hydration, energy substrate availability, pain, and anxiety as well as reporting group differences on these measures. Neither active phase labor duration nor total labor duration was found to be significantly correlated with any of these measures. When the mean active phase labor duration for those correctly classified as being in active phase labor (338 minutes) was used to divide the sample into two distinct labor duration groups (i.e., < 338 and ≥ 338 min), urine specific gravity measures taken at the active phase labor onset diagnosis was the only major study variable with significant mean differences between the groups. The shorter active phase labor duration group was less hydrated than the longer active phase labor duration group (specific gravity = 1.017 vs. 1.012; $t = 2.647$; $p = 0.010$). Paired-

sample analyses demonstrated that, among all women delivering vaginally, β-hydroxybutyric acid levels increased significantly over time ($p < 0.001$) whereas pain and anxiety significantly decreased over time ($p < 0.001$). When limiting analyses to those correctly classified as being in active labor and achieving a vaginal delivery, β-hydroxybutyric acid levels and pain remained significant whereas anxiety ($t = 2.318$, $p = 0.027$) and hydration ($t = 1.770$, $p = 0.086$) were trending toward significance with Bonferroni correction. Relationships between labor duration and multiple contextual variables (e.g., maternal body mass index, infant birth weight) are also reported in this manuscript. These pilot data reinforce that a large percentage of women are misclassified as being in active labor based on subsequent rates of cervical dilation. Suggestions for future research are included.

The third manuscript describes (1) paired-sample differences between maternal serum LDH samples collected upon a provider diagnosis of active phase labor onset and 24-30 hours post-delivery in order to identify how maternal serum LDH profiles change between the time points, (2) the relationships between total LDH and isoenzyme levels and the following variables: rates of cervical dilation during the first 4 hours after diagnosis of active phase onset; active phase labor duration; and total labor duration and (3) differences in LDH levels between several comparison groupings, i.e., between women correctly classified and misclassified as being in active phase labor.

Among the LDH paired-samples (n = 75), all differences between the time points were significant with Bonferroni correction ($p < 0.001$). Specifically, post-delivery total LDH, LDH_3, LDH_4, H-LDH, and M-LDH increased post-delivery over values seen at active phase of labor onset diagnosis while LDH_1, LDH_2, LDH_5, and the H/M ratio had decreased. Rates of cervical dilation over the first 4 hours after a diagnosis of active phase labor onset was negatively correlated with the post-delivery percentage distribution of LDH_1 (Spearman's rho = -0.275, $p = 0.014$) and positively with LDH_3 (Spearman's rho = 0.289, $p = 0.010$) and LDH_4 (Spearman's rho = 0.282, $p = 0.012$). Only post-delivery LDH_3 was significantly related to active phase and total labor durations, showing inverse correlations [$r = -0.275$ ($p = 0.014$) and $r = -0.292$ ($p = 0.009$), respectively].

Although comparisons between correctly classified and misclassified active phase labor onset groups found that LDH measures were not statistically different, several near-significant findings emerged. A post-hoc comparison between the lower (≤ 0.28 cm/hour) and upper (≥ 1.04 cm/hour) quartiles of dilation rates for the first 4 hours after active labor onset diagnosis demonstrated that, among the post-delivery LDH samples, parturients with the most slowly progressing dilation (n = 18) had higher relative levels of LDH_1 ($t = 2.070$; $p = 0.045$) and LDH_5 ($t = 2.261$; $p = 0.032$) and lower levels of LDH_3 ($t = 2.567$; $p = 0.014$) and LDH_4 ($t = 2.044$; $p = 0.048$) when compared to those with the most rapid cervical dilation (n = 21) during this time frame. Under the assumption that post-delivery serum LDH measures reflect uterine

muscle enzymatic states existing immediately before active labor onset diagnosis, during active labor, and/or at delivery, parturients with the most efficient cervical dilation during the first four hours post-active phase onset diagnosis had a LDH profile better equipped to handle the anaerobic environment imposed by uterine contractions during labor. Since uterine muscle changes may occur up to and beyond the onset of active phase labor, it is suggested that a misclassified active phase labor onset may inadvertently bypass essential time needed for the physiologic LDH profile shift to manifest.

Provider management of parturients with correctly classified versus misclassified active phase onset was significantly different. Oxytocin augmentation rates were 47.8% among women admitted in true active labor and 80.0% for women misclassified as being in active labor ($\chi 2 = 10.188$; $p = 0.001$). Rates of oxytocin implementation at < 6 cm dilatation for these groups were 26.1% and 62.2%, respectively ($\chi 2 = 12.057$; $p = 0.001$). Likewise, among women receiving an amniotomy, implementation of this intervention at < 6 cm was less common among those with correctly classified active phase onset at 41.3% compared to 51.1% in women misclassified ($\chi 2 = 4.125$; $p = 0.042$). Overall, parturients with correctly classified active phase onsets had labor durations that were approximately 4 hours shorter than those with misclassified active phase onsets ($p < 0.001$) in spite of the provision of these aggressive interventions at higher percentages in the women

misclassified as being in active labor. All three cesareans performed in the active phase for slow labor progress followed a misclassification of active phase labor onset.

It is concluded that, when differentiating active phase from latent phase labor, watchful patience over immediate intervention is seemingly prudent and may allow important physiological events within the uterine muscle to more fully manifest. Directions for future research are included.

Dedicated to my children, Maclane Patrick Neal, Peyton Noëlle Neal, & Brennen Michael Neal, for giving me perspective, inspiration and, above all, joy.

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PUBLICATIONS

1. Neal, J.L. (2001). RhD isoimmunization and current management modalities. *Journal of obstetric gynecologic and neonatal nursing, 30*(6), 589-606.

FIELDS OF STUDY

Major Field: Nursing

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CHAPTER 1

ACTIVE PHASE LABOR LENGTH AND RATE OF CERVICAL DILATION IN NULLIPAROUS WOMEN: A SYSTEMATIC REVIEW

Introduction

Attempts to define the norms and limits of labor length have yielded variable results. Much of the difficulty undoubtedly stems from the fact that labor does not readily lend itself to measurement. Not only is prospectively defining the onset of active phase labor a significant challenge, but attempts to divide the continuum of labor into phases and stages adds to the complexity. Moreover, multiple fixed factors such as parity (Lyrenas, 2002) and maternal (Nuthalapaty, Rouse, & Owen, 2004; Vahratian, Zhang, Troendle, Savitz, & Riz, 2004) and infant weight (Turner et al., 1990) as well as multiple commonly employed interventions including amniotomy used either alone or in conjunction with oxytocin (Brisson-Carroll, Fraser, Breart, Krauss, & Thornton, 1996; Fraser, Turcot, Krauss, & Brisson-Carrol, 2000; Fraser, Vendittelli, Krauss, & Breart, 1998) can significantly affect labor length. In spite of these measurement difficulties, further efforts to identify the norms and limits of labor length are necessary because this knowledge is the backbone of clinical decision making in the intrapartum setting. In particular, because spontaneously laboring

women are typically admitted to labor units after a diagnosis of active phase labor onset and, once admitted, are closely monitored to ensure adequate progress, optimally defining the indices of active phase labor is especially pertinent. The purpose of this systematic review is to identify the norms and limits of *active phase labor length* and *active phase cervical dilation rates* in low-risk, nulliparous women with spontaneous labor onset in order to better define labor expectations.

Background

Active phase labor length, when appropriately defined, can subsequently be used to define the norms and limits of active phase cervical dilation rates. Indeed, the pattern of cervical dilation over time (cm/hr) in the active phase of labor is the main criterion by which labor progress in the first stage of labor is assessed. Thus, determining standardized minimum rates of cervical dilation that best distinguish normal from abnormal labor progression is of great clinical importance because it is when minimal rates of dilation are not met that it is clinically indicated to consider intervention in the normal process of labor. Rates too stringently defined may lead to unnecessary early intervention while rates too leniently defined may forego potentially helpful intervention. The former may result in iatrogenic morbidities including unnecessary cesareans (Goffinet et al., 1997; Johnson et al., 1997; Oscarsson, Amer-Wahlin, Rydhstroem, & Kallen, 2006) while the latter may result in uterine rupture resulting from obstructed labor, postpartum hemorrhage, or sepsis (World Health

Organization. Division of Family Health. Maternal Health and Safe Motherhood Programme., 1994b).

Clinical practice guidelines regarding labor length and rates of cervical dilation among nulliparous women are largely based on findings by Friedman (Friedman, 1978; Friedman, 1954; Friedman, 1955) and Friedman & Kroll (Friedman & Kroll, 1969; Friedman & Kroll, 1971) who have reported that, for most women, labor typically follows a near-identical sigmoid curve varying only in slope. Based on these studies by Friedman, when dilation is between approximately 4-9 cm, nulliparous women are reported to dilate at a mean rate of 3.0 cm/hr while at the 5th percentile the rate is 1.2 cm/hr (Friedman, 1978; Friedman, 1955). These studies, however, included some subjects without a spontaneous labor onset and some who were not low-risk by contemporary standards.

Philpott & Castle (1972a) and the World Health Organization (1994a) have contributed to this literature, finding that 21.8% and 30.9% of nulliparae, respectively, dilate at rates averaging < 1cm/hr during the active phase of labor. In addition, these studies and others have found that 10.3-11.7% of low-risk nulliparae with a spontaneous active phase labor onset dilate at rates slower than 0.50-0.64 cm/hr (Perl & Hunter, 1992; Philpott & Castle, 1972a; Philpott & Castle, 1972b; World Health Organization. Division of Family Health. Maternal Health and Safe Motherhood Programme., 1994a) suggesting that intervention to accelerate labor should not be considered until rates of cervical dilation fall below these limits.

The aforementioned studies have molded worldwide obstetrical practice over the past half-century. However, more recent analyses by investigators such as Albers, Schiff, & Gorwoda (1996), Albers (1999), Zhang et al. (2002), and Jones & Larson (2003) have reported that normal active phase labor lasts longer than previously thought, thus calling into question the standards existing since the work of Friedman. Hence, the measures of central tendency that best define active phase labor length and active phase cervical dilation rates in low-risk nulliparae are once more in question as are the limits of these measures. Since this knowledge is critical to the assessment of labor progress and whether labor accelerative intervention should be considered, this systematic review aims to more clearly define the clinical expectations of active phase labor length and rates of cervical dilation in the active phase among healthy, nulliparous women. In addition, a critical review of the classic literature that has substantially contributed to contemporary expectations of active phase labor will be presented.

Sources

MEDLINE and CINAHL searches were performed with the following search criteria: keywords = labor (labour) length, labor (labour) duration, length of labor (labour), duration of labor (labour), active phase labor (labour), active phase length, and active phase duration in all fields; limitations = 1970 – September, 2007 in the English language, published in healthcare journals. MEDLINE and CINAHL yielded 356 and 122 publications, respectively. Duplicates were removed, abstracts were

reviewed, and those seemingly meeting the inclusion criteria of this systematic review, as described below, were electronically or manually retrieved and reviewed.

In addition, the Cochrane Database of Systematic Reviews (3rd quarter 2007) was searched under the following criteria: keywords = labor (labour) length, labor (labour) duration, length of labor (labour), duration of labor (labour), active phase labor (labour), active phase length, active phase duration, and active phase; limitations = systematic reviews, recently updated reviews, new reviews. Reviews with an intrapartum focus (n = 12) were identified and the 37 references *included in* these reviews that seemingly met the inclusion criteria of the present review were electronically or manually retrieved. Manual searches were not used. In all, approximately 14% (n = 48) of the sought publications were not available through the authors' institutional affiliations and, thus, not reviewed.

Study Selection

Studies included in this systematic review were limited to those sampling nulliparous women. Inclusion criteria were as follows: singleton fetus; cephalic presentation or no indication of alternative presentations; low-risk (no identified major complications of pregnancy); ≥ 36 weeks' gestation; spontaneous active labor onset (no inductions); cervical dilatation of 3-5 cm at study enrollment (Note: if an alternate cervical dilatation criteria was used, a mean or median cervical dilatation of 3-5 cm must have been identified); labor length from 3-5 cm through complete cervical dilatation (approximated at 10 cm when necessary) must have been presented or

calculable from study data. Some studies reported the inclusion of 'primiparous' women, a term often inappropriately used in reference to pregnant women who have never before given birth. In these cases, attempts to directly contact the authors were made to ascertain if the included women had a parity of 0 or 1; if 0 (nulliparous), the study was included in the current review. Authors were also contacted for additional clarifications as necessary.

All trials meeting the pre-defined inclusion criteria were included without consideration of their results. Because intervention outcomes were not being compared, there was no need to exclude studies based on threats to internal validity. Data from studies meeting all inclusion criteria were abstracted and results compiled. SPSS 15.0 (SPSS Inc., Chicago, IL) was used for all data analyses. The 14 studies included in this systematic review (Albers, 1999; Alexander, Lucas, Ramin, McIntire, & Leveno, 1998; Alexander, Sharma, McIntire, & Leveno, 2002; Bofill et al., 1997; Cammu, Clasen, Van Wettere, & Derde, 1994; Cammu & Van Eeckhout, 1996; Clark, Carr, Loyd, Cook, & Spinnato, 1998; Fontaine & Adam, 2000; Garite, Porto, Carlson, Rumney, & Reimbold, 1993; Garite, Weeks, Peters-Phair, Pattillo, & Brewster, 2000; Jones & Larson, 2003; Rogers, Gilson, & Kammerer-Doak, 1999; Svardby, Nordstrom, & Sellstrom, 2007; Zeisler, Tempfer, Mayerhofer, Barrada, & Husslein, 1998) are listed in Tables 1.1 and 1.2.

The method used to determine cervical dilation rates was dictated by the data available within the included studies. Although polynomial regression best addresses

the curvilinear nature of cervical dilation this analytical method could not be used since raw data were unavailable. When conceptualized as a straight line, methods to determine rates of cervical dilation include the following: (1) estimating the active phase slope (cm/hr) for each subject using ordinary least-squares regression and averaging these slopes to estimate the summary statistics for the cohort; (2) estimating cervical dilatation (cm) at active phase onset for the cohort and calculating the slope from this point through complete cervical dilatation based on the time (hr) required to accomplish this change. Because raw data were unavailable, the latter method was used.

Results

The mean length of active phase labor was reported in twelve studies (Albers, 1999; Alexander et al., 1998; Alexander et al., 2002; Bofill et al., 1997; Cammu et al., 1994; Cammu & Van Eeckhout, 1996; Clark et al., 1998; Fontaine & Adam, 2000; Garite et al., 1993; Garite et al., 2000; Jones & Larson, 2003; Rogers et al., 1999) (see Table 1.3). Among participants in these studies (n = 2990), there was a weighted mean cervical dilatation of 3.93 ± 0.30 cm at active phase onset. The weighted mean active phase length was 6.45 ± 1.68 hours while the weighted mean rate of cervical dilation, based on linear cohort calculations, was 1.01 ± 0.27 cm/hr. For studies providing an active phase length standard deviation (Albers, 1999; Alexander et al., 1998; Alexander et al., 2002; Bofill et al., 1997; Cammu et al., 1994; Cammu & Van Eeckhout, 1996; Clark et al., 1998; Garite et al., 1993; Jones & Larson, 2003; Rogers

et al., 1999), the weighted active phase length at the mean + 2 standard deviations for enrolled subjects (n = 2695) was 13.61 hours while the cervical dilation rate was 0.48 cm/hr. Perhaps, the finding best indicating that the duration of normal active phase labor varies widely is that, among those studies providing a standard deviation of active phase length (Albers, 1999; Alexander et al., 1998; Alexander et al., 2002; Bofill et al., 1997; Cammu et al., 1994; Cammu & Van Eeckhout, 1996; Clark et al., 1998; Garite et al., 1993; Jones & Larson, 2003; Rogers et al., 1999), the weighted mean of the standard deviations was 3.59 hours.

In three studies, the authors used an alternative measure of central tendency, namely the median, either in addition to reported means (Alexander et al., 2002) or exclusively (Svardby et al., 2007; Zeisler et al., 1998) when reporting active phase labor lengths (see Table 1.4). Among participants in these studies (n = 718), the weighted mean cervical dilatation at active phase onset was 3.92 ± 0.42 cm. The weighted mean active phase of labor length, based on the medians provided in the studies (i.e., a mean of the medians), was 4.91 ± 1.01 hours. The weighted mean rate of cervical dilation was 1.30 ± 0.31 cm/hr for all studies measuring active phase length via median.

Discussion

The results of this review suggest that active phase labor among low-risk, nulliparous women with a spontaneous labor onset is longer and has a wider range of *normal* than is generally appreciated. Likewise, this review found that overall linear

rates of cervical dilation in the active phase are not as steeply sloped as traditionally believed since the work of Friedman. Accordingly, many nulliparous active phase labors in contemporary practice are likely being misclassified as slowly-progressing. These findings may, in part, explain the high rates of intrapartum interventions employed to accelerate labor.

Studies by Friedman

Rigorous review of several classic studies used to define the norms and limits of active phase labor length and rates of active phase cervical dilation in contemporary practice yield results that are more similar to the findings of the present review than one may expect. As previously noted, Friedman (1954, 1955, & 1978) and Friedman & Kroll (1969 & 1971) performed extensive research to bring these issues to light. In 1969, Friedman & Kroll introduced a computer program developed to analyze labor progression which they subsequently applied to thousands of labors. To be included, the following points must have been known: [1] time of onset of labor (Point A); [2] ≥ 1 non-regressive point between 3.0 and 6.0 cm dilatation (Point C); [3] ≥ 1 non-regressive point between 6.5 and 9.0 cm dilatation (Point D); [4] time of delivery (Point G). These 4 points were then used to extrapolate other critical points (e.g., B, E, F), if unknown, to form the representative sigmoid curve for which Friedman has gained recognition (see Figure 1.1).

Works by Friedman (1954, 1955, & 1978) and Friedman & Kroll (1969 & 1971), with a focus on primigravid or nulliparous women, all described the active

phase of labor length as the time from approximately 2.5 cm through complete cervical dilatation, approximated at 10 cm (Point B to F). Active-phase labor was further divided into 3 sub-phases, i.e., [1] an acceleration phase, [2] a phase of maximum slope, and [3] a deceleration phase. The *acceleration phase* was described by a rapid change in the slope of the cervical dilation and approximated the time needed for the cervix to dilate from 2.5 cm to 4 cm (Point B to C). The *phase of maximum slope* was described as a period of rapid cervical dilation that progresses linearly from approximately 4 cm to 9 cm cervical dilatation (Point C to E). When steeply inclined, total labor tends to be short; when less inclined, labor is longer. Initially, Friedman presented the mean rate of cervical dilation in the phase of maximum slope to be 3.7 cm/hr (Friedman, 1954). Subsequently, mean and statistical limit rates in this phase were reported to be 3.0 and 1.2 cm/hr, respectively (Friedman, 1955 & 1978). The *deceleration phase* was identified when the rate of dilation once again slowed as full dilatation was reached. This phase approximated the time needed for the cervix to dilate from 9 cm to 10 cm (Point E to F).

Total active-phase labor and deceleration phase lengths are provided in many of Friedman's works (Friedman, 1955 & 1978; Friedman & Kroll, 1971). Conversely, the durations of the acceleration phase and the phase of maximum slope are not provided. However, because the phase of maximum slope involves a total cervical change of approximately 5 cm (from 4 to 9 cm), its length can be calculated based on

rates of cervical dilation in this phase and, as a result, acceleration phase length can be calculated. Results calculated from the Friedman data are shown in Table 1.5.

The majority of active-phase labor length time is spent in the acceleration and deceleration phases according to calculations based on Friedman's data. For example, in his 1955 and 1971 studies, the combined acceleration and deceleration phases accounted for 65.9% (3.23 hrs) and 70.7% (3.25 hrs) of active-phase length, respectively, at the mean (Friedman, 1955; Friedman & Kroll, 1971). Moreover, since active-phase labor was 11.7 hours at the mean + 2 standard deviations, the acceleration and deceleration phases accounted for 61.1-64.4% (7.15-7.53 hours) of active-phase length (Friedman, 1955 & 1978; Friedman & Kroll, 1971).

Proper interpretation of Friedman's findings is of utmost importance. Major obstetrical texts have incorrectly presented his results regarding active-phase labor among nulliparae. For example, the authors of *Williams Obstetrics*, now in its 22nd edition, wrote "…rates of cervical dilatation [in the active phase] ranged from a minimum of 1.2 up to 6.8 cm/hr" (Cunningham et al., 2005). In another contemporary obstetrical text, the authors describe the rates of dilation during the active phase as 3.0 and 1.2 cm/hr at the mean and 5th percentile, respectively (Norwitz, Robinson, & Repke, 2002). In both examples, these rates apply only to the phase of maximum slope and not active labor as a whole (Friedman, 1955 & 1978). Such misrepresentations, when applied clinically, may lead to inappropriate labor management particularly manifested by excessive intervention.

While statistical limits for the phase of maximum slope are commonly reported in obstetrical literature and textbooks (i.e., the 1.2 cm/hr limit), calculations directly based on Friedman's work are more enlightening. When viewed in its entirety, the active phase of labor (i.e., 2.5-10 cm cervical dilatation *or* acceleration phase + phase of maximum slope + deceleration phase) has a mean slope lying between 1.53-1.70 cm/hr (Friedman, 1954, 1955, & 1978; Friedman & Kroll, 1971) (See Table 1.6). This is vastly different from the mean of 3.0-3.7 cm/hr in the phase of maximum slope. Perhaps more importantly, the active phase slope has a statistical limit of approximately *0.64 cm/hr* (calculated as the difference between 10 cm and 2.5 cm divided by the statistical limit of 11.7 hours), which is nearly half the statistical limit in the phase of maximum slope (Friedman, 1955 & 1978; Friedman & Kroll, 1971).

Studies by Philpott and Castle

In the 1970s, Philpott & Castle introduced a graphic tool called a "*cervicograph*" (Philpott & Castle, 1972a; Philpott, 1972). This tool was composed of two lines termed the '*alert line*' and the '*action line*' and displayed cervical dilatation (cm) on the ordinate and time (hrs) on the horizontal axis. The alert line was graphically straight and joined points representing 1 cm dilatation at zero time and full dilatation (10 cm) nine hours later, a rate of 1 cm/hr (see Figure 1.2). If cervicographic progress crossed to the right of the alert line (i.e., progressed at < 1 cm/hr), then arrangements were made to transfer the parturient from peripheral level care to a more intensive care center. The action line was drawn parallel to the alert line but was 4

hours to the right. Once this line was reached, more aggressive management interventions such as oxytocin augmentation were employed in an attempt to correct slow labor progress.

Study findings by Philpott & Castle were based on low-risk, primigravid Rhodesian African women (n = 624) who had cervical dilatations of ≥ 3 cm on admission and whose labor management decisions were based on a cervicograph (Philpott & Castle, 1972a). Results showed that 21.8% (n = 136) of parturients crossed the alert line (i.e., dilated at < 1 cm/hr) and, of these, 50% (n = 68) went on to also cross the action line. In all, 10.9% of all study parturients crossed the action line and only these women received labor accelerative intervention.

The alert line, as designed by Philpott & Castle, was meant to represent the cervical dilation rate of the slowest 10% of primigravid patients in the active phase (Philpott & Castle, 1972a; Philpott, 1972); instead, it represented > 20% of the sample, therefore providing evidence that the statistical limit for the rate of active phase cervical dilation is < 1 cm/hr. Indeed, it was the *action line* rather than the alert line that represented the slowest 10.9% of primigravid patients in this study. Since enrollees had cervical dilatations of ≥ 3 cm upon study admission (parturients to the left and right of the alert line at delivery had mean admission dilatations of 5.2 and 3.84 cm, respectively), it was not possible for the action line to be crossed until cervical dilation slowed to at least below 0.64 cm/hr (calculated as the difference between 10 cm and 3 cm divided by 7 hours plus the additional 4 hours needed to

reach the action line) (Philpott & Castle, 1972a). Thus, any parturient admitted at 3 cm cervical dilation who dilated at a minimum rate of *0.64 cm/hr* would remain to the left of the action line, hence, avoiding intervention. This rate is identical to Friedman's active phase slope presented earlier. For women admitted at more advanced dilatations, rates of cervical dilation necessary to remain left of the action line would be even *slower*.

Study by the World Health Organization

The World Health Organization (WHO), under the Maternal Health and Safe Motherhood Program, has produced and promoted the use of the labor partograph as a tool for the early detection of abnormal labor progress and prevention of prolonged labor (World Health Organization. Division of Family Health. Maternal Health and Safe Motherhood Programme., 1994b). The final version of the WHO partograph closely resembles that promoted by Philpott with the central feature being the cervicograph (Philpott & Castle, 1972a; Philpott, 1972). Use of this tool has been credited with decreasing rates of prolonged labor, augmented labor, cesareans, and intrapartum fetal deaths (World Health Organization. Division of Family Health. Maternal Health and Safe Motherhood Programme., 1994; World Health Organization. Division of Family Health. Maternal Health and Safe Motherhood Programme., 1994a). With this graphic tool, no action is indicated for active phase labors remaining on or to the left of the alert line except artificial rupture of the fetal membranes (World Health Organization. Division of Family Health. Maternal Health

and Safe Motherhood Programme., 1994a). According to WHO guidelines, if cervical dilation moves between the alert and action lines, transfer to a more intensive care center is indicated although intervention or augmentation is not performed unless complications develop. Movement to or across the action line indicates full medical assessment with a view to augmentation, termination of labor, or supportive therapy.

A large multicenter trial (n = 35,484) on the impact of partography on labor management and outcome was conducted by the WHO in the early 1990s (World Health Organization. Division of Family Health. Maternal Health and Safe Motherhood Programme., 1994; World Health Organization. Division of Family Health. Maternal Health and Safe Motherhood Programme., 1994a). Data were presented on a subgroup of "normal" nulliparous women admitted in the active phase of labor, i.e., cervix ≥ 3 cm with ≥ 1 uterine contraction(s) in 10 minutes lasting ≥ 20 seconds (n = 2397) (World Health Organization. Division of Family Health. Maternal Health and Safe Motherhood Programme., 1994a). "Normal" encompassed spontaneous labor onset of a singleton pregnancy at 37-42 weeks gestation with a live fetus in cephalic presentation; the pregnancy must have been without significant past obstetric or antenatal complications. Among these normal nulliparae, 30.9% (n = 741) moved to the right of the alert line (i.e., averaged < 1 cm/hr) and, of these, 37.9% (n = 281) went on to reach or cross the action line. In total, 11.7% of normal nulliparous women admitted in the active phase reached or crossed the action line (i.e., dilated at < 0.64 cm/hr) (World Health Organization. Division of Family Health. Maternal Health

and Safe Motherhood Programme., 1994a) which is similar to the 10.9% rate reported by Philpott & Castle (Philpott & Castle, 1972a; Philpott & Castle, 1972b). This provides further evidence that it is the *action line* rather than the alert line that better differentiates the slowest 10% of nulliparous labors. Indeed, based on the *admission* cervical dilatation (i.e., 3, 4, 5, 6, 7, or 8 cm), "normal" nulliparae admitted in the active phase *and* without augmentation had linear cervical dilation rates of 0.12, 0.35, 0.53, 0.65, 0.60, and 0.53 cm/hr, respectively at the 10^{th} percentile (World Health Organization. Division of Family Health. Maternal Health and Safe Motherhood Programme., 1994a). This aligns with the findings of the present systematic review wherein the mean cervical dilatation at active phase onset was 3.93 ± 0.30 cm and the rate of cervical dilation at the statistical limit was 0.48 cm/hr (see Table 1.3).

Clinical Significance

Active phase length and cervical dilation rates are issues intimately linked to the topic of labor dystocia. Dystocia is characterized by the "slow, abnormal progression of labor" (American College of Obstetricians and Gynecologists, 2003). It is a poorly specified diagnostic category that encompasses abnormalities of *power* (inefficient or insufficient uterine contractions and/or maternal expulsive forces), the *passenger* (position, size, or presentation of the fetus), and/or the *passage* (pelvis or soft tissues) (American College of Obstetricians and Gynecologists, 2003; Cunningham et al., 2005). Inefficient uterine contractions (*power*) are regarded to be the most common complication of labor in women never before giving birth and the

greatest contributor to the broader category of dystocia (O'Driscoll, Meagher, & Boylan, 1993). Albeit a nebulous diagnosis, dystocia has been identified as the leading indication for primary cesarean sections (American College of Obstetricians and Gynecologists, 2003; Cunningham et al., 2005), accounting for as much as 50% of all cesareans performed in nulliparous women (*Evaluation of cesarean delivery / [developed under the direction of the task force on cesarean delivery rates, Roger K. Freeman ... et al.]* 2000). Because dystocia is the original indication for most repeat cesareans, it follows that the majority of cesareans in the United States are related to the diagnosis of dystocia (Cunningham et al., 2005). At present, primary and total cesarean rates are 20.6% (Martin et al., 2006) and 31.1% (Hamilton, Martin, & Ventura, 2007), respectively. Among term, low-risk women giving birth for the first time *and* with a vertex presenting fetus, a cesarean rate of 25% was reported by the Centers for Disease Control and Prevention in 2005 (U.S. Department of Health and Human Services. Office of Disease Prevention and Health Promotion., n.d.). All of these cesarean rates are now higher than ever before and farther from national objectives (U.S. Department of Health and Human Services. Office of Disease Prevention and Health Promotion., n.d.).

In clinical practice, dystocia is generally defined as a delay in cervical dilation progression beyond which accelerative interventions, e.g., oxytocin administration, are considered justifiable. Multiple definitions of dystocia, based on cervical dilation rates, exist. Perhaps the most common definition stems from the multifaceted labor

management program *active management of labor* (AML) that was pioneered by O'Driscoll and colleagues with the goal of shortening primigravid labor (O'Driscoll et al., 1993; O'Driscoll, Stronge, & Minogue, 1973). Following the diagnosis of labor, AML accepts 1 cm/hr as the slowest acceptable rate of dilation; slower rates receive prompt accelerative interventions to correct supposed inefficient uterine action (O'Driscoll et al., 1993). Clinical trials of AML have demonstrated that large proportions of women, perhaps even the majority, dilate at < 1 cm/hr at some point during labor (Akoury, Brodie, Caddick, McLaughin, & Pugh, 1988; Cammu & Van Eeckhout, 1996; Clark et al., 1998; Cluett, Pickering, Getliffe, & St George Saunders, 2004; Frigoletto et al., 1995; Lopez-Zeno, Peaceman, Adashek, & Socol, 1992; Rogers et al., 1999). Hence, high rates of accelerative intervention are common with AML with reported oxytocin augmentation rates ranging between 41-75% (Akoury et al., 1988; Cammu & Van Eeckhout, 1996; Clark et al., 1998; Frigoletto et al., 1995; Lopez-Zeno et al., 1992; Rogers et al., 1999). Interestingly, the founders of AML have incrementally decreased their definition of prolonged labor from 48 to 36 to 30 to 24 (O'Driscoll, Jackson, & Gallagher, 1969) and, eventually, to 12 hours (O'Driscoll et al., 1993; O'Driscoll et al., 1973). The rates of uterine stimulation with AML suggest that the clinical expectations of nulliparous labor have surpassed normalcy. Even when more conservative definitions of dystocia are employed [e.g. a period of ≥ 4 hrs after ≥ 3 cm cervical dilatation and near 100% effacement during which the mean rate of dilation is < 0.5 cm/hr (Society of Obstetricians and Gynaecologists of Canada,

1995)], a diagnosis of dystocia is common. A research team using these criteria randomized low-risk, nulliparous women to either early or late amniotomy and found dystocia rates of 33% and 48%, respectively (Fraser, Marcoux, Moutquin, & Christen, 1993). Based on these data, it must be considered that current definitions of dystocia, in terms of cervical dilation rates, may be inappropriately defined.

A matter of statistical and, perhaps, clinical relevance is that labor length may not hold to a statistically normal curve for the population. Specifically, labor length may be positively skewed (Zhang, Yancey, Klebanoff, Schwarz, & Schweitzer, 2001; Zhang et al., 2002); this non-normality is statistically addressed via use of non-parametric statistics or data transformations (e.g., log transformation) prior to the use of parametric statistics. Without data transformation, median labor length may be the superior measure of central tendency with half of the population falling above and half below this value. With positively skewed data, the median will lie to the left of the mean on the horizontal axis. This finding was borne out in the present systematic review where the median and mean active phase labor lengths were 4.91 and 6.45 hours, respectively.

Cervical dilation patterns during the active phase of labor for parturient cohorts are not linear. Some investigators have concluded that a sigmoid pattern develops (Friedman, 1954, 1955, & 1978; Friedman & Kroll, 1969) while others suggest that a hyperbolic pattern lacking a deceleration phase predominates (World Health Organization. Division of Family Health. Maternal Health and Safe Motherhood

Programme., 1994a; Zhang et al., 2002). In either scenario, cervical dilation rates accelerate throughout the majority of active phase labor. For example, Zhang et al. (2002) found that slopes of cervical dilation (cm/hr) progressively steepen with each passing centimeter; median rates between 3-4, 4-5, 5-6, 6-7, 7-8, 8-9, and 9-10 cm were 0.4, 0.6, 1.2, 1.7, 2.2, 2.4, and 2.4 cm/hr, respectively. At the 5th percentile, these dilation rates were 0.1, 0.2, 0.3, 0.5, 0.7, 0.8, and 0.7 cm/hr, respectively. Before 7 cm dilatation, it was not uncommon for there to be no perceivable change in dilation for > 2 hours. When viewed linearly to encompass the entirety of active phase labor, calculations based on Zhang et al. (2002) data find the median and 5th percentile dilation rates to be 1.56 and 0.47 cm/hr, respectively. Therefore, when expected rates of dilation in the active phase are viewed linearly as is common in contemporary practice, the likelihood of accelerative intervention is much greater, especially in earlier active labor. The rates of cervical dilation found in this systematic review are not exempt from this issue; while the mean rate of cervical dilation was 1.01 ± 0.27 cm/hour, progression in the early part of the active phase will typically be slower than this average while progression in the later active phase will typically be more rapid. Although more complex, utilizing a hyperbolic labor curve in prospective clinical decision-making may facilitate more discriminate use of labor accelerative interventions.

Discussions about where the maximum active phase of labor length should be drawn would be moot if there were a clear point where incidences of perinatal

morbidities sharply rise. Such a point has not yet been clearly identified. Moreover, the extent to which the relationship between prolonged labor and labor morbidity is causal is by no means certain. It remains unclear if the risks associated with longer labors are more related to time in labor or to the interventions commonly applied to shorten labor. The World Health Organization maintains that slow progress should be a reason for evaluation rather than for intervention (World Health Organization. Division of Reproductive Health. Maternal and Newborn Health/Safe Motherhood.). More outcome-based research in this area is warranted.

Summary

In summary, among healthy, nulliparous women at term, active phase labor length was found to have a mean of 6.45 ± 1.68 hours while the average rate of cervical dilation in the active phase was 1.01 ± 0.27 cm/hr. At the mean + 2 standard deviations, active phase length was 13.61 hours while cervical dilation was 0.48 cm/hr. This review concludes that current definitions of active phase labor length and expected rates of cervical dilation in the active phase are overly stringent for this population. Revision of existing norms and limits may be warranted and efforts to do so must supersede efforts to change labor to fit existing expectations.

References

American College of Obstetricians and Gynecologists. (2003). ACOG Practice Bulletin Number 49, December 2003: Dystocia and augmentation of labor. *Obstetrics and gynecology*, *102*(6), 1445-1454.

Akoury, H. A., Brodie, G., Caddick, R., McLaughin, V. D., & Pugh, P. A. (1988). Active management of labor and operative delivery in nulliparous women. *American Journal of Obstetrics and Gynecology, 158*, 255-258.

Albers, L. L. (1999). The duration of labor in healthy women. *Journal of Perinatology: Official Journal of the California Perinatal Association, 19*(2), 114-119.

Albers, L. L., Schiff, M., & Gorwoda, J. G. (1996). The length of active labor in normal pregnancies. *Obstetrics and Gynecology, 87*, 355-359.

Alexander, J. M., Lucas, M. J., Ramin, S. M., McIntire, D. D., & Leveno, K. J. (1998). The course of labor with and without epidural analgesia. *American Journal of Obstetrics and Gynecology, 178*(3), 516-520.

Alexander, J. M., Sharma, S. K., McIntire, D. D., & Leveno, K. J. (2002). Epidural analgesia lengthens the Friedman active phase of labor. *Obstetrics and Gynecology, 100*(1), 46-50.

Bofill, J. A., Vincent, R. D., Ross, E. L., Martin, R. W., Norman, P. F., Werhan, C. F., et al. (1997). Nulliparous active labor, epidural analgesia, and cesarean delivery for dystocia. *American Journal of Obstetrics and Gynecology, 177*(6), 1465-1470.

Brisson-Carroll, G., Fraser, W., Breart, G., Krauss, I., & Thornton, J. (1996). The effect of routine early amniotomy on spontaneous labor: A meta-analysis. *Obstetrics and Gynecology, 87*(5), 891-896.

Cammu, H., Clasen, K., Van Wettere, L., & Derde, M. P. (1994). 'To bathe or not to bathe' during the first stage of labor. *Acta Obstetricia Et Gynecologica Scandinavica, 73*(6), 468-472.

Cammu, H., & Van Eeckhout, E. (1996). A randomised controlled trial of early versus delayed use of amniotomy and oxytocin infusion in nulliparous labour. *British Journal of Obstetrics and Gynaecology, 103*(4), 313-318.

Clark, A., Carr, D., Loyd, G., Cook, V., & Spinnato, J. (1998). The influence of epidural analgesia on cesarean delivery rates: A randomized, prospective clinical trial. *American Journal of Obstetrics and Gynecology, 179*(6), 1527-1533.

Cluett, E. R., Pickering, R. M., Getliffe, K., & St George Saunders, N.J. (2004). Randomised controlled trial of labouring in water compared with standard of augmentation for management of dystocia in first stage of labour. *BMJ (Clinical Research Ed.), 328*(7435), 314.

Cunningham, FG, Leveno, KJ, Bloom, SL, Hauth, JC, Gilstrap, LC, Wenstrom, KD (Ed.). (2005). *Williams obstetrics* (22nd ed.). New York: McGraw-Hill.

Evaluation of cesarean delivery / [developed under the direction of the task force on cesarean delivery rates, roger K. freeman ... et al.](2000). In Freeman R. K. (Ed.). Washington, D.C.: American College of Obstetricians and Gynecologists.

Fontaine, P., & Adam, P. (2000). Intrathecal narcotics are associated with prolonged second-stage labor and increased oxytocin use. *The Journal of Family Practice, 49*(6), 515-520.

Fraser, W. D., Marcoux, S., Moutquin, J. M., & Christen, A. (1993). Effect of early amniotomy on the risk of dystocia in nulliparous women. The Canadian early amniotomy study group. *The New England Journal of Medicine, 328*(16), 1145-1149.

Fraser, W. D., Turcot, L., Krauss, I., & Brisson-Carrol, G. (2000). Amniotomy for shortening spontaneous labour. *Cochrane Database of Systematic Reviews (Online),* (2), CD000015.

Fraser, W., Vendittelli, F., Krauss, I., & Breart, G. (1998). Effects of early augmentation of labour with amniotomy and oxytocin in nulliparous women: A meta-analysis. *British Journal of Obstetrics and Gynaecology, 105*(2), 189-194.

Friedman, E. A. (Ed.). (1978). *Labor: Clinical evaluation and management* (2nd ed.). New York: Appleton-Century-Crofts.

Friedman, E. A., & Kroll, B. H. (1969). Computer analysis of labour progression. *The Journal of Obstetrics and Gynaecology of the British Commonwealth, 76*(12), 1075-1079.

Friedman, E. (1954). The graphic analysis of labor. *American Journal of Obstetrics and Gynecology, 68*(6), 1568-1575.

Friedman, E. A. (1955). Primigravid labor: A graphicostatistical analysis. *Obstetrics and Gynecology, 6*(6), 567-589.

Friedman, E. A., & Kroll, B. H. (1971). Computer analysis of labor progression. III. Pattern variations by parity. *The Journal of Reproductive Medicine, 6*(4), 179-183.

Frigoletto, F. D. J., Lieberman, E., Lang, J. M., Cohen, A., Barss, V., Ringer, S., et al. (1995). A clinical trial of active management of labor. *The New England Journal of Medicine, 333*, 745-750.

Garite, T. J., Porto, M., Carlson, N. J., Rumney, P. J., & Reimbold, P. A. (1993). The influence of elective amniotomy on fetal heart rate patterns and the course of labor in term patients: A randomized study. *American Journal of Obstetrics and Gynecology, 168*(6), 1827-31; discussion 1831-2.

Garite, T. J., Weeks, J., Peters-Phair, K., Pattillo, C., & Brewster, W. R. (2000). A randomized controlled trial of the effect of increased intravenous hydration on the course of labor in nulliparous women. *American Journal of Obstetrics & Gynecology, 183*(6), 1544-1548.

Goffinet, F., Fraser, W., Marcoux, S., Breart, G., Moutquin, J. M., & Daris, M. (1997). Early amniotomy increases the frequency of fetal heart rate abnormalities. Amniotomy study group. *British Journal of Obstetrics and Gynaecology, 104*(5), 548-553.

Hamilton, B. E., Martin, J. A., & Ventura, S. J. (2007). Births: Preliminary data for 2006. *National Vital Statistics Reports: From the Centers for Disease Control and Prevention, National Center for Health Statistics, National Vital Statistics System, 56*(7), 1-18.

Johnson, N., Lilford, R., Guthrie, K., Thornton, J., Barker, M., & Kelly, M. (1997). Randomised trial comparing a policy of early with selective amniotomy in uncomplicated labour at term. *British Journal of Obstetrics and Gynaecology, 104*(3), 340-346.

Jones, M., & Larson, E. (2003). Length of normal labor in women of Hispanic origin. *Journal of Midwifery & Women's Health, 48*(1), 2-9.

Lopez-Zeno, J. A., Peaceman, A. M., Adashek, J. A., & Socol, M. L. (1992). A controlled trial of a program for the active management of labor. *The New England Journal of Medicine, 326*, 450-454.

Lyrenas, S. (2002). Labor in the grand multipara. *Gynecologic and Obstetric Investigation, 53*(1), 6-12.

Martin, J. A., Hamilton, B. E., Sutton, P. D., Ventura, S. J., Menacker, F., & Kirmeyer, S. (2006). Births: Final data for 2004. *National Vital Statistics Reports: From the Centers for Disease Control and Prevention, National Center for Health Statistics, National Vital Statistics System, 55*(1), 1-101.

Norwitz, E. R., Robinson, J. N., & Repke, J. T. (2002). Labor and delivery. In S. G. Gabbe, J. R. Niebyl & J. L. Simpson (Eds.), *Obstetrics: Normal and problem pregnancies* (4th ed.). Philadelphia: Churchill Livingstone.

Nuthalapaty, F. S., Rouse, D. J., & Owen, J. (2004). The association of maternal weight with cesarean risk, labor duration, and cervical dilation rate during labor induction. *Obstetrics & Gynecology, 103*(3), 452-456.

O'Driscoll, K., Meagher, D., & Boylan, P. (Eds.). (1993). *Active management of labor: The Dublin experience* (3rd ed.). Aylesbury, England: Mosby.

O'Driscoll, K., Jackson, R. J., & Gallagher, J. T. (1969). Prevention of prolonged labour. *British Medical Journal, 2*(5655), 477-480.

O'Driscoll, K., Stronge, J. M., & Minogue, M. (1973). Active management of labour. *British Medical Journal, 3*(5872), 135-137.

Oscarsson, M. E., Amer-Wahlin, I., Rydhstroem, H., & Kallen, K. (2006). Outcome in obstetric care related to oxytocin use. A population-based study. *Acta Obstetricia Et Gynecologica Scandinavica, 85*(9), 1094-1098.

Perl, F. M., & Hunter, D. J. (1992). What cervical dilatation rate during active labour should be considered abnormal? *European Journal of Obstetrics, Gynecology, and Reproductive Biology, 45*(2), 89-92.

Philpott, R. H. (1972). Graphic records in labour. *British Medical Journal, 4*(5833), 163-165.

Philpott, R. H., & Castle, W. M. (1972a). Cervicographs in the management of labour in primigravidae. I. The alert line for detecting abnormal labour. *The Journal of Obstetrics and Gynaecology of the British Commonwealth, 79*(7), 592-598.

Philpott, R. H., & Castle, W. M. (1972b). Cervicographs in the management of labour in primigravidae. II. The action line and treatment of abnormal labour. *The*

Journal of Obstetrics and Gynaecology of the British Commonwealth, 79(7), 599-602.

Rogers, R., Gilson, G., & Kammerer-Doak, D. (1999). Epidural analgesia and active management of labor: Effects on length of labor and mode of delivery. *Obstetrics and Gynecology, 93*(6), 995-998.

Society of Obstetricians and Gynaecologists of Canada. (1995). *Policy statement number 40: Dystocia*

Svardby, K., Nordstrom, L., & Sellstrom, E. (2007). Primiparas with or without oxytocin augmentation: A prospective descriptive study. *Journal of Clinical Nursing, 16*(1), 179-184.

Turner, M. J., Rasmussen, M. J., Turner, J. E., Boylan, P. C., MacDonald, D., & Stronge, J. M. (1990). The influence of birth weight on labor in nulliparas. *Obstetrics and Gynecology, 76*(2), 159-163.

U.S. Department of Health and Human Services. Office of Disease Prevention and Health Promotion. (n.d.). *Healthy People 2010.* Retrieved June 16, 2008, from the World Wide Web: http://www.health.gov/healthypeople/

Vahratian, A., Zhang, J., Troendle, J. F., Savitz, D. A., & Riz, A. M. (2004). Maternal prepregnancy overweight and obesity and the pattern of labor progression in term nulliparous women. *Obstetrics & Gynecology, 104*(5), 943-951.

World Health Organization. Division of Family Health. Maternal Health and Safe Motherhood Programme. (1994). Partograph in management of labour. *Lancet, 343*(8910), 1399-1404.

World Health Organization. Division of Family Health. Maternal Health and Safe Motherhood Programme. (1994a). *The partograph: The application of the WHO partograph in the management of labour. Report of a WHO multicentre study 1990-1991.* No. WHO/FHE/MSM/94.4). Geneva: World Health Organization.

World Health Organization. Division of Family Health. Maternal Health and Safe Motherhood Programme. (1994b). *Preventing prolonged labour: A practical guide.* No. WHO/FHE/MSM/93.8). Geneva: World Health Organization.

World Health Organization. Division of Reproductive Health. Maternal and Newborn Health/Safe Motherhood. *Care in normal birth: A practical guide. Report of a technical working group.* No. WHO/FRH/MSM/96.24). Geneva: World Health Organization.

Zeisler, H., Tempfer, C., Mayerhofer, K., Barrada, M., & Husslein, P. (1998). Influence of acupuncture on duration of labor. *Gynecologic and Obstetric Investigation, 46*(1), 22-25.

Zhang, J., Yancey, M. K., Klebanoff, M. A., Schwarz, J., & Schweitzer, D. (2001). Does epidural analgesia prolong labor and increase risk of cesarean delivery? A natural experiment. *American Journal of Obstetrics and Gynecology, 185*(1), 128-134.

Zhang, J., Troendle, J. F., & Yancey, M. K. (2002). Reassessing the labor curve in nulliparous women. *American Journal of Obstetrics and Gynecology, 187*(4), 824-828.

Trial	Subject Type	Inclusion / Exclusion Criteria
Garite et al., 1993	Nulliparae*	**Inclusion:** Singleton pregnancy; ≥ 36 - < 42 weeks gestation; spontaneous active labor with a cervical dilatation between 4-6 cm; intact membranes; vertex presentation at or below -2 station; no fetal distress or chorioamnionitis on admission; no previous cesarean section; no pre-eclampsia or complications such as placenta previa; amniotic fluid index between 5-25 cm.
Cammu et al., 1994	Nulliparae	**Inclusion:** Low-risk; ≥ 37 weeks gestation; singleton fetus; cephalic presentation; spontaneous labor onset; cervical dilatation ≥ 3 to ≤ 5 cm; ruptured membranes with clear liquor; no evidence of dystocia at inclusion.
Cammu & Van Eeckhout, 1996	Nulliparae	**Inclusion:** Spontaneous labor; ≥ 37 weeks gestation; singleton fetus; cephalic presentation; normal admission cardiotocogram and clear amniotic fluid on admission; maternal height ≥ 150 cm; ≥ 1 antenatal outpatient clinic visit.
Bofill et al., 1997	Nulliparae	**Inclusion:** ≥ 36 - ≤ 42 weeks gestation; singleton fetus; spontaneous, regular contractions with cervical dilatation of ≥ 4 cm (but < 8 cm) with ≥ 80% effacement and engagement of the fetal vertex. **Exclusion:** Serious medical problems, e.g., insulin-dependent diabetes mellitus, chronic hypertension requiring medication, pregnancy-induced hypertension, etc.; those receiving cervical ripening; oxytocin induction.
Alexander et al., 1998	Nulliparae	**Inclusion:** Normal, term pregnancy; spontaneous labor onset defined as uterine contractions and cervical dilatation ≥ 3 cm; oxytocin augmentation used during labor; vertex presentation; non-operative vaginal delivery. **Exclusion:** Identified pregnancy complication; cervical dilatation > 5 cm; multiple gestations.

Table 1.1 Studies included in active phase labor length and rate of cervical dilation in nulliparous women systematic review

(continued)

Table 1.1 continued

Clark et al., 1998	Nulliparae	**Inclusion:** ≥ 36 weeks gestation; vertex presentation; spontaneous labor defined as ≥ 50% effacement or ruptured membranes in the presence of regular and painful uterine contractions (≥ 2 every 15 minutes). **Exclusion:** Maternal or fetal conditions precluding a trial of labor; thrombocytopenia or coagulation disorder precluding epidural placement; multiple gestation.
Zeisler et al., 1998	Nulliparae	**Inclusion:** Uneventful pregnancy; singleton pregnancy; > 36 week gestation †; cephalic presentation†; spontaneous onset of labor †; spontaneous vaginal delivery. **Exclusion:** Diabetes; pregnancy-induced hypertension; rhesus incompatibility; fetal growth retardation; fetal malformation; cervical ripening with prostaglandins; poor obstetric history.
Albers, 1999	Nulliparae*	**Inclusion:** Low-risk women; singleton pregnancy; ≥ 37 - ≤ 42 weeks gestation; cephalic presentation; spontaneous onset of labor with regular uterine contractions and a cervical dilatation ≤ 4 cm; ruptured membranes < 24 hours. **Exclusion:** Medical problems (hypertension, gestational diabetes, asthma, drug use); oxytocin induction or augmentation; epidural analgesia; operative delivery (cesarean, forceps, vacuum extraction); advanced labor.
Rogers et al., 1999	Nulliparae	**Inclusion:** *Active management of labor group*: Term; spontaneous labor onset defined as regular, painful, palpable uterine contractions ≤ 5 minutes apart with cervical effacement ≥ 80%; epidural analgesia administered during labor; delivered vaginally. *Control group*: Term; spontaneous labor onset defined as cervical dilatation of 3-4 cm with regular, painful uterine contractions; epidural analgesia administered during labor; delivered vaginally.

(continued)

Table 1.1 continued

Fontaine & Adam, 2000	Nulliparae*	**Inclusion:** Singleton pregnancy; ≥ 36 weeks gestation; spontaneous labor onset; cervical dilatation ≤ 7 cm on admission [cervical dilatation < 6 cm for active phase labor length analyses]. **Exclusion:** Induced labor; group misclassification; epidural use; other undefined reasons.
Garite et al., 2000	Nulliparae	**Inclusion:** Uncomplicated singleton gestations; ≥ 36 weeks gestation; spontaneous active labor with dilatation between 2-5 cm with or without ruptured membranes; cephalic presentation. **Exclusion:** Pre-eclampsia; cardiac disease; renal disease; chorioamnionitis, pyelonephritis, or febrile illness before randomization.
Alexander et al., 2002	Nulliparae	**Inclusion:** Healthy women; singleton pregnancy; cephalic presentation; ≥ 37 weeks gestation; spontaneous labor onset; nonanomalous fetus.
Jones & Larson, 2003	Nulliparae*	**Inclusion:** Hispanic women; 15-44 years old; singleton pregnancy; 37-42 weeks gestation; vertex presentation; normal, spontaneous, uncomplicated vaginal birth. **Exclusion:** Multiple gestation; malpresentation; cephalopelvic disproportion; forceps, vacuum, cesarean births; prolonged ruptured membranes; social and medical problems (substance abuse, hypertension, diabetes, and asthma); oxytocin induction or augmentation; regional anesthesia.
Svärdby et al., 2007	Primigravidae ‡	**Inclusion:** Uncomplicated pregnancy; ≥ 37 - < 42 weeks gestation; singleton delivery; cephalic presentation; spontaneous onset of labor.

* Study also included primiparous and/or multiparous groups / sub-groups.
† Through direct contact with authors, the indicated information was clarified.
‡ Through direct contact with authors, it was clarified that primigravid vs. primiparous women were included in the study.

Trial	Prospective or Retrospective	Trial Type	Treatment Groups / Sub-groups
Garite et al., 1993	Prospective	Randomized	▪ Amniotomy group (n = 97) ▪ Intact group (n = 94)
Cammu et al., 1994	Prospective	Randomized	▪ Bathing group (n = 54) ▪ Non-bathing group (n = 56)
Cammu & Van Eeckhout, 1996	Prospective	Randomized	▪ Active management of labor (AML) group (routine early amniotomy and early oxytocin use) (n = 152) ▪ Selective intervention group (no routine amniotomy and more selective oxytocin use (n = 154)
Bofill et al., 1997	Prospective	Randomized	▪ Epidural analgesia for labor pain relief (n = 49) ▪ Narcotics for labor pain relief (n = 51)
Alexander et al., 1998	Retrospective	Secondary analysis of randomized trial	▪ Epidural analgesia for labor pain relief (n = 126) ▪ Meperidine boluses for labor pain relief (n = 73)
Clark et al., 1998	Prospective	Randomized	▪ Epidural analgesia for labor pain relief (n = 156) ▪ Meperidine (intravenous) for labor pain relief (n = 162)
Zeisler et al., 1998	Prospective	Observational	▪ Acupuncture treatment group (n = 57) ▪ Control group (no acupuncture) (n = 63)
Albers, 1999	Prospective	Observational	▪ No treatment (n = 806)

Table 1.2 Type of study and treatment(s) within the studies included in the active phase labor length and rate of cervical dilation in nulliparous women systematic review

(continued)

Table 1.2 continued

Rogers et al., 1999	Retrospective	Randomized	▪ *AML group; epidural analgesia at ≤ 4 cm (n = 85)** ▪ *AML group; epidural analgesia at > 4 cm (n = 27)** ▪ Control group; epidural analgesia at ≤ 4 cm (n = 68) ▪ Control group; epidural analgesia at > 4 cm (n = 43)
Fontaine & Adam, 2000	Retrospective	Chart Review with random selection	▪ Intrathecally injected narcotics (ITN) group (n = 50) ▪ Intravenous narcotics or no analgesia (No ITN) group (n = 50)
Garite et al., 2000	Prospective	Randomized	▪ Isotonic IV fluids at 125 ml/hr during labor (n = 94) ▪ Isotonic IV fluids at 250 ml/hr during labor (n = 101)
Alexander et al., 2002	Retrospective	Secondary analysis of randomized trial	▪ Patient-controlled epidural analgesia group (n = 220) ▪ Patient-controlled intravenous meperidine group (n = 214)
Jones & Larson, 2003	Retrospective	Chart Review	▪ No treatment (n = 120)
Svärdby et al., 2007	Prospective	Observational	▪ Not augmented during labor (n = 50) ▪ Augmented during active phase labor (n = 88) ▪ Augmented during second stage labor (n = 26)

* Treatment group not included in systematic review because cervical dilatation at active phase onset was unknown.

Trial	Treatment	*N*	Dilatation (cm) at active-phase onset*†	Active phase length (hrs)		Active phase slope (cm/hr) ‡	
				Mean (SD)	Mean + 2 SD	Mean	Limit
Garite et al., 1993	Amniotomy group	97	4.3 (0.6) §	5.78 (3.43)	12.64	0.99	0.45
	Intact group	94	4.4 (0.7) §	7.62 (3.88)	15.38	0.73	0.36
Cammu et al., 1994	Bathing group	54	3.8 (0.9)	4.07 (2.32)	8.71	1.52	0.71
	Non-bathing group	56	4.0 (1.0)	4.4 (2.83)	10.06	1.36	0.60
Cammu & Van Eeckhout, 1996	AML	152	3.2 (1.1)	4.23 (2.35)	8.93	1.61	0.76
	Selective intervention	154	3.2 (1.1)	4.72 (2.57)	9.86	1.44	0.69
Bofill et al., 1997	Epidural analgesia	49	4.2 (1.0)	6.25 (2.38)	11.01	0.93	0.53
	Narcotics	51	4.2 (0.9)	5.95 (2.55)	11.05	0.97	0.52
Alexander et al., 1998	Epidural group	126	4	7.9 (3.0)	13.9	0.76	0.43
	Meperidine group	73	4	6.3 (3.0)	12.3	0.95	0.49
Clark et al., 1998	Epidural analgesia	156	4	5.18 (2.7)	10.58	1.16	0.57
	Meperidine (IV)	162	4	4.57 (2.35)	9.27	1.31	0.65
Albers, 1999	None	806	4	7.7 (4.9)	17.5	0.78	0.34
Rogers et al., 1999	Control group; epidural at ≤ 4 cm	68	3-4	10.7 (4.2)	19.1	0.61	0.34
	Control group; epidural at > 4 cm	43	3-4	13.0 (5.4)	23.8	0.50	0.27
Fontaine & Adam, 2000	ITN	50	4	5.17 (--)	--	1.16	--
	No ITN	50	4	4.43 (--)	--	1.35	--
Garite et al., 2000	IV fluids at 125 ml/hr	94	3.6 (--)	8.1 (--)	--	0.79	--
	IV fluids at 250 ml/hr	101	3.8 (--)	6.9 (--)	--	0.90	--

Table 1.3 Studies with mean measures of active phase labor length in active phase labor length and rate of cervical dilation in nulliparous women systematic review (n = 12)

(continued)

Table 1.3 continued

Alexander et al., 2002	Epidural group	220	4.1 (1.0)	6.0 (3.2)	12.4	0.98	0.48
	Meperidine group	214	4.2 (1.0)	5.0 (3.2)	11.4	1.16	0.51
	Meperidine (IM)	39	3	6.6 (3.0)	12.6	1.06	0.56
	Tramadol (IM)	44	3	7.8 (4.4)	16.6	0.90	0.42
Jones & Larson, 2003	None	120	4	6.2 (3.6)	13.4	0.97	0.45
	Weighted mean values		*3.93 (0.30)*	*6.45 (1.68)*	*13.61 (3.51)*	*1.01 (0.27)*	*0.48 (0.13)*

* Group mean (SD) shown when provided in study.
† When a range is given, a mean value was used in slope calculations, e.g. a 3-4 cm range was estimated at 3.5 cm.
‡ Calculated based on assumption that end of active phase is at 10 cm which approximates complete cervical dilatation.
§ Dilatation of groups prior to nulliparous and multiparous data being separated out (data for nulliparous women only was not provided).

Trial	Treatment	*n*	Dilatation (cm) at active-phase onset*	Active phase length (hrs)		Active phase slope (cm/hr) †	
				Median	75th %ile	Mean	75th %ile
Zeisler et al., 1998	Acupuncture group	57	3	3.27	--	2.14	--
	Control group	63	3	5.35	--	1.31	--
Alexander et al., 2002	Epidural group	220	4.1 (1.0)	5.2	8.0	1.13	0.74
	Meperidine group	214	4.2 (1.0)	4.0	7.0	1.45	0.83
Svärdby et al., 2007	Not augmented	50	4 ‡	4.75	--	1.26	--
	Augmentation during active phase labor	88	4 ‡	6.82	--	0.88	--
	Augmentation during second stage labor	26	4 ‡	6.33	--	0.95	--
Weighted mean values			*3.92 (0.42)*	*4.91 (1.01)*	*7.51 (0.50)*	*1.30 (0.31)*	*0.78 (0.05)*

Table 1.4 Studies with median measures of active phase labor length in active phase labor length and rate of cervical dilation in nulliparous women systematic review (n = 3)

* Group mean (SD) shown when provided in study.
† Calculated based on assumption that end of active phase is at 10 cm which approximates complete cervical dilatation.
‡ Through direct contact with authors, it was clarified that active phase onset was defined as 4 cm dilatation.

Author(s)		Acceleration Phase † (2.5-4 cm)	+	Phase of Maximum Slope* (4-9 cm)	+	Deceleration Phase (9-10 cm)	=	Active Phase (2.5-10 cm)
Friedman, 1955	Mean	***(2.33)***	+	***(1.67)***	+	0.9	=	4.9
	Mean + 2 SD	x	+	***(4.17)***	+	y	=	11.7
Friedman & Kroll, 1971	Mean	***(2.41)***	+	***(1.35)***	+	0.84	=	4.6
	Mean + 2 SD	x	+	***(4.55)***	+	y	=	11.7
Friedman, 1978	Mean	***(2.09)***	+	***(1.67)***	+	0.84	=	4.6
	Mean + 2 SD	x	+	***(4.17)***	+	y	=	11.7

Table 1.5 Friedman active phase and sub-phase labor lengths (hrs) for nulliparae/primigravidae

Values in bolded parentheses were calculated based on Friedman's data but were not directly available through his published works. After the length of the phase of maximum slope was calculated, the acceleration phase length was calculable (see below).

* Phase of maximum slope lengths were calculated based on slopes provided in each study, e.g., the 1955 study found a mean maximum slope of 3.0 cm/hr; thus, because the phase of maximum slope involves a cervical change of 5 cm, the mean duration of the phase of maximum slope was calculated as (5.0 cm) ÷ (3.0 cm/hr) = 1.67 hrs.

† Acceleration phase lengths were calculated as total active phase length – deceleration phase length – phase of maximum slope length.

x Non-calculable acceleration phase secondary to limited data available in Friedman publications.

y Non-calculable deceleration phase secondary to limited data available in Friedman publications.

Author(s)	*n*	Active phase length (hrs)		Phase of maximum slope (cm/hr)		Active phase slope (cm/hr)*	
		Mean (SD)	Mean + 2 SD	Mean (SD)	Limit	Mean	Limit
Friedman, 1954	100	4.4 (1.9)	8.2	3.7 (2.1)	--	1.70	0.91
Friedman, 1955	500	4.9 (3.4)	11.7	3.0 (1.9)	1.2	1.53	0.64
Friedman & Kroll, 1971	4175	4.6 (3.6)	11.7	3.7 (5.7)	1.1	1.63	0.64
Friedman, 1978	--	4.6 (3.6)	11.7	3.0 (1.9)	1.2	1.63	0.64

Table 1.6 Active phase slope calculations based on Friedman active phase labor length studies of nulliparae/primigravidae

* Calculated based on mean and statistical limit time required for the cervix to dilate from 2.5 through complete cervical dilatation (approximated at 10 cm).

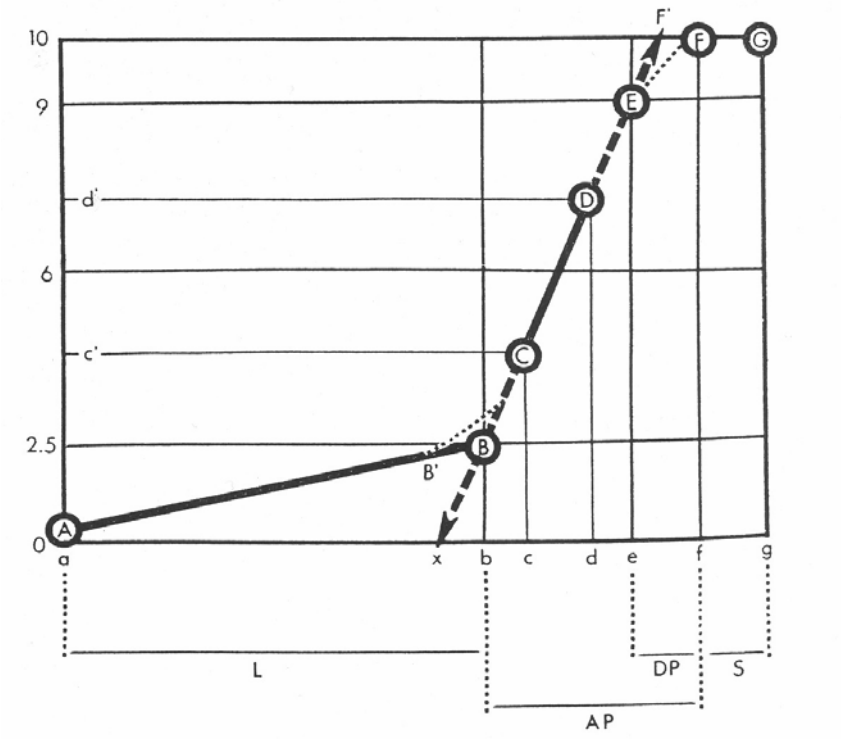


Figure 1.1 Friedman labor curve (Friedman & Kroll, 1969)

Legend

- Vertical axis (y-axis) = cervical dilatation (cm)
- Horizontal axis (x-axis) = time (hrs)
- Point A = time of labor onset
- Point B = approximate time when active phase labor is expected to begin based on the x-intercept formed by Points C & D
- Point B' = true active phase labor onset (if known)
- Point C = non-regressive point between 3.0 and 6.0 cm dilatation
- Point D = non-regressive point between 6.5 and 9.0 cm dilatation and ≥1 cm more than Point C
- Point E = approximate time when the deceleration phase is expected to begin based on the x-intercept formed by Points C & D
- Point F = true second stage onset (if known)
- Point F' = approximate time of second stage onset
- Point G = time of delivery
- x-intercept = used to calculate all missing points in the active phase
- L = latent phase of labor length
- AP = active phase of labor length
- DP = deceleration phase of labor length
- S = second stage labor length

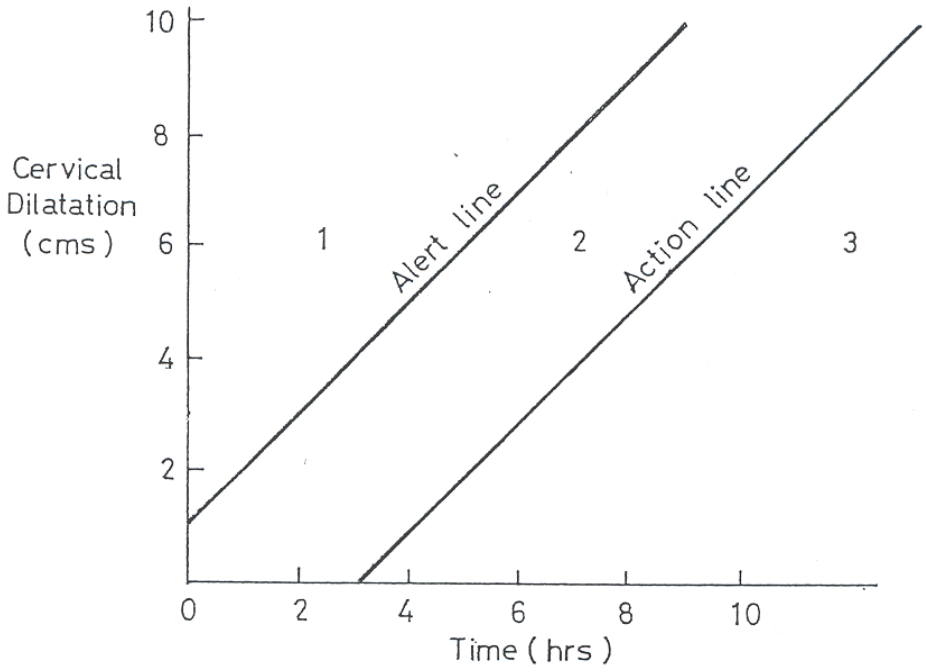


Figure 1.2 Cervicograph proposed by Philpott & Castle (Philpott & Castle, 1972)

The Alert Line on the cervicograph, showing the clinical subgroups:

- Group 1: Those delivered before cervicograph reached the Alert Line.
- Group 2: Those whose cervicograph crossed the Alert Line but who were delivered before it reached the Action Line.
- Group 3: Those whose cervicograph crossed the Action Line.

CHAPTER 2

RELATIONSHIPS BETWEEN LABOR LENGTH AND SYSTEMICALLY MEASURED MATERNAL OXYGENATION, HYDRATION, AND ENERGY SUBSTRATE

Introduction

Muscle fatigue is quantified as a decline in the power capacity [work output] of muscle (Enoka & Duchateau, 2008). While there is no global mechanism responsible for muscle fatigue, skeletal muscle is known to fatigue more quickly in states of decreased oxygenation (Amann et al., 2006; Hepple, 2002; Romer, Haverkamp, Lovering, Pegelow, & Dempsey, 2006), hydration (Barr, Costill, & Fink, 1991; Judelson et al., 2007; Maughan, 1992; Maughan, Bethell, & Leiper, 1996; Maughan, 2001; Noakes, 1993; Shirreffs, 2005), and energy substrate availability (Callow, Morton, & Guppy, 1986; Hultman & Greenhaff, 1991; Karelis, Peronnet, & Gardiner, 2002; Marcil, Karelis, Peronnet, & Gardiner, 2005). The relationship between these three physiological factors and fatigue in uterine smooth muscle during labor, however, is less well known yet clinically relevant since uterine fatigue may culminate in longer labors and more surgical deliveries. Thus, relationships and differences in systemically measured

maternal oxygenation, hydration, and energy substrate is the focus of this investigation with labor duration being the outcome variable of interest.

Background

Uterine fatigue is a likely contributor to inefficient uterine contractile activity during labor which, in turn, is regarded to be the greatest contributor to labor dystocia (O'Driscoll et al., 1993). Dystocia, i.e., "slow, abnormal progression of labor" (American College of Obstetricians and Gynecologists, 2003), although a poorly defined diagnostic category, has been identified as the most common indication for primary (first time) cesarean deliveries (American College of Obstetricians and Gynecologists, 2003; Cunningham et al., 2005), accounting for as much as 50% of all cesareans performed in nulliparous women (*Evaluation of cesarean delivery / [developed under the direction of the task force on cesarean delivery rates, Roger K. Freeman ... et al.]* 2000). Indirectly, dystocia accounts for even more cesareans since many repeat cesareans are performed after primary operations for dystocia (Cunningham et al., 2005). For this reason, the American College of Obstetricians and Gynecologists (ACOG) wrote that it is "appropriate to focus on low-risk nulliparous patients with term singleton fetuses with vertex presentations when evaluating strategies for lowering the primary cesarean delivery rate" (*Evaluation of cesarean delivery / [developed under the direction of the task force on cesarean delivery rates, Roger K. Freeman ... et al.]* 2000).

In the United States, rates of cesarean delivery are higher than ever before with primary and total rates being 20.6% (Martin et al., 2006) and 31.1% (Hamilton et al., 2007), respectively. Among term, low-risk women giving birth for the first time *and* with a vertex presenting fetus, a cesarean rate of 25% was reported by the Centers for Disease Control and Prevention in 2005 (U.S. Department of Health and Human Services. Office of Disease Prevention and Health Promotion., n.d.). These rates are up to three times higher than the 10-15% cesarean rate deemed justifiable for any world region by the World Health Organization (World Health Organization, 1985). Reaffirming this figure, Althabe & Belizán (2006) recently suggested that a cesarean rate between 5-10% seems to achieve the best outcomes, whereas a rate higher than 15% seems to result in more harm than good. As cesarean rates rise, increased risk of maternal (Davis, 1999; Eisenkop, Richman, Platt, & Paul, 1982; Henderson & Love, 1995; van Ham, van Dongen, & Mulder, 1997) and neonatal (Hales, Morgan, & Thurnau, 1993; Levine, Ghai, Barton, & Strom, 2001; Morrison, Rennie, & Milton, 1995; National Institutes of Health, 2006; Parilla, Dooley, Jansen, & Socol, 1993) morbidities follow.

Inherent in a diagnosis of dystocia is a much greater likelihood of slower cervical dilation and, ultimately, increased labor duration for those achieving vaginal delivery. Because uterine efficiency during labor can be gauged only by its ability to cause the cervix to dilate during the first stage of labor and to cause the fetal head to descend during the second stage, each as measured by time, labor

duration is an appropriate outcome measure when investigating potential contributors to uterine fatigue and dystocia. Adequate oxygenation, hydration, and energy substrate availability are potentially important variables in optimal uterine perfusion and function and, thus, may be related to uterine efficiency during labor. Studies have reported that hypoxia rapidly decreases uterine contractile force (Monir-Bishty, Pierce, Kupittayanant, Shmygol, & Wray, 2003), more rapid intravenous fluid administration may shorten labor duration (Garite et al., 2000), and ketosis in labor may have deleterious effects on uterine function and is associated with the need for augmentation (Foulkes & Dumoulin, 1985). These studies, however, were limited to *in vitro* analyses (Monir-Bishty et al., 2003), by measures made at undisclosed sampling time points (Foulkes & Dumoulin, 1985), or even by a lack of physiological measurement (e.g., hydration) (Garite et al., 2000).

The conceptual framework guiding the current investigation is dynamic (see Figure 2.1). From left to right, decreased oxygenation, decreased hydration status, and decreased energy substrate availability are hypothesized to lead to increased uterine muscle fatigue and, subsequently, increased labor duration. There are also others factors not directly impacting uterine muscle fatigue that may increase labor duration, e.g., higher maternal anxiety, pain, and/or body mass index (BMI) and infant birth weight. From right to left, increased labor duration may impact uterine muscle fatigue and can also contribute to decreased hydration status and decreased energy substrate availability, likely in a time-dependent

manner. If the *systemic* measurement of any of these variables is found to be related to labor duration, alternative labor management strategies may be supported, e.g., [1] adequate and effective treatment of anemic or near-anemic states existing near the time of labor onset and assurance of adequate SaO_2 during labor, [2] assessments of adequate hydration and nutrition prior to and during labor.

The objectives of the present investigation were to identify the relationships between labor duration and maternal oxygenation, hydration, and energy substrate availability, each as measured systemically at active phase labor admission and again 4 hours later in low-risk nulliparous women. In addition, the study aimed to determine if, among the variables (i.e., oxygenation, hydration, and energy substrate as well as pain and anxiety), there were differences at either time point between two distinct labor duration groups based on the mean labor duration of those correctly classified as being in active labor. Likewise, the study aimed to determine if repeated measure differences existed in any of the aforementioned physiological variables *between* the labor duration groups. Paired-sample differences were used to describe within-subject differences in the variables as measured at active phase labor admission and again 4 hour later. Finally, correlations between labor duration and several additional variables reported to have relationships with labor duration were described (i.e., maternal age and BMI; gestational age at delivery; cervical dilatation at labor admission; maximal maternal temperature during labor; infant birth weight and length).

Methods

A prospective study was conducted at a suburban, academic, Midwestern medical care center in which 4774 women were delivered in 2007. Institutional Review Board approval was obtained for all work in the study, and written, informed and HIPAA consents were obtained from all women. Recruitment primarily occurred in the labor and delivery triage unit or in the labor room as soon after admission for a diagnosis of active phase labor as possible. Recruitment occurred between April, 2007 and February, 2008.

This was a study of nulliparous women of low obstetric risk (no significant medical history, absence of major complication of pregnancy, e.g., pre-eclampsia or diabetes) with a labor care provider *diagnosis* of spontaneous labor in the early active-phase of the first stage of labor. Active phase onset diagnosis required that cervical dilatation be ≥ 3 - ≤ 5 cm in the presence of regular uterine contractions (≥ 2 contractions in any 10 minute window objectively determined by external monitoring or palpation) *and* a provider decision to admit for labor. Additional inclusion criteria were: 1) 18-39 years of age; 2) singleton gestation; 3) gestational age ≥ 37 - ≤ 42 weeks (259-294 days); 4) anticipated vaginal delivery; 5) with or without ruptured membranes; 6) cephalic presentation; 7) weight < 250 lbs (< 114 kg) at study entry; 8) no identified fetal anomalies or growth issues; 9) afebrile at study entry; and 10) able to read and speak English. Participants with augmentation of labor after being diagnosed with active phase labor onset were retained in the study while women

undergoing labor inductions were excluded. Amniotomy, narcotic analgesia, epidural anesthesia, oxytocin augmentation, and other labor management decisions were at the discretion of the managing physician or certified nurse-midwife. These data were obtained from the medical record.

Operational definitions used in the present study included the following: *active phase of labor duration* encompassed the time cervical dilatation was determined to be ≥ 3 - ≤ 5 cm in the presence of regular uterine contractions *and* there was a provider decision to admit for labor through determination of complete cervical dilatation (approximated at 10 cm). *Total labor duration* was the time from active phase of labor onset through delivery.

In light of the knowledge that many parturients admitted for supposed active phase labor are likely still in latent labor as indicated by subsequent rates of cervical dilation, investigator adapted criteria for *misclassified* and *correctly classified* active labor onset were established *a priori* and applied retrospectively to group subjects. A *misclassified active labor onset* was defined as average cervical dilation < 0.5 cm/hour for 4 hours after a physician/midwife *diagnosis* of active labor onset. *Correctly classified active labor onset* encompassed labors progressing at ≥ 0.5 cm/hour over this same time frame. Rationale for these definitions were derived from the definition of primary dystocia (termed "dysfunctional labor") put forth by the Society of Obstetricians and Gynaecologists of Canada, i.e., a period of ≥ 4 hours after ≥ 3 cm cervical dilatation and near 100% effacement during which the mean rate of dilation is <

0.5 cm/hour (Society of Obstetricians and Gynaecologists of Canada, 1995) in conjunction with the finding that approximately one-half of low-risk parturients are not in active labor at 4 cm dilatation based on traditional definitions put forth by Friedman (Peisner & Rosen, 1986). Secondary dystocia was diagnosed when, after ≥ 2 hours of correctly classified active phase onset, the cervical dilation rate became < 0.5 cm/hour for 4 hours at any point during labor. Thus, no subject could have both a misclassified active phase onset and secondary dystocia. Cesareans were classified according to when they were performed (i.e., active phase or second stage) and whether the physician documented a dystocia (e.g., arrest of dilation or arrest of fetal descent) or non-dystocia (e.g., non-reassuring fetal heart patterns) indication.

Systemic measures of maternal oxygenation, hydration, and energy substrate levels were made in this study. Maternal oxygenation was operationalized as hemoglobin-bound oxygen (Hb-bound O_2) which represents approximately 97% of all O_2 in the blood; the remainder of O_2 is physically dissolved in the blood (Guyton & Hall, 2006). Hb-bound O_2 (ml O_2 / dL blood) = [Hb] x 1.34 ml O_2 per gram of Hb (a physiological constant representing the O_2 carrying capacity of 100% saturated Hb) x O_2 saturation (SaO_2) (normal physiological range for Hb-bound O_2 = 15.21 – 20.77 ml O_2 / dL blood). Hemoglobin concentration measures were made at active phase labor onset diagnosis in the hospital laboratory via a Beckman Coulter® LH 750 (Beckman Coulter, Inc., Fullerton, CA), an automated quantitative hematology analyzer that

utilizes a refined electronic particle counting principle to quantitate white cells, red cells, and platelets [normal physiological range for Hb (females) = 11.7-15.5 g/dL]. Hemoglobin collection did not impose any additional invasiveness since a complete blood count is a standard medical order for all women admitted to this unit. SaO_2, a measure of O_2 bound to Hb, was measured via a Nellcor® N-595 pulse oximeter (Tyco Healthcare, Pleasanton, CA) for 3-5 minutes as near as possible to the diagnosis of active phase labor onset and again four hours later if birth had not occurred (normal physiological range for SaO_2= 96-100%) . Score™ analysis software (Mallinckrodt, St. Louis, MO) was used to trend the data and calculate mean SaO_2 for each time point.

Hydration status was determined by urine specific gravity measurements made via an Atago Clinical Digital Refractometer PAL-10S (range = 1.000-1.060; accuracy ±0.001) (Atago Co., Ltd.) (normal physiological range for urine specific gravity = 1.003-1.035). Urine specimens were obtained either via clean-catch or removed from the Foley catheter if present. Energy substrate measures were determined via blood glucose and β-hydroxybutyric acid fingerstick measurements by a Precision Xtra™ blood glucose (range = 20-500 mg/dL) and ketone (range = 0.0-6.0 mmol/L) monitoring system (Abbott Laboratories, Abbott Park, IL) (normal physiological values: glucose = 70-110 mg/dL; β-hydroxybutyric acid < 0.6 mmol/L). Hydration and energy substrate measures were made as near as possible to the diagnosis of active phase onset and again four hours later if birth had not occurred.

In addition to the aforementioned physiological variables, measures of maternal pain and anxiety were collected as they may potentially impact labor duration. Contraction-related pain was measured by visual analog scale (VAS), a 10 cm straight vertical line scale with the words “no pain” and “worst possible pain” at the bottom and top, respectively (range = 0-10.0). A similar tool has been tested in laboring women (Gaston-Johansson, Fridh, & Turner-Norvell, 1988; Gaston-Johansson, 1996; Sittner, Hudson, Grossman, & Gaston-Johansson, 1998) and has demonstrated reliability and validity (Gallagher, Bijur, Latimer, & Silver, 2002; Gaston-Johansson et al., 1988; Gaston-Johansson, Hofgren, Watson, & Herlitz, 1991; Gaston-Johansson, Franco, & Zimmerman, 1992; Gaston-Johansson, 1996; Grossman et al., 1992). Anxiety was also measured by VAS, a 10 cm straight horizontal line scale with the words “no anxiety” and “worst possible anxiety” at the left and right, respectively. VAS for anxiety has been used during labor (Chang, Wang, & Chen, 2002) and is significantly correlated with standard, full-length measures of anxiety, e.g., state anxiety within the State-Trait Anxiety Inventory ($r = 0.64$; $p < 0.001$) (Elkins, Staniunas, Rajab, Marcus, & Snyder, 2004), the anxiety scale of the Delusional-Symptom-Status-Inventory ($r = 0.35$; $p < 0.01$) (Tamiya et al., 2002), and the Taylor Manifest Anxiety Scale ($r = 0.29$; $p < 0.05$) (Tamiya et al., 2002).

Demographic variables were expressed as mean (SD) if continuous and as n (%) if categorical. To test for relationships, Pearson product moment correlation coefficients (r) were calculated; with a medium effect size (0.30), $\alpha = 0.05$, and

power = 0.80, a sample of 85 was required (Cohen, 1988). To determine differences between two group means, Student's *t* tests were performed; with a medium to large effect size (0.65), alpha (α) of 0.05, and power of 0.80, 45 subjects per group were required (Cohen, 1988). Thus, a total sample of 90 women achieving vaginal birth with complete data was needed. Repeated measures analysis of variance was used to compare between group differences in the variables as measured over time, i.e., active phase labor onset diagnosis and again four hours later. Paired *t* tests were used to determine differences in the variables occurring over time in any given subject. 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 SPSS (version 15.0, Chicago, IL).

Results

A total of 93 parturients were enrolled in the study and included in the analysis. There was no attrition. Demographics of the study sample are shown in Table 2.1. The majority of the sample self-classified as non-Hispanic whites. Among all parturients achieving vaginal delivery (n = 83), active phase and total labor durations were 7.44 ± 3.26 and 8.89 ± 3.66 hours, respectively. Among parturients achieving vaginal delivery *and* with a correctly classified active phase labor onset (n = 43), active phase and total labor durations were 5.64 ± 1.85 and

6.97 ± 2.43 hours, respectively. Women with misclassified active phase onsets with eventual vaginal delivery (n = 40) had mean active phase and total labor durations that were 3.74 and 3.98 hours longer, respectively (9.38 ± 3.36 hours and 10.95 ± 3.67 hours), when compared to women with correctly classified active phase onsets ($p < 0.001$). There was only one case of secondary dystocia based on the dilation rate criteria which, ultimately, culminated in a second stage cesarean for arrest of fetal descent. Among all cesareans (n = 10), six were performed in the active phase (arrest of dilation = 3; non-reassuring fetal heart patterns = 3) and four were performed in the second stage for arrest of fetal descent. All neonates were admitted to the well baby newborn nursery except one who was admitted to the special care nursery after cesarean delivery for maternal arrest of dilation.

When all women delivering vaginally were considered together, neither active phase labor duration nor total labor duration was found to be significantly correlated with maternal oxygenation, hydration, energy substrate, pain, or anxiety at either baseline or baseline + 4 hours. However, urine specific gravity at active phase onset diagnosis and active phase duration were moving toward a near-significant inverse relationship ($r = -0.182$; $p = 0.104$). When analyses were limited to only those with a correctly classified active phase onset, no significance was found.

Among women with a correctly classified active phase onset and subsequent vaginal delivery (n = 43), the mean active phase and total labor

durations were 338 and 418 minutes, respectively. These means were subsequently used to divide the sample into two distinct labor duration groups for between-group comparison. For all women in the sample delivering vaginally (n = 83), those with an active phase duration < 338 minutes (n = 22) were compared to those with an active phase duration ≥ 338 minutes (n = 61). Urine specific gravity measures taken at the active phase labor onset diagnosis was the only major study variable found to be significantly different between these groups. The shorter active phase labor duration group was less hydrated than the longer active phase labor duration group (specific gravity = 1.017 vs. 1.012; t = 2.647; p = 0.010). Of interest, maternal temperature *at labor admission* was higher in those with an active phase duration < 338 minutes (98.1° F vs. 97.6°) (t = 2.637; p = 0.010). Division of the sample into groups based on mean total labor duration [i.e., < 418 (n = 25) and ≥ 418 min (n = 58)] yielded no significant differences in any physiological variable between the groups although urine specific gravity at active phase onset diagnosis was near-significant (1.016 vs. 1.012, respectively) (t = 1.960; p = 0.053). Likewise, urine specific gravity measures taken four hours after a diagnosis of active phase onset was non-significantly higher (indicating less hydration) in the shorter total labor length group (1.014 vs. 1.011, respectively) (t = 1.663; p = 0.101).

When limiting analyses to only those with a correctly classified active phase onset and subsequent vaginal delivery (n = 43), active phase labor duration group comparisons [i.e., < 338 (n = 22) and ≥ 338 min (n = 21)] yielded non-

significantly lesser hydration in the shorter active phase group at active phase onset (specific gravity = 1.017 vs. 1.013; t = 1.455; p = 0.153) as well as non-significantly higher baseline glucose in this group (93 vs. 86 mg/dL; t = 1.677; p = 0.101). Total labor duration group comparisons [i.e., < 418 (n = 24) and ≥ 418 min (n = 19)] resulted in no statistically significant mean differences between the groups. However, women with shorter total labor durations had non-significantly greater circulating glucose at active phase labor onset (93 vs. 86 mg/dL; t = 1.736; p = 0.090) but were non-significantly lesser hydrated four hours after a diagnosis of active phase onset (specific gravity = 1.014 vs. 1.010; t = 1.430; p = 0.162). These groups had only a maximum of 24 subjects, hence the statistics were underpowered.

Repeated measures analysis of variance yielded no statistically significant differences between maternal oxygenation, hydration, energy substrate, pain or anxiety measures when labor duration groups were formed based the mean labor length of those correctly classified as being in active labor (i.e., 338 minutes for active phase labor and 418 minutes for total labor) although these tests were likely underpowered statistically. Repeated measure analysis of β-hydroxybutyric acid measures was complicated due to the non-normal distribution of these variables at both data collection time points per Kolmogorov-Smirnov testing ($p < 0.05$). With each measure being positively skewed, logarithmic data transformations were used which was able to normalize the second time point β-hydroxybutyric acid measures but not the first. For this reason, it was decided to forego the repeated

measure of this variable and, instead, differences between the time points were calculated with values used in non-parametric group comparisons via Mann-Whitney U. No differences between mean labor length groups emerged. Repeated measures statistics computed after limiting analyses to only those with a correctly classified active phase onset and subsequent vaginal delivery yielded no significant findings.

Paired-sample analyses were performed between measures made at the diagnosis of active phase labor onset and again 4 hours later (i.e., oxygenation, urine specific gravity, glucose, β-hydroxybutyric acid, pain, and anxiety). Among all women delivering vaginally *and* with measures made at each time point, β-hydroxybutyric acid levels increased significantly over time ($p < 0.001$) whereas pain and anxiety significantly decreased over time ($p < 0.001$) with Bonferroni correction (see Table 2.2). The significant decrease in pain over time is likely explained by the epidural anesthesia used by all but five women. Subsequently, the decrease in anxiety is not unexpected since pain and anxiety are significantly positively related (i.e., pain and anxiety among all women at time point 1 ($r = 0.357$, $p = 0.001$) and at time point 2 (Spearman's rho = 0.331, $p = 0.004$). When limiting analyses to those correctly classified as being in active labor and achieving a vaginal delivery, β-hydroxybutyric acid levels and pain remained significantly different over time in the same directions noted above for all women whereas anxiety ($t = 2.318$, $p = 0.027$) and hydration ($t = 1.770$, $p = 0.086$) were trending toward significance after Bonferroni correction (see Table 2.3).

To address the final aim of the present study, relationships between variables potentially related to labor duration and labor duration were investigated. Among all parturients delivering vaginally, cervical dilatation at labor admission had a significantly modest inverse relationship with active phase labor duration whereas maximum maternal temperature during labor (mean = 98.7 ± 1.1° F; range = 95.8 – 101.7° F) had a significant medium positive relationship with active phase labor duration (see Table 2.4). In addition, total labor duration had a medium positive correlation with maximum maternal temperature during labor and low positive correlations with maternal BMI, infant birth weight, and infant birth length. When limiting analyses to those with a correctly classified active phase labor onset, total labor duration was found to hold medium positive correlations with maternal BMI, maximum maternal temperature during labor, infant birth weight, and infant birth length (see Table 2.4). Interestingly, maternal temperature *at labor admission* had a medium inverse relationship with total labor duration in parturients with a correctly classified active phase labor onset ($r = -0.393$, $p < 0.01$). Intercorrelations between urine specific gravity, glucose, and β-hydroxybutyric acid are shown in Table 2.5. While significant positive correlations were expected between physiological measures made at time point 1 and time point 2 (e.g., urine specific gravity), other relationships emerged showing the interconnectedness of these variables. For example, at baseline, lower glucose was associated with higher β-hydroxybutyric acid levels (Spearman's rho = -0.293, $p = 0.007$). The one relationship found to be significant

between different variables *and* across the time points (i.e., urine specific gravity at time point 1 and glucose at time point 2) is more difficult to explain.

Discussion

Contributors to increased labor length are likely heterogeneous and variable. At the cellular level, adequate perfusion and delivery of oxygen and energy substrate will facilitate more efficient myometrial contractions whereas deficient states may lead to uterine fatigue. The findings in the present study suggest that, in otherwise healthy nulliparous women, systemically measured hydration and glucose levels may impact labor duration while Hb-bound O_2 and β-hydroxybutyric acid levels do not. Further investigations based on a larger sample size are necessary to illuminate these preliminary findings.

In vitro studies have reported that hypoxia is capable of impairing oxidative phosphorylation and reducing uterine myometrial contractile force on a rapid time scale (Monir-Bishty et al., 2003). Acidosis, associated with hypoxia because of the anaerobic metabolism byproducts, may ensue which can profoundly inhibit uterine contractions in human pregnant myometrium as demonstrated by a reduction or abolishment of contractions with decreased intracellular (Parratt, Taggart, & Wray, 1994; Parratt, Taggart, & Wray, 1995b; Pierce, Kupittayanant, Shmygol, & Wray, 2003) or even extracellular pH (Pierce et al., 2003). A significant intracellular alkalinization over the last few weeks of pregnancy has been reported which may contribute to strong and efficient contractions during labor (Parratt, Taggart, & Wray, 1995a).

Because approximately 97% of all blood oxygen (O_2) is chemically bound with hemoglobin (Hb), adequate O_2 delivery to metabolically active tissues, like uterine muscle, is dependent upon sufficient concentrations of Hb as well as adequate O_2 saturation (SaO_2). Thus, it is plausible that decreased maternal Hb-bound O_2 (↓ [Hb] and/or ↓ SaO_2) may lead to decreased uterine efficiency via uterine fatigue and increased labor lengths. This hypothesis was not, however, supported in the present study as there was neither a significant relationship between labor durations and Hb-bound O_2 nor differences in Hb-bound O_2 between any labor duration groupings based on the mean duration. Our findings align with those of Friedman (1978) who reported that the Hb levels of nulliparous women (n = 252) obtained just prior to or early in labor lacked a significant relationship with active phase length. Also supporting findings by Friedman (1978), the present study found low positive correlations between Hb levels and maternal age ($r = 0.234$; $p = 0.033$), infant birth weight ($r = 0.228$; $p = 0.038$), and gestational age ($r = 0.324$; $p = 0.003$). Of note, only 8 women had Hb values < 11 g/dL and only 2 had values < 10.5 g/dL; all but one SaO_2 measure was > 95%. Therefore, Hb-bound O_2 measures had minimal variability.

Adequate hydration during labor also would potentially assist in the delivery of O_2 and nutrients as well as facilitate the elimination of waste from the contracting uterus. While the importance of hydration during exercise has been demonstrated among athletes (Barr et al., 1991; Judelson et al., 2007; Maughan, 1992; Maughan et al., 1996; Maughan, 2001; Noakes, 1993; Shirreffs, 2005) only

one study to date has investigated maternal hydration as a potential variable in labor progress (Garite et al., 2000). Garite et al. (2000) randomized low-risk, nulliparous women in spontaneous labor (n = 195) to receive 125 or 250 mL per hour of intravenous isotonic fluids. In the 250 mL group, there were strong trends toward a shorter mean first stage of labor length (483 vs. 413 min; $p = 0.060$) and a shorter total labor length (552 vs. 484 min; $p = 0.060$). The number of labors lasting > 12 hours was significantly lower in the 250 mL group (13% vs. 26%; $p = 0.047$) for women delivering vaginally and there were fewer cesareans in the 250 mL group (10 vs. 16). These data indicate that inadequate hydration in labor may decrease uterine efficiency potentially through a uterine fatigue pathway. The Garite et al. (2000) study did not, however, measure maternal hydration by scientific means (e.g., urine specific gravity), thus, actual hydration status remained unknown.

The hydration findings of the present study are counterintuitive to skeletal muscle physiology and contradict the findings of Garite et al. (2000). Maternal hydration at active phase labor diagnosis was non-significantly inversely related to active phase duration among all women admitted for active phase labor onset suggesting that less hydrated parturients may have shorter active phase labors. When dividing parturients into groups based on mean active phase labor length for those correctly classified as being in active labor, those in the shorter active phase labor duration groups were less hydrated at the time of active phase onset diagnosis, a finding that was significant for the total sample (i.e., correctly

classified *and* misclassified active phase onset). Although the reasons behind these between-group-differences are not completely forthcoming, a half-century ago it was demonstrated that better hydrated states decrease the central release of antidiuretic hormone and oxytocin through blood volume expansion (Henry, Gauer, & Reeves, 1956). Under this physiologic premise, treatment of preterm labor typically includes assurance of adequate hydration although its efficacy remains unproven; while some studies support this practice (Bieniarz, Burd, Motew, & Scommegna, 1971; Goodlin, Quaife, & Dirksen, 1981) others do not (Frentzen, Johnson, & Simpson, 1987; Ingemarsson, 1976; Pircon, Strassner, Kirz, & Towers, 1989). As hypervolemia *may* slow preterm labor, it may do the same for term labor which may explain the present study findings. In better hydrated states, the increased intravascular volume may also dilute and subsequently attenuate the effects of certain circulating hormones that may be essential to labor, e.g., corticotropin-releasing hormone and estrogens. Interestingly, the women in the present study received intravenous isotonic hydration at an average rate of 334 ± 135 ml/hour up to the time of vaginal delivery; the average volume received from the time of admission to delivery was 2685 ± 955 ml. These fluids included a standard order of 125 ml/hour during labor, a standard 1500 ml fluid bolus prior to epidural placement, additional boluses for clinical reasons (e.g., non-reassuring fetal heart patterns, maternal hypotension), and volumes associated with antibiotic administration. Even with the intravenous volumes received, hydration states did not significantly change

between the measurement time points among all parturients ($t = 1.402$; $p = 0.165$) or those correctly classified as being in active labor ($t = 1.770$; $p = 0.086$).

Nutrition needs during labor are not well-studied although it has been reported that women in the third trimester of pregnancy exhibit a state of "accelerated starvation" with rapid rises in plasma β-hydroxybutyric acid [the principal labor ketone (Bencini & Symonds, 1972; Posner & Silverstone, 1977)] and a concomitant fall in plasma glucose (Metzger, Ravnikar, Vileisis, & Freinkel, 1982). This process of accelerated lipolysis conserves glucose for the fetus but renders pregnant women extremely vulnerable to ketosis (Foulkes & Dumoulin, 1985). Ketones arise in the liver as a result of fat metabolism when glycogen stores are unavailable (e.g., in starvation states or with excessive exercise) and are normally oxidized to carbon dioxide, water, and alternate energy that is usable by tissues such as a contracting uterus (Foulkes & Dumoulin, 1985; Watanabe et al., 2001). Ketones produced in quantities above the level of need results in ketosis. Rates of fat catabolism are likely accelerated on labor wards where food is commonly withheld to minimize the risk of gastric content inhalation during anesthetic induction, an extremely rare but serious event first described by Mendelson (1946).

During labor, comparable to an exercise state, the metabolic demands rapidly lead to ketosis in the absence of glycogen stores; some believe this has a detrimental effect on labor progress (Dumoulin & Foulkes, 1984). Ketonuria reportedly occurs in 45% of nulliparous labors and has been reported to be

associated with the need for augmentation of labor suggesting that ketosis in labor may have deleterious effects on uterine function (Foulkes & Dumoulin, 1985). In nulliparous women whose labors had a spontaneous onset, labors lasting < 6 hours, 6-12 hours, and > 12 hours had ketosis incidences of 22%, 46%, and 72%, respectively (Foulkes & Dumoulin, 1985). The present study found no evidence that β-hydroxybutyric acid measures were related to active phase or total labor durations. The availability of adequate concentrations of glucose, however, may be important to efficient labor progress, especially at the diagnosis of active phase labor onset. The differences in glucose means between labor duration groups among those correctly classified as being in active labor were trending toward statistical significance and, hence, warrant further research.

Maternal anxiety during labor results in large increases in circulating catecholamines, i.e., norepinephrine and epinephrine (Lederman, McCann, Work, & Huber, 1977; Lederman, Lederman, Work, & McCann, 1978; Lederman, Lederman, Work, & McCann, 1985) which may impact labor length through adrenergic actions (Bulbring & Tomita, 1987; Segal, Csavoy, & Datta, 1998). In the usual physiologic range for laboring women, catecholamines have been reported to decrease contractions by at least one-third below baseline (Segal et al., 1998). Epinephrine levels are demonstrated to be positively correlated with anxiety and labor length ($p < 0.01$) (Lederman et al., 1978). In the present study, maternal anxiety at the diagnosis of active phase of labor onset was non-significantly higher in the longer active phase labor length group among all

parturients. Although pain may possibly lengthen labor through the aforementioned catecholamine mechanism, no statistically significant relationships or mean differences were found in the present study.

Significant relationships that were identified between many of the contextual variables and labor duration are not surprising. For example, it has been reported that increases in maternal weight are associated with labor length increases (Nuthalapaty et al., 2004; Vahratian et al., 2004) as well as increases in cesareans (Bergholt, Lim, Jorgensen, & Robson, 2007; Seligman et al., 2006). Likewise, infant birth weight has been reported to be positively correlated with nulliparous labor length (Turner et al., 1990). The present study supports these findings, demonstrating that maternal BMI, infant birth weight, and infant birth length were all positively correlated with total labor length; these factors also all held medium to high positive intercorrelations ($p \leq 0.006$).

Among all parturients achieving vaginal delivery in the present study, 7 (8.4%) had maximum temperatures during labor $\geq 100.4°$ F. The finding of a medium positive correlation between maximum maternal temperature during labor and labor duration makes intuitive sense although it remains unclear if the risk of elevated temperature is more related to time in labor or to interventions commonly applied during labor. For example, while the length of time that the fetal membranes were ruptured was significantly related to maximum maternal temperature (Spearman's rho = 0.328; $p = 0.002$) so was the number of documented cervical exams during labor (Spearman's rho = 0.349; $p = 0.001$)

which may be an independent risk factor for maternal fever development during parturition in the presence of ruptured membranes. It is also interesting that among women who underwent artificial amniotomy (n = 59), 72.9% underwent this intervention at less than 6 cm cervical dilatation; these women had higher maximal temperatures during labor when compared to those undergoing later amniotomy ($t = 2.012$; $p = 0.049$).

This study has several limitations. First, in our power analysis, we assumed a medium effect size; however, this resulted in the overall sample size being insufficient for some statistics, especially in group comparisons. Further sample divisions (e.g., correctly classified active phase onset only) compounded this problem. Thus, the results of this study are best represented as pilot data. Second, because there is no accurate method to determine the true onset of labor or its various phases or stages, any report of labor length is tenuous. The definitions of labor length used in the present study are not exempt from this difficulty. Our chosen criteria for differentiating correctly classified from misclassified active phase labor onset resulted in equal group sizes. It could not be discounted that a small percentage of women in the misclassified active phase onset group may indeed have had primary dystocia although this contribution would likely have been negligible. The obvious implication is that clinical criteria for determining the onset of active phase labor are poorly defined and/or clinical expectations of cervical dilation in early active labor are too stringent. Third, with the known importance of oxygenation, hydration, and energy substrate

availability to muscle metabolism, it remains possible that the *systemic* measures used in the present study are not an adequate reflection of events occurring within the uterus during labor at the cellular level. Additional studies utilizing different measurement techniques may be more enlightening. Moreover, the potential significance of these factors on labor duration may have been muted by commonly used interventions that may accelerate the labor process, e.g., amniotomy and oxytocin augmentation used singly or in combination (Brisson-Carroll et al., 1996; Fraser et al., 2000; Fraser et al., 1998).

Future research further investigating the relationships of systemically measured maternal hydration and energy substrate availability and labor duration in a larger sample of women is warranted. Placing these variables in context with the many fixed factors and interventional factors that, in combination, impact labor length differently than any isolated factor may allow clinicians to better individualize the care of laboring women and set more realistic expectations of labor progress.

Summary

The primary objectives of the present study were to investigate the relationships between labor duration and systemically measured maternal oxygenation, hydration, and energy substrate availability in low-risk nulliparous women as well as to determine differences between labor duration groupings. While hydration and glucose measures emerged as variables of continued interest, oxygenation and β-hydroxybutyric acid measures were not related to labor

duration in this sample of healthy, uncompromised nulliparous women. Multiple contextual variables were found to be significantly related to labor duration. These data also reinforced that a large percentage of women are likely misclassified as being in active labor based on subsequent rates of cervical dilation.

References

Althabe, F. & Belizán, J. M. (2006). Caesarean section: the paradox. *Lancet, 368*, 1472-1473.

American College of Obstetricians and Gynecologists. (2003). ACOG Practice Bulletin Number 49, December 2003: Dystocia and augmentation of labor. *Obstetrics and gynecology*, *102*(6), 1445-1454.

Amann, M., Romer, L. M., Pegelow, D. F., Jacques, A. J., Hess, C. J., & Dempsey, J. A. (2006). Effects of arterial oxygen content on peripheral locomotor muscle fatigue. *Journal of Applied Physiology (Bethesda, Md.: 1985), 101*(1), 119-127.

Barr, S. I., Costill, D. L., & Fink, W. J. (1991). Fluid replacement during prolonged exercise: Effects of water, saline, or no fluid. *Medicine and Science in Sports and Exercise, 23*(7), 811-817.

Bencini, F. X., & Symonds, E. M. (1972). Ketone bodies in fetal and maternal blood during parturition. *The Australian & New Zealand Journal of Obstetrics & Gynaecology, 12*(3), 176-178.

Bergholt, T., Lim, L. K., Jorgensen, J. S., & Robson, M. S. (2007). Maternal body mass index in the first trimester and risk of cesarean delivery in nulliparous women in spontaneous labor. *American Journal of Obstetrics and Gynecology, 196*(2), 163.e1-163.e5.

Bieniarz, J., Burd, L., Motew, M., & Scommegna, A. (1971). Inhibition of uterine contractility in labor. *American Journal of Obstetrics and Gynecology, 111*(7), 874-879.

Brisson-Carroll, G., Fraser, W., Breart, G., Krauss, I., & Thornton, J. (1996). The effect of routine early amniotomy on spontaneous labor: A meta-analysis. *Obstetrics and Gynecology, 87*(5), 891-896.

Bulbring, E., & Tomita, T. (1987). Catecholamine action on smooth muscle. *Pharmacological Reviews, 39*, 49-96.

Callow, M., Morton, A., & Guppy, M. (1986). Marathon fatigue: The role of plasma fatty acids, muscle glycogen and blood glucose. *European Journal of Applied Physiology and Occupational Physiology, 55*(6), 654-661.

Chang, M., Wang, S., & Chen, C. (2002). Effects of massage on pain and anxiety during labour: A randomized controlled trial in Taiwan. *Journal of Advanced Nursing, 38*(1), 68-73.

Cohen, J. (1988). *Statistical power analysis for the behavioral sciences.* Hillsdale, New Jersey: Lawrence Erlbaum Associates, Inc.

Cunningham, FG, Leveno, KJ, Bloom, SL, Hauth, JC, Gilstrap, LC, Wenstrom, KD (Ed.). (2005). *Williams obstetrics* (22nd ed.). New York: McGraw-Hill.

Davis, J. D. (1999). Management of injuries to the urinary and gastrointestinal tract during cesarean section. *Obstetrics and Gynecology Clinics of North America, 26*(3), 469-480.

Dumoulin, J. G., & Foulkes, J. E. (1984). Ketonuria during labour. *British Journal of Obstetrics and Gynaecology, 91*(2), 97-98.

Eisenkop, S. M., Richman, R., Platt, L. D., & Paul, R. H. (1982). Urinary tract injury during cesarean section. *Obstetrics and Gynecology, 60*(5), 591-596.

Elkins, G., Staniunas, R., Rajab, M. H., Marcus, J., & Snyder, T. (2004). Use of a numeric visual analog anxiety scale among patients undergoing colorectal surgery. *Clinical Nursing Research, 13*(3), 237-244.

Enoka, R. M., & Duchateau, J. (2008). Muscle fatigue: What, why and how it influences muscle function. *The Journal of Physiology, 586*(1), 11-23.

Evaluation of cesarean delivery / [developed under the direction of the task force on cesarean delivery rates, roger K. freeman ... et al.](2000). In Freeman R. K. (Ed.). Washington, D.C.: American College of Obstetricians and Gynecologists.

Foulkes, J., & Dumoulin, J. G. (1985). The effects of ketonuria in labour. *The British Journal of Clinical Practice, 39*(2), 59-62.

Fraser, W. D., Turcot, L., Krauss, I., & Brisson-Carrol, G. (2000). Amniotomy for shortening spontaneous labour. *Cochrane Database of Systematic Reviews (Online),* (2), CD000015.

Fraser, W., Vendittelli, F., Krauss, I., & Breart, G. (1998). Effects of early augmentation of labour with amniotomy and oxytocin in nulliparous women: A meta-analysis. *British Journal of Obstetrics and Gynaecology, 105*(2), 189-194.

Frentzen, B. H., Johnson, J. W., & Simpson, S. (1987). Nutrition and hydration: Relationship to preterm myometrial contractility. *Obstetrics and Gynecology, 70*(6), 887-891.

Friedman, E. A. (Ed.). (1978). *Labor: Clinical evaluation and management* (2nd ed.). New York: Appleton-Century-Crofts.

Gallagher, E. J., Bijur, P. E., Latimer, C., & Silver, W. (2002). Reliability and validity of a visual analog scale for acute abdominal pain in the ED. *The American Journal of Emergency Medicine, 20*(4), 287-290.

Garite, T. J., Weeks, J., Peters-Phair, K., Pattillo, C., & Brewster, W. R. (2000). A randomized controlled trial of the effect of increased intravenous hydration on the course of labor in nulliparous women. *American Journal of Obstetrics & Gynecology, 183*(6), 1544-1548.

Gaston-Johansson, F. (1996). Measurement of pain: The psychometric properties of the pain-O-meter, a simple, inexpensive pain assessment tool that could change health care practices. *Journal of Pain and Symptom Management, 12*(3), 172-181.

Gaston-Johansson, F., Franco, T., & Zimmerman, L. (1992). Pain and psychological distress in patients undergoing autologous bone marrow transplantation. *Oncology Nursing Forum, 19*(1), 41-48.

Gaston-Johansson, F., Fridh, G., & Turner-Norvell, K. (1988). Progression of labor pain in primiparas and multiparas. *Nursing Research, 37*(2), 86-90.

Gaston-Johansson, F., Hofgren, C., Watson, P., & Herlitz, J. (1991). Myocardial infarction pain: Systematic description and analysis. *Intensive Care Nursing, 7*(1), 3-10.

Goodlin, R. C., Quaife, M. A., & Dirksen, J. W. (1981). The significance, diagnosis, and treatment of maternal hypovolemia as associated with fetal/maternal illness. *Seminars in Perinatology, 5*(2), 163-174.

Grossman, S. A., Sheidler, V. R., McGuire, D. B., Geer, C., Santor, D., & Piantadosi, S. (1992). A comparison of the Hopkins pain rating instrument with standard visual analogue and verbal descriptor scales in patients with cancer pain. *Journal of Pain and Symptom Management, 7*(4), 196-203.

Guyton, A. C., & Hall, J. E. (Eds.). (2006). *Textbook of medical physiology* (11th ed.). Philadelphia: Elsevier/Saunders.

Hales, K. A., Morgan, M. A., & Thurnau, G. R. (1993). Influence of labor and route of delivery on the frequency of respiratory morbidity in term neonates. *International Journal of Gynaecology and Obstetrics, 43*(1), 35-40.

Hamilton, B. E., Martin, J. A., & Ventura, S. J. (2007). Births: Preliminary data for 2006. *National Vital Statistics Reports: From the Centers for Disease Control and Prevention, National Center for Health Statistics, National Vital Statistics System, 56*(7), 1-18.

Henderson, E., & Love, E. J. (1995). Incidence of hospital-acquired infections associated with caesarean section. *The Journal of Hospital Infection, 29*(4), 245-255.

Henry, J. P., Gauer, O. H., & Reeves, J. L. (1956). Evidence of the atrial location of receptors influencing urine flow. *Circulation Research, 4*(1), 85-90.

Hepple, R. T. (2002). The role of O2 supply in muscle fatigue. *Canadian Journal of Applied Physiology = Revue Canadienne De Physiologie Appliquee, 27*(1), 56-69.

Hultman, E., & Greenhaff, P. L. (1991). Skeletal muscle energy metabolism and fatigue during intense exercise in man. *Science Progress, 75*(3-4), 361-370.

Ingemarsson, I. (1976). Effect of terbutaline on premature labor. A double-blind placebo-controlled study. *American Journal of Obstetrics and Gynecology, 125*(4), 520-524.

Judelson, D. A., Maresh, C. M., Farrell, M. J., Yamamoto, L. M., Armstrong, L. E., Kraemer, W. J., et al. (2007). Effect of hydration state on strength, power, and resistance exercise performance. *Medicine and Science in Sports and Exercise, 39*(10), 1817-1824.

Karelis, A. D., Peronnet, F., & Gardiner, P. F. (2002). Glucose infusion attenuates muscle fatigue in rat plantaris muscle during prolonged indirect stimulation in situ. *Experimental Physiology, 87*(5), 585-592.

Lederman, R. P., Lederman, E., Work, B. A. J., & McCann, D. S. (1978). The relationship of maternal anxiety, plasma catecholamines, and plasma cortisol to progress in labor. *American Journal of Obstetrics and Gynecology, 132*, 495-500.

Lederman, R. P., Lederman, E., Work, B. J., & McCann, D. S. (1985). Anxiety and epinephrine in multiparous women in labor: Relationship to duration of labor and fetal heart rate pattern. *American Journal of Obstetrics and Gynecology, 153*, 870-877.

Lederman, R. P., McCann, D. S., Work, B. J., & Huber, M. J. (1977). Endogenous plasma epinephrine and norepinephrine in last-trimester pregnancy and labor. *American Journal of Obstetrics and Gynecology, 129*, 5-8.

Levine, E. M., Ghai, V., Barton, J. J., & Strom, C. M. (2001). Mode of delivery and risk of respiratory diseases in newborns. *Obstetrics and Gynecology, 97*(3), 439-442.

Marcil, M., Karelis, A. D., Peronnet, F., & Gardiner, P. F. (2005). Glucose infusion attenuates fatigue without sparing glycogen in rat soleus muscle during prolonged electrical stimulation in situ. *European Journal of Applied Physiology, 93*(5-6), 569-574.

Martin, J. A., Hamilton, B. E., Sutton, P. D., Ventura, S. J., Menacker, F., & Kirmeyer, S. (2006). Births: Final data for 2004. *National Vital Statistics Reports: From the Centers for Disease Control and Prevention, National Center for Health Statistics, National Vital Statistics System, 55*(1), 1-101.

Maughan, R. J. (1992). Fluid balance and exercise. *International Journal of Sports Medicine, 13 Suppl 1*, S132-5.

Maughan, R. J. (2001). Food and fluid intake during exercise. *Canadian Journal of Applied Physiology = Revue Canadienne De Physiologie Appliquee, 26 Suppl*, S71-8.

Maughan, R. J., Bethell, L. R., & Leiper, J. B. (1996). Effects of ingested fluids on exercise capacity and on cardiovascular and metabolic responses to prolonged exercise in man. *Experimental Physiology, 81*(5), 847-859.

Mendelson, C. L. (1946). The aspiration of stomach contents into the lungs during obstetric anesthesia. *American Journal of Obstetrics and Gynecology, 52*, 191.

Metzger, B. E., Ravnikar, V., Vileisis, R. A., & Freinkel, N. (1982). "Accelerated starvation" and the skipped breakfast in late normal pregnancy. *Lancet, 1*(8272), 588-592.

Monir-Bishty, E., Pierce, S. J., Kupittayanant, S., Shmygol, A., & Wray, S. (2003). The effects of metabolic inhibition on intracellular calcium and

contractility of human myometrium. *BJOG: An International Journal of Obstetrics and Gynaecology, 110*(12), 1050-1056.

Morrison, J. J., Rennie, J. M., & Milton, P. J. (1995). Neonatal respiratory morbidity and mode of delivery at term: Influence of timing of elective caesarean section. *British Journal of Obstetrics and Gynaecology, 102*(2), 101-106.

National Institutes of Health. (2006). State of the science conference: Cesarean delivery on maternal request. March 27-29, 2006.

Noakes, T. D. (1993). Fluid replacement during exercise. *Exercise and Sport Sciences Reviews, 21*, 297-330.

Nuthalapaty, F. S., Rouse, D. J., & Owen, J. (2004). The association of maternal weight with cesarean risk, labor duration, and cervical dilation rate during labor induction. *Obstetrics & Gynecology, 103*(3), 452-456.

O'Driscoll, K., Meagher, D., & Boylan, P. (Eds.). (1993). *Active management of labor: The Dublin experience* (3rd ed.). Aylesbury, England: Mosby.

Parilla, B. V., Dooley, S. L., Jansen, R. D., & Socol, M. L. (1993). Iatrogenic respiratory distress syndrome following elective repeat cesarean delivery. *Obstetrics and Gynecology, 81*(3), 392-395.

Parratt, J. R., Taggart, M. J., & Wray, S. (1995a). Changes in intracellular pH close to term and their possible significance to labour. *Pflugers Archiv : European Journal of Physiology, 430*(6), 1012-1014.

Parratt, J. R., Taggart, M. J., & Wray, S. (1995b). Functional effects of intracellular pH alteration in the human uterus: Simultaneous measurements of pH and force. *Journal of Reproduction and Fertility, 105*(1), 71-75.

Parratt, J., Taggart, M., & Wray, S. (1994). Abolition of contractions in the myometrium by acidification in vitro. *Lancet, 344*(8924), 717-718.

Peisner, D. B., & Rosen, M. G. (1986). Transition from latent to active labor. *Obstetrics and Gynecology, 68*(4), 448-451.

Pierce, S. J., Kupittayanant, S., Shmygol, T., & Wray, S. (2003). The effects of pH change on Ca(++) signaling and force in pregnant human myometrium. *American Journal of Obstetrics and Gynecology, 188*(4), 1031-1038.

Pircon, R. A., Strassner, H. T., Kirz, D. S., & Towers, C. V. (1989). Controlled trial of hydration and bed rest versus bed rest alone in the evaluation of preterm uterine contractions. *American Journal of Obstetrics and Gynecology, 161*(3), 775-779.

Posner, N. A., & Silverstone, F. A. (1977). Carbohydrate metabolism in pregnancy: Management of the diabetic gravida. *Obstetrics and Gynecology Annual, 6*, 67-125.

Romer, L. M., Haverkamp, H. C., Lovering, A. T., Pegelow, D. F., & Dempsey, J. A. (2006). Effect of exercise-induced arterial hypoxemia on quadriceps muscle fatigue in healthy humans. *American Journal of Physiology. Regulatory, Integrative and Comparative Physiology, 290*(2), R365-75.

Segal, S., Csavoy, A. N., & Datta, S. (1998). The tocolytic effect of catecholamines in the gravid rat uterus. *Anesthesia and Analgesia, 87*, 864-869.

Seligman, L. C., Duncan, B. B., Branchtein, L., Gaio, D. S. M., Mengue, S. S., & Schmidt, M. I. (2006). Obesity and gestational weight gain: Cesarean delivery and labor complications. *Revista De Saude Publica, 40*(3), 457-465.

Shirreffs, S. M. (2005). The importance of good hydration for work and exercise performance. *Nutrition Reviews, 63*(6), S14-21.

Sittner, B., Hudson, D. B., Grossman, C. C., & Gaston-Johansson, F. (1998). Adolescents' perceptions of pain during labor. *Clinical Nursing Research, 7*(1), 82-93.

Society of Obstetricians and Gynaecologists of Canada. (1995). *Policy statement number 40: Dystocia*

Tamiya, N., Araki, S., Ohi, G., Inagaki, K., Urano, N., Hirano, W., et al. (2002). Assessment of pain, depression, and anxiety by visual analogue scale in Japanese women with rheumatoid arthritis. *Scandinavian Journal of Caring Sciences, 16*(2), 137-141.

Turner, M. J., Rasmussen, M. J., Turner, J. E., Boylan, P. C., MacDonald, D., & Stronge, J. M. (1990). The influence of birth weight on labor in nulliparas. *Obstetrics and Gynecology, 76*(2), 159-163.

U.S. Department of Health and Human Services. Office of Disease Prevention and Health Promotion. (n.d.). *Healthy People 2010.* Retrieved June 16, 2008, from the World Wide Web: http://www.health.gov/healthypeople/

Vahratian, A., Zhang, J., Troendle, J. F., Savitz, D. A., & Riz, A. M. (2004). Maternal prepregnancy overweight and obesity and the pattern of labor progression in term nulliparous women. *Obstetrics & Gynecology, 104*(5), 943-951.

van Ham, M A, van Dongen, P W, & Mulder, J. (1997). Maternal consequences of caesarean section. A retrospective study of intra-operative and postoperative maternal complications of caesarean section during a 10-year period. *European Journal of Obstetrics, Gynecology, and Reproductive Biology, 74*(1), 1-6.

Watanabe, T., Minakami, H., Sakata, Y., Matsubara, S., Tamura, N., Obara, H., et al. (2001). Effect of labor on maternal dehydration, starvation, coagulation, and fibrinolysis. *Journal of Perinatal Medicine, 29*(6), 528-534.

World Health Organization. (1985). Joint interregional conference on appropriate technology for birth. Fortaleza, Brazil, April 22-26, 1985.

Maternal age (yrs)	25.06 (4.91)	Range: 18-36
Gestational age at delivery (days)	276.26 (7.14)	Range: 259-290
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	43 (46.2%)	
Not married	50 (53.8%)	
Gravidity	1.32 (0.69)	Range: 1-5
Maternal body mass index	29.84 (4.56)	Range: 18.0-41.7
Cervical dilatation at active phase onset diagnosis (cm)	3.55 (0.52)	Range: 3.0-5.0
Cervical effacement at active phase onset diagnosis		
60-79%	11 (11.8%)	
≥ 80%	82 (88.2%)	
Fetal station at active phase onset diagnosis		
-3 or above	1 (1.1%)	
-2	52 (55.9%)	
-1	32 (34.4%)	
0	6 (6.5%)	
Not reported	2 (2.2%)	
Mode of delivery		
Spontaneous vaginal	65 (69.9%)	
Instrumented vaginal (i.e., vacuum / forceps)	18 (19.4%)	
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%)	

Table 2.1 Demographic and labor variables describing study sample (n = 93)

(continued)

Table 2.1 continued

Epidural use		
No	5 (5.4%)	
Yes (at < 6 cm)	79 (84.9%)	
Yes (at ≥ 6 cm)	9 (9.7%)	
Active phase labor duration (min)*	446.6 (195.8)	Range: 121-1186
Second stage labor duration (min)*	86.9 (67.8)	Range: 8-283
Total labor duration (min)*	533.4 (219.8)	Range: 166-1253
Infant weight (g)	3395.41 (456.96)	Range: 2329-4722
Infant length (cm)	49.56 (2.19)	Range: 44.0-54.5
Infant gender		
Male	46 (49.5%)	
Female	47 (50.5%)	

For continuous variables, mean (SD) provided.
For categorical variables, n (%) provided.

* Includes only parturients delivering vaginally (n = 83).

	Hb-bound O_2 (ml O_2 / dL blood)	Hydration (urine specific gravity)	Glucose (mg/dL)	ß-hydroxybutyric acid † (mmol/L)	Pain †	Anxiety
	n = 75	n = 72	n = 75	n = 75	n = 74	n = 74
Normal Value (Physiological)	*(15.21-20.77)*	*(1.003-1.035)*	*(70-110)*	*(<.60)*	*(--)*	*(--)*
Baseline	16.70 (1.46)	1.013 (.007)	89.7 (13.2)	.30 [.20, .90]	5.90 [.45, 9.40]	4.09 (2.76)
Baseline + 4 hrs	16.69 (1.47)	1.011 (.007)	88.4 (12.7)	.50 [.30, 1.28]	.60 [.00, 7.35]	2.74 (2.56)
Paired Test Value	t = .198	t = 1.402	t = .657	z = -4.964 *	z = -5.785 *	t = 4.319 *

Table 2.2 Paired-sample analyses of study variables among *all women* delivering vaginally and with data available at each data collection time point

Baseline = Active Phase of Labor Onset Diagnosis.
Mean (SD); Median [10^{th} percentile, 90^{th} percentile].
Bonferroni correction for multiple tests was $p < 0.008$ (i.e., $p = 0.05/6$).

* $p < 0.001$ (2-tailed).

† Variable not normally distributed at baseline and/or baseline + 4 hrs per the Kolmogorov-Smirnov test ($p < 0.05$), thus, the Wilcoxon Signed Ranks non-parametric test of paired samples used.

	Hb-bound O_2 (ml O_2 / dL blood)	Hydration (urine specific gravity)	Glucose (mg/dL)	ß-hydroxybutyric acid (mmol/L)	Pain †	Anxiety
	n = 35	n = 34	n = 35	n = 35	n = 35	n = 35
Normal Value (Physiological)	*(15.21-20.77)*	*(1.003-1.035)*	*(70-110)*	*(<.60)*	*(--)*	*(--)*
Baseline	16.68 (1.50)	1.014 (.008)	88.2 (14.5)	.429 (.320)	6.2 [.00, 9.44]	3.92 (2.85)
Baseline +4 hrs	16.69 (1.59)	1.012 (.007)	87.9 (10.9)	.680 (.468)	.70 [.00, 8.04]	2.91 (2.80)
Paired Test Value	t = .082	t = 1.770	t = .128	t = 4.828 *	z = -4.341 *	t = 2.318

Table 2.3 Paired-sample analyses of study variables among *women correctly classified as being in active labor* with vaginal delivery and with data available at each data collection time point

Baseline = Active Phase of Labor Onset Diagnosis.
Mean (SD); Median [10^{th} percentile, 90^{th} percentile].
Bonferroni correction for multiple tests was $p < 0.008$ (i.e., $p = 0.05/6$).

* $p < 0.001$ (2-tailed).

† Variable not normally distributed at baseline + 4 hrs per the Kolmogorov-Smirnov test ($p < 0.05$), thus, the Wilcoxon Signed Ranks non-parametric test of paired samples used.

	All Parturients (n = 83)		Parturients With Correctly Classified Active Phase Onset (n = 43)	
Variable	Active Phase Labor Duration	Total Labor Duration	Active Phase Labor Duration	Total Labor Duration
Maternal age	.167	.180	.228	.232
Maternal BMI	.157	.219 *	.250	.304 *
Gestational age at delivery	.155	.169	.142	.203
Cervical dilatation at labor admission †	-.230 *	-.157	-.161	-.033
Maximum maternal temp. during labor	.361 **	.417 **	.264	.421 **
Infant birth weight	.185	.292 **	.225	.390 **
Infant birth length	.204	.281 *	.221	.370 *

Table 2.4 Relationships between labor length and several contextual variables among parturients delivering vaginally

* *$p < 0.05$ (2-tailed). **$p < 0.01$ (2-tailed).

† Variable not normally distributed per the Kolmogorov-Smirnov test ($p < 0.05$), thus, Spearman's rho non-parametric test of correlation used.

	1	2	3	4	5 †	6 †
1. Urine specific gravity (time point1)	1	.427**	.063	.350**	.185	-.016
2. Urine specific gravity (time point 2)		1	-.087	.216	.204	.257*
3. Glucose (time point 1)			1	.116	-.293**	-.196
4. Glucose (time point 2)				1	.112	-.045
5. ß-hydroxybutyric acid (time point 1) †					1	.558**
6. ß-hydroxybutyric acid (time point 2) †						1

Table 2.5 Correlation matrix between study variables among parturients delivering vaginally

* *p < 0.05 (2-tailed). **p < 0.01 (2-tailed).

† Variable not normally distributed per the Kolmogorov-Smirnov test (p < 0.05), thus, Spearman's rho non-parametric test of correlation used.

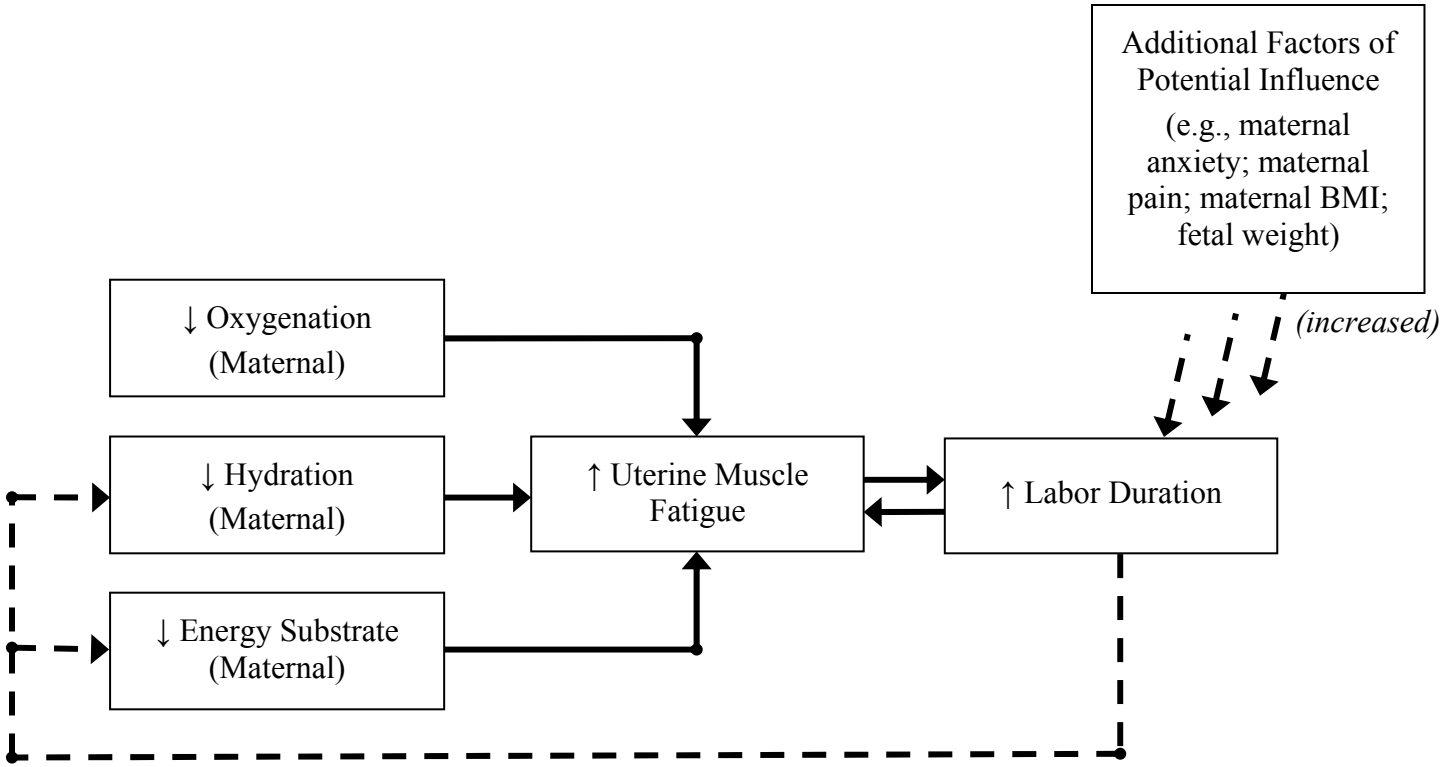


Figure 2.1 Maternal oxygenation, hydration, & energy substrate influence on labor duration framework

CHAPTER 3

MATERNAL SERUM LACTATE DEHYDROGENASE AS A POTENTIAL MARKER OF UTERINE PREPAREDNESS FOR LABOR

Background

Uterine muscle undergoes changes related to metabolism during pregnancy many of which are thought to facilitate effective contractile activity during labor. Such changes are important because intrauterine pressure generated during contractions is sufficient to reduce or even occlude arterial blood flow (Brar, Platt, DeVore, Horenstein, & Medearis, 1988; Greiss & Anderson, 1968; Larcombe-McDouall, Buttell, Harrison, & Wray, 1999) resulting in intermittent states of contraction-related hypoxia. Hypoxia, in turn, is capable of impairing oxidative phosphorylation and reducing contractile force on a rapid time scale (Monir-Bishty et al., 2003). Acidosis may ensue which also can profoundly inhibit uterine contractions in human pregnant myometrium (Parratt, Taggart, & Wray, 1995b; Parratt et al., 1994; Pierce et al., 2003). Thus, to remain efficient, a laboring uterus must contend with intermittent, contraction-related anaerobic states while continuing to meet metabolic and energy-producing needs.

Among the key enzymatic changes that occur in the pregnant uterus that may better allow the smooth muscle to function well during anaerobic states are

the changes seen in lactate dehydrogenase (LDH) [nicotinamide adenine dinucleotide oxidoreductase]. LDH is a predominantly intracellular, cytoplasmic enzyme found in nearly all body tissues and is detectable in five isoenzyme forms. These isoenzymes are composed of two different types of polypeptide chains, commonly called 'H' and 'M,' which can combine to form homotetramer isoenzymes [LDH_1 (H_4) and LDH_5 (M_4)] and heterotetramer, or mixed, isoenzymes [LDH_2 (H_3M_1), LDH_3 (H_2M_2), LDH_4 (H_1M_3)]. The relative proportions of isoenzymes vary according to tissue type and the distribution gives each tissue a characteristic isoenzyme profile. As shown in early work, more H-subunit dominant isoenzymes are available in tissues relying on aerobic metabolism, such as the heart, while M-LDH subunits are more abundant in tissues using anaerobic metabolism, such as skeletal muscle and liver (Richterich, Schafroth, & Aebi, 1963; Roman, 1969; Wroblewski & Gregory, 1961). Through the conversion of pyruvate to lactate, M-LDH assists in maintaining adenosine triphosphate (ATP) production when oxygen is deficient, e.g., during uterine contractions.

Being predominantly intracellular, LDH is normally only released from the cell as a result of cell damage or increased permeability. Thus, total serum measurement of LDH provides a non-specific measure of cellular damage. Determining specific LDH isoenzyme patterns can be useful in the differential diagnosis of certain pathologic states since tissue damage releases the isoenzymes

contained therein, leading to a change in the serum profile measured systemically. In this way, serum LDH profile changes can be used to narrowly identify potential tissues of origin. Isoenzyme measures have been shown to be valuable in diagnosing pathologic processes such as myocardial infarction (Jablonsky, Leung, & Henderson, 1985; Rotenberg et al., 1988; Wroblewski, Ross, & Gregory, 1960), liver disease (Castaldo et al., 1991; Rotenberg et al., 1989), testicular germ cell tumors (von Eyben et al., 1988; von Eyben et al., 2001; von Eyben et al., 2001), ovarian cancer (Schneider, Halperin, Langer, Bukovsky, & Herman, 1997), pleural effusion (Lossos, Intrator, Berkman, & Breuer, 1999; Paavonen, Liippo, Aronen, & Kiistala, 1991; Vergnon et al., 1984), and pre-eclampsia (He, Bremme, Kallner, & Blomback, 1995; Tsoi, Zheng, Xu, & Kay, 2001). Given the tremendous amount of work performed and stress endured by the uterus during labor coupled with rapid uterine involution beginning immediately after delivery, it is hypothesized that appropriately timed systemic measures of total and/or fraction LDH may reflect the enzymatic profile and work capacity of pregnant uterine muscle at the time of labor onset, during labor, and/or at delivery. Such measures may describe the extent to which the myometrium was prepared to carry out the events of parturition.

Myometrial Lactate Dehydrogenase

Early studies of *myometrial* samples have found that total LDH values are higher in pregnant than non-pregnant uteri (Geyer & Riebschlager, 1974;

Makkonen, 1977; Richterich et al., 1963) with increases continuing into late pregnancy (38-42 weeks gestation) (Makkonen, 1977). Of particular significance is the finding that, during pregnancy, M-LDH isoenzymes reportedly increase in proportion to H-LDH (Geyer & Riebschlager, 1974; Makkonen, Puhakainen, Hanninen, & Castren, 1982) and may even exceed it (Richterich et al., 1963). Regarding individual isoenzymes, LDH_3 and/or LDH_4 have been reported to be in greatest concentrations in the pregnant myometrium (Geyer & Riebschlager, 1974; Hawkins & Whyley, 1966; Meade & Rosalki, 1963a). During normal labor, myometrial LDH levels have been shown to decline from pregnant myometrial levels measured at term; this was due especially to a lowering of M-LDH which declined by approximately 59% between these time points compared to a more modest H-LDH decline of 29% (Makkonen et al., 1982). These studies suggest that pregnant uteri have LDH profiles that are better equipped to endure oxygen deficient states although it is unknown when during pregnancy these profile shifts are optimized. The declining level of myometrial cell LDH during labor is likely to be the main source of increased total LDH measured in maternal serum during and after labor (Heimback & Prezyna, 1960; Konttinen & Pyoeraelae, 1963; Makkonen et al., 1982).

Maternal Serum Lactate Dehydrogenase

A majority of the early investigations on this topic have concluded that total maternal serum LDH concentrations during the antepartum period usually

remain similar to non-pregnant levels (Atuk et al., 1961; Benzie, Doran, Harkins, Owen, & Porter, 1974; Brody, 1957; Hawkins & Whyley, 1966; Heimback & Prezyna, 1960; Knutson, Cornatzer, Moore, & Nelson, 1958; Linton & Miller, 1959; Makkonen, Penttila, & Castren, 1980; Miotti, Alter, Moltz, & Sabb, 1973; Smith, Schwartz, & Schwartz, 1959; Stone, Lending, Slobody, & Mestern, 1960; West & Zimmerman, 1958) although upward trends in the third trimester have also been reported (Friedman & Lapan, 1961; Hagerman & Wellington, 1959; Meade & Rosalki, 1962; Meade & Rosalki, 1963b; West & Zimmerman, 1958). During labor and/or at delivery, most investigations have concluded that maternal serum LDH concentrations are commonly higher than is normally found during the pre-labor period (Heimback & Prezyna, 1960; Konttinen & Pyoeraelae, 1963; Makkonen et al., 1980; Meade & Rosalki, 1962; Meade & Rosalki, 1963b; Sward, Woyton, Dobryszycka, & Bauer, 1972; West & Zimmerman, 1958) although a few have found no difference (Abramov, Abramov, Abrahamov, Durst, & Schenker, 1996; Atuk et al., 1961; Stone et al., 1960). In studies of isoenzyme measures, increased LDH levels during labor have been reported to be due to elevations in LDH_3 and LDH_4 (Meade & Rosalki, 1962; Meade & Rosalki, 1963a). Others have found that serum samples taken during labor have lower levels of LDH_1 ($p < 0.01$) and higher levels of LDH_5 ($p < 0.01$) than is present before labor at 38-42 weeks gestation (Makkonen et al., 1980).

In the postpartum period, although one identified investigation reported no change in maternal serum LDH levels after delivery (Abramov et al., 1996), most have demonstrated that levels are elevated (Atuk et al., 1961; Hagerman & Wellington, 1959; Kristensen, Horder, & Pedersen, 1979; Meade & Rosalki, 1962; Smith et al., 1959). Among pregnancy studies, total serum LDH suggests a curve reaching its peak between delivery and 24 (Heimback & Prezyna, 1960; Meade & Rosalki, 1962) or 48 hours postpartum (Atuk et al., 1961; Fylling, 1961) followed by a tapering toward normal. No studies could be identified that measured isoenzyme levels in the days following delivery.

Discrepant findings regarding serum LDH measures are due, at least in part, to determinations being made at different or undisclosed pregnancy time points, small sample sizes, and/or measurement technique differences. Consequently, the normal patterns of these enzymes in the serum during labor and early puerperium have not been well-characterized. Appropriately timed systemic measures of total and/or fraction LDH may allow certain events surrounding parturition to be described more coherently. Since maternal serum LDH levels peak at 24-48 hours after the tissue level event causing their release (Atuk et al., 1961; Fylling, 1961; Heimback & Prezyna, 1960; Meade & Rosalki, 1962), measures within this time window, in otherwise healthy women, most likely represent the enzymatic profile of the uterine muscle at the time of labor onset,

during labor, and/or at delivery. By proxy, such measures may be a retrospective indicator of uterine smooth muscle preparedness for labor.

The objectives of the present investigation were to describe paired-sample differences between maternal serum LDH samples collected upon a provider diagnosis of active phase labor onset and 24-30 hours post-delivery in order to identify how maternal serum LDH profiles changed between the time points. We also sought to describe the relationships between total LDH and isoenzyme levels and the following variables: rates of cervical dilation during the first 4 hours after diagnosis of active phase onset; active phase labor duration; and total labor duration. Finally, the study aimed to determine if there are differences in LDH levels between several comparison groupings, i.e., between women correctly classified and misclassified as being in active phase labor. This last aim might allow a shift in the isoenzyme profile that accompanies a progressing labor to be identified.

Methods

A prospective study was conducted at a suburban, academic, Midwestern medical care center in which 4774 women were delivered in 2007. Institutional Review Board approval was obtained for all work in the study, and written, informed and HIPAA consents were obtained from all women. Recruitment primarily occurred in the labor and delivery triage unit or in the labor room as

soon after admission for a diagnosis of active phase labor as possible. Recruitment occurred between April, 2007 and February, 2008.

This was a study of nulliparous women of low obstetric risk (no significant medical history, absence of major complication of pregnancy, e.g., pre-eclampsia or diabetes) with a labor care provider *diagnosis* of spontaneous labor in the early active-phase of the first stage of labor. Active phase onset diagnosis required that cervical dilatation be ≥ 3 - ≤ 5 cm in the presence of regular uterine contractions (≥ 2 contractions in any 10 minute window objectively determined by external monitoring or palpation) *and* a provider decision to admit for labor. Additional inclusion criteria were: 1) 18-39 years of age; 2) singleton gestation; 3) gestational age ≥ 37 - ≤ 42 weeks (259-294 days); 4) anticipated vaginal delivery; 5) with or without ruptured membranes; 6) cephalic presentation; 7) weight < 250 lbs (< 114 kg) at study entry; 8) no identified fetal anomalies or growth issues; 9) afebrile at study entry; and 10) able to read and speak English. Participants with augmentation of labor after being diagnosed with active phase labor onset were retained in the study while women undergoing labor inductions were excluded. Amniotomy, narcotic analgesia, epidural anesthesia, oxytocin augmentation, and other labor management decisions were at the discretion of the managing physician or certified nurse-midwife. These data were obtained from the medical record.

LDH total and isoenzyme concentrations were measured in maternal sera at two distinct time points. The first sample was collected as near to the diagnosis of active phase labor onset as logistically possible (considered the baseline sample) with sampling most often occurring concurrently with intravenous line placement, a standard order in the facility. The second sample was collected at 24-30 hours post-vaginal delivery. Each sample was collected into an 8.5mL BD Vacutainer® serum separator tube (Ref # 367988) (Becton-Dickinson, Franklin Lakes, NJ). Samples not collected during intravenous site placement were collected via either a 20- or 22-gauge needle from the antecubital vein or below. The blood was allowed to clot at room temperature for not longer than 60 minutes and then centrifuged at 2500 rpm for 10 minutes. The sera were separated, immediately refrigerated, and determinations performed as soon as convenient, typically within 48-72 hours after collection. Serum with visible hemolysis was discarded since the LDH released from the damaged erythrocytes might be expected to give spurious high LDH results. At the baseline sample time point, hemolyzed samples were redrawn if the labor had not progressed beyond the aforementioned labor onset criteria; at the post-delivery time point, hemolyzed samples were redrawn within 30 minutes of the initial sampling. For women delivered via cesarean, post-delivery LDH samples were not collected due to the likelihood of these values being elevated secondary to surgical tissue damage. All LDH measurements were made in The Ohio State University Medical Center

Laboratory via a SYNCHRON LX System, an agarose gel electrophoresis system (Beckman Coulter, Inc., Fullerton, CA). Total LDH values were in units per liter (U/L) and isoenzymes were in relative distribution (%). LDH H- and M-subunit levels were calculated from relative distributions via standard formulas (Daneshrad et al., 2003).

Operational definitions used in the present study included the following: *active phase of labor duration* encompassed the time cervical dilatation was determined to be ≥ 3 - ≤ 5 cm in the presence of regular uterine contractions *and* there was a provider decision to admit for labor through determination of complete cervical dilatation (approximated at 10 cm). *Total labor duration* was the time from active phase of labor onset through delivery.

In light of the knowledge that many parturients admitted for supposed active phase labor are likely still in latent labor as indicated by subsequent rates of cervical dilation, investigator adapted criteria for *misclassified* and *correctly classified* active labor onset were established *a priori* and applied retrospectively to group subjects. A *misclassified active labor onset* was defined as average cervical dilation < 0.5 cm/hour for 4 hours after a physician/midwife *diagnosis* of active labor onset. *Correctly classified active labor onset* encompassed labors progressing at ≥ 0.5 cm/hour over this same time frame. Rationale for these definitions were derived from the definition of primary dystocia (termed "dysfunctional labor") put forth by the Society of Obstetricians and

Gynaecologists of Canada, i.e., a period of ≥ 4 hours after ≥ 3 cm cervical dilatation and near 100% effacement during which the mean rate of dilation is < 0.5 cm/hour (Society of Obstetricians and Gynaecologists of Canada, 1995) in conjunction with the finding that approximately one-half of low-risk parturients are not in active labor at 4 cm dilatation based on traditional definitions put forth by Friedman (Peisner & Rosen, 1986). Secondary dystocia was diagnosed when, after ≥ 2 hours of correctly classified active phase onset, the cervical dilation rate became < 0.5 cm/hour for 4 hours at any point during labor. Thus, no subject could have both a misclassified active phase onset and secondary dystocia. Cesareans were classified according to when they were performed (i.e., active phase or second stage) and whether the physician documented a dystocia (e.g., arrest of dilation or arrest of fetal descent) or non-dystocia (e.g., non-reassuring fetal heart patterns) indication.

Data Analysis and Sample Size: Demographic variables were expressed as mean (SD) if continuous and as n (%) if categorical. To determine differences between LDH measures at baseline (i.e., at diagnosis of active phase onset with subsequent labor admission) and 24 hours post-delivery, paired-analysis *t* tests were used and Bonferroni corrections applied to address the multiple tests. To test for relationships, Pearson product moment correlation coefficients (*r*) were calculated; with a medium effect size (0.30), $\alpha = 0.05$, and power = 0.80, a sample of 85 was required (Cohen, 1988). To determine differences between two groups,

Student's *t* tests were performed; with a medium to large effect size (0.65), alpha (α) of 0.05, and power of 0.80, 45 subjects per group were required (Cohen, 1988). Thus, a total minimum sample size of 90 women achieving vaginal birth with complete data was needed. 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 SPSS (version 15.0, Chicago, IL).

Results

A total of 91 parturients were enrolled in the study and included in the analysis. There was no attrition. Demographics of the study sample are shown in Table 3.1. The majority of the sample self-classified as non-Hispanic whites. Among all women with measurable labor durations, active phase (n = 85) and total labor (n = 81) durations were 7.55 ± 3.42 and 8.90 ± 3.70 hours, respectively. When limiting analyses to only parturients with a correctly classified active phase onset, active phase (n = 45) and total labor (n = 42) durations were 5.68 ± 1.99 and 6.90 ± 2.40 hours, respectively. Women with misclassified active phase onsets had mean active phase and total labor durations that were 3.96 and 4.15 hours longer, respectively (9.64 ± 3.50 hours and 11.05 ± 3.66 hours), when compared to women with a correctly classified active phase ($p < 0.001$). There was only one case of secondary dystocia based on the dilation rate criteria which,

ultimately, culminated in a second stage cesarean for arrest of fetal descent. Among all cesareans (n = 10), six were performed in the active phase (arrest of dilation = 3; non-reassuring fetal heart patterns = 3) and four were performed in the second stage for arrest of fetal descent.

To address the first study objective, LDH samples were collected at the diagnosis of active phase labor onset and again at 24-30 hours post-vaginal delivery so differences between these time points could be determined. In all, paired-samples obtained from 75 subjects are included in the final analysis. LDH samples drawn from four women at the first time point were excluded from analyses due to hemolysis and repeat samples were not obtained. At the second time point, LDH values were determined in 79 subjects; subjects delivered via cesarean (n = 10) were not sampled post-operatively and two samples were unable to be collected due to patient discharge prior to collection time. Among the 75 paired-samples, all differences between the time points were significant with Bonferroni correction ($p < 0.001$) (See Table 3.2 and Figure 3.1). Specifically, post-delivery total LDH, LDH_3, LDH_4, H-LDH, and M-LDH increased post-delivery over values seen at active phase of labor onset diagnosis while LDH_1, LDH_2, LDH_5, and the H/M ratio had decreased. Significant differences with the same upward and downward LDH trends as those mentioned above were seen both in the correctly classified (n = 39) and the misclassified (n = 36) active phase onset groups ($p \leq 0.001$). Interestingly, at active phase of labor onset diagnosis,

no single isoenzyme level was significantly correlated with the total LDH level and, hence, no one enzyme decisively determined the total LDH level. However, at 24-30 hours post-delivery, total LDH concentrations had moderate negative correlations with LDH_1 ($r = -0.418$, $p < 0.001$) and LDH_2 ($r = -0.424$, $p < 0.001$) and moderate positive correlations with LDH_3 ($r = 0.364$, $p = 0.001$) and LDH_4 ($r = 0.489$, $p < 0.001$).

To address the second study objective, maternal serum LDH measures made at each time point (i.e., at active phase onset diagnosis; 24-30 hours post-vaginal delivery) were correlated with the continuous study variables [i.e., dilation rates (cm/hour) at 4 hrs post-active phase onset diagnosis; active phase labor duration; and total labor duration]. LDH measures made at the active phase of labor onset diagnosis held no statistically significant relationships with any of the continuous study variables in any of the parturient groupings (i.e., all parturients; only parturients with a correctly classified active phase onset; only parturients with a misclassified active phase onset).

Correlation coefficients calculated between maternal serum LDH measures made 24-30 hours post-vaginal delivery and the continuous study variables yielded several significant relationships. Among all parturients, significant relationships were found between rates of cervical dilation over the first 4 hours after a diagnosis of active phase labor onset and some of the post-delivery LDH values (see Table 3.3). Specifically, as rates of cervical dilation

during the 4 hour assessment period increased, percentage distributions of LDH_1 decreased (Spearman's rho = -0.275, p = 0.014) while LDH_3 (Spearman's rho = 0.289, p = 0.010) and LDH_4 (Spearman's rho = 0.282, p = 0.012) increased. When investigating relationships with active phase and total labor durations among all parturients, only post-delivery LDH_3 was significant, showing inverse correlations [r = -0.275 (p = 0.014) and r = -0.292 (p = 0.009), respectively].

When limiting post-delivery correlation analyses to only those with correctly classified active phase onset (n = 40), no statistical significance emerged and the only relationship approaching significance involved rates of cervical dilation over the first 4 hours after a diagnosis of active phase labor onset and post-delivery LDH_1 (Spearman's rho = -0.305, p = 0.056). Likewise, when limiting analyses to only those with a misclassified active phase onset (n = 39), no statistical significance was found. These sub-analyses were hindered by small sample sizes that did not meet a necessary sample size of 85 subjects.

For the third study objective, maternal serum LDH total and isoenzyme relative distribution differences between groups of interest were calculated (i.e., correctly classified and misclassified active phase labor onset; those augmented and not augmented with oxytocin; those never augmented or augmented at ≥ 6 cm and those augmented at < 6 cm; those with < 2° perineal laceration and those with ≥ 2° laceration/episiotomy). Among LDH samples drawn at the diagnosis of active phase labor onset, there were no significant differences between any of the

groups of interest. Post-vaginal delivery serum LDH total and isoenzyme relative distribution differences between the groups are shown in Table 3.4. Comparisons between correctly classified and misclassified active phase labor onset groups found that LDH measures were not statistically different although total LDH, LDH_3, and M-LDH were near-significantly higher in those with correctly classified active phase onset ($p < 0.10$). Oxytocin use was less often implemented in those who had lower post-delivery LDH_1 and higher post-delivery LDH_3. Those never receiving exogenous oxytocin or receiving it later in labor (i.e., after 6 cm dilatation) had significantly lower LDH_1 and H/M ratios and higher LDH_3. Comparisons between parturients with perineal episiotomy/laceration ≥ 2 degree (indicating skeletal muscle involvement) as compared to those with < 2 degree laceration or none were not significant, thus, eliminating these skeletal muscles as significant contributors to post-vaginal delivery LDH values. A shortcoming of these analyses is that many of the group sizes were smaller than the 45 subjects per group indicated in the power analysis.

Supplemental analyses of the study data yielded several additional findings of interest. Among all parturients (i.e., combining correctly classified and misclassified active phase onset groups), active phase labor duration had a weak positive correlation with maternal age ($r = .244$, $p < 0.05$) while total labor duration was weakly correlated with maternal BMI ($r = .224$, $p < 0.05$), infant birth weight ($r = .299$, $p < 0.01$), and infant birth length ($r = .282$, $p < 0.05$).

Interestingly, married women (n = 36) had significantly shorter total labor durations than unmarried women (n = 45) ($t = 2.318$, $p < 0.05$). As one may expect, cervical dilatation at the diagnosis of active phase onset was weakly and negatively correlated with active phase duration (Spearman's rho = -.249, $p < 0.05$) although it was not significantly related to total labor duration. Between parturients with correctly classified versus misclassified active phase onset, there were no significant differences in any of these aforementioned variables. The median rate of cervical dilatation over the first four hours after an active phase onset diagnosis was 0.52 cm/hour (10^{th} percentile = 0.12 cm/hour; 25^{th} percentile = 0.28cm/hour; 75^{th} percentile = 1.04 cm/hour; 90^{th} percentile = 1.60 cm/hour). Over the initial four hours after a provider diagnosis of active phase onset, differences in median cervical dilation rates were significantly different between those correctly classified versus misclassified as being in active phase labor (1.02 and 0.27 cm/hour, respectively, $p < 0.001$). At ≥ 5 cm dilatation, cervical dilation rates between these groups were not significantly different. The impacts of amniotomy and oxytocin augmentation on labor duration are difficult to discern from the present study since no distinct protocol regarding the implementation of these interventions was followed and parturients may have received neither, one, or both of these interventions. All but five women received epidural anesthesia, therefore, the impact of epidural use on labor durations could not be statistically determined.

Discussion

The maternal serum total LDH paired-sample finding of the present study, demonstrating an increase in total LDH levels between sample collection time points, aligns with others who have demonstrated that postpartum serum total LDH levels are elevated (Atuk et al., 1961; Hagerman & Wellington, 1959; Kristensen et al., 1979; Meade & Rosalki, 1962; Smith et al., 1959). We cannot account for reasons why one identified study in which repeated measures were performed found no difference in total serum LDH measures over time (Abramov et al., 1996). Our report of paired-sample isoenzyme findings, to our knowledge, is a unique contribution to the literature. We found that relative proportions of LDH_1, LDH_2, and LDH_5 significantly decreased from the time of active phase labor onset diagnosis to post-delivery while relative proportions of LDH_3 and LDH_4 increased significantly.

The chosen criteria for differentiating correctly classified from misclassified active phase labor onset resulted in half of our sample being misclassified. The obvious implication is that clinical criteria for determining the onset of active phase labor are poorly defined. As is common in contemporary practice, the majority of these determinations were made by the midwife / physician via phone with neither the eyes nor hands of the primary care provider being laid on the women. In no case was a woman admitted to a labor suite and

later released from the hospital undelivered even after subsequent evaluation demonstrated the original diagnosis of active labor was incorrect.

Perhaps the most notable results of the present study were the findings of significant correlations between rates of cervical dilation over the first four hours after a diagnosis of active phase onset and post-delivery LDH values among all parturients. Post-delivery LDH values likely represent the enzymatic composition of the uterine muscle during the periods immediately before active labor onset diagnosis, during active labor, and/or at delivery. It is interesting to find significant positive relationships between cervical dilation rates over the first four hours post-active phase diagnosis *and* post-delivery LDH_3 and LDH_4 as well as near-significant positive relationships with total LDH (Spearman's rho = .199, p = 0.079), M-LDH (Spearman's rho = .209, p = 0.065), and H-LDH (Spearman's rho = .196, p = 0.084). Likewise, the negative correlation between the relative distribution of post-delivery LDH_1 and dilation rates over the first four hours was of interest. These findings suggest that there are distinct myometrial composition differences between women with correctly classified versus misclassified active phase onset. Parturients in true active labor have, at some point during pregnancy, shifted to a LDH profile that is better equipped to handle the anaerobic environment imposed by uterine contractions during labor. This aligns with early studies that have found such a shift in the human *myometrial* isoenzyme profile (Geyer & Riebschlager, 1974; Makkonen et al., 1982; Richterich et al., 1963).

Such shifts have even been reported in pregnant rats (Battellino, Sabulsky, & Blanco, 1971).

In the present study, t-test analysis between those with correctly classified versus misclassified active phase onset failed to show statistical significance although several trends emerged. Underlying reasons that the t-test results were not significant include the possibility that [1] the chosen differentiation point of < or ≥ 0.5 cm/hour for 4 hours after a diagnosis of active phase onset was not adequately discriminating, [2] the effect size used when determining sample size was too large, or [3] there was indeed no significance. In light of this, a post-hoc comparison between the lower (≤ 0.28 cm/hour) and upper (≥ 1.04 cm/hour) quartiles of dilation rates for the first 4 hours after active labor onset diagnosis was performed. These results demonstrated that, among the post-delivery LDH samples, parturients with the most slowly progressing dilation (n = 18) had higher relative levels of LDH_1 ($t = 2.070$; $p = 0.045$) and LDH_5 ($t = 2.261$; $p = 0.032$) and lower levels of LDH_3 ($t = 2.567$; $p = 0.014$) and LDH_4 ($t = 2.044$; $p = 0.048$) when compared to those with the most rapid cervical dilation (n = 21) during this time frame. Hence, assuming that post-delivery serum LDH measures are a reflection of uterine muscle enzymatic states immediately before active labor onset diagnosis, during active labor, and/or at delivery, women with the most efficient cervical dilation during the first four hours post-active phase onset

diagnosis have a LDH profile that is better equipped to handle the anaerobic environment imposed by uterine contractions during labor.

Although the present study supports that those with more rapid dilation rates during the first four hours post-active phase onset diagnosis developed an increased capacity to contend with anaerobic states based on LDH profiles, it is unclear when these changes occurred. In non-pregnant states, estrogenic hormones stimulate LDH activity (Burke, Harris, & McGuire, 1978; Nagy, Hirka, Kurcz, & Baranyai, 1978; Nagy, Hirka, Kurcz, Anda, & Baranyai, 1978; Richards & Hilf, 1972) and decrease the H/M subunit ratio in non-uterine tissue (Nagy, Hirka, Kurcz, & Baranyai, 1978; Nagy, Hirka, Kurcz, Anda et al., 1978) with increased synthesis being predominantly of an anaerobic type (Richards & Hilf, 1972). In uterine muscle, positive correlations between estrogen and LDH levels have been demonstrated in non-pregnant states (Hagerman & Wellington, 1959; Maggiulli, Gustafson, Rector, & Hilf, 1977). During pregnancy through labor, estrogens measured in maternal plasma continue to rise, terminating abruptly after delivery (Cunningham, Leveno, Bloom, Hauth, Gilstrap, & Wenstrom, 2005). With the discrete role of estrogen in stimulating LDH activity and affecting isoenzyme patterns in other tissues, the increases in estrogen with advancing pregnancy though labor may explain why upward trends in total maternal serum LDH measures (Friedman & Lapan, 1961; Hagerman & Wellington, 1959; Meade & Rosalki, 1962; Meade & Rosalki, 1963b; West & Zimmerman, 1958) and

profile shifts favoring anaerobic conditions during late pregnancy (Geyer & Riebschlager, 1974; Makkonen et al., 1982; Richterich et al., 1963) have been reported. Since these uterine muscle changes may occur up to and beyond the onset of active phase labor, a misclassified active phase labor onset may inadvertently bypass essential time needed for the physiologic LDH profile shift to manifest.

A misclassification of active phase labor onset, an occurrence seen in 49.5% of women in this study, may have profound clinical implications. Despite parturients with correctly classified versus misclassified active labor onsets having similar admission cervical dilatations (3.59 ± 0.55 and 3.53 ± 0.49, respectively; Mann-Whitney U = 990.5; p = 0.707), provider management of labor was quite different between these groups. Oxytocin augmentation rates were 47.8% among women admitted in true active labor and 80.0% for women misclassified as being in active labor ($\chi 2 = 10.188$; p = 0.001). Rates of oxytocin implementation at < 6 cm dilatation for these groups were 26.1% and 62.2%, respectively ($\chi 2 = 12.057$; p = 0.001). Likewise, among women receiving an amniotomy, implementation of this intervention at < 6 cm was less common among those with correctly classified active phase onset at 41.3% compared to 51.1% in women misclassified ($\chi 2 = 4.125$; p = 0.042). Overall, parturients with correctly classified active phase onsets had labor durations that were approximately 4 hours shorter than those with misclassified active phase onsets (p

< 0.001) in spite of the provision of these aggressive interventions at higher percentages in the women misclassified as being in active labor. These findings align with those from a study aiming to delay labor admission until labor was in the active phase wherein women were randomized to either a *delayed* or *direct admission* group (Lauzon & Hodnett, 2001; McNiven, Williams, Hodnett, Kaufman, & Hannah, 1998). Those with delayed admission spent less time in the labor unit (weighted mean difference = -5.20 hours, p = 0.001), received less intrapartum oxytocics (odds ratio = 0.44, 95% confidence interval = 0.24-0.80), and reported higher levels of control during labor.

Interestingly, in the current study, all three cesareans performed in the active phase for slow labor progress followed a misclassification of active phase labor onset. This is a relevant discussion point since other investigators have found that parturients admitted in active versus latent phase labor have significantly fewer overall cesareans, fewer cesareans for dystocia, and fewer cesareans among those augmented during labor (p < 0.0001) (Rahnama, Ziaei, & Faghihzadeh, 2006). The LDH profile differences between those correctly classified and misclassified as being in active phase labor may play some role in determining labor progress and outcome although this remains unclear. Perhaps more importantly, the unveiled LDH differences between these groups may simply represent one of many existing intrinsic uterine muscle differences that may be important to labor success. When differentiating active phase from latent

phase labor, watchful patience over immediate intervention is seemingly prudent and may allow important physiological events within the uterine muscle to manifest.

This study was limited by a smaller than desired sample size especially in regards to testing for group differences. In addition, although uterine muscle is likely the key contributor to systemic maternal LDH measures in the peripartum period (Heimback & Prezyna, 1960; Konttinen & Pyoeraelae, 1963; Makkonen et al., 1982), other potentially contributing sources cannot be eliminated. The placenta (Dobryszycka, Bauer, Woyton, & Sward, 1970; Hagerman & Wellington, 1959; Little, 1959; Meade & Rosalki, 1962; Meade & Rosalki, 1963a), skeletal muscle (Makkonen et al., 1982), and even intravascular hemolysis in the uterine sinusoids (Heimback & Prezyna, 1960) have been suggested to be potentially significant contributors to maternal measures. However, with the placenta being most represented by LDH_4 and LDH_5 (Bauer, Sward, Woyton, & Dobryszycka, 1970; Hawkins & Whyley, 1966; Wieme & Van Maercke, 1961), skeletal muscle containing large concentrations of LDH_5 (Makkonen et al., 1982; Weiner, 2006), and hemolysis leading the near-exclusive release of LDH_1 and LDH_2 (Weiner, 2006), one would expect that if any of these were key contributors to peripartum LDH increases, predominant increases in LDH_1, LDH_2, and LDH_5 would have been found. Indeed, the relative measures of all of these isoenzymes ($p < 0.001$) and absolute measures of LDH_1 ($p = 0.001$)

and LDH_5 ($p = 0.003$) diminished in maternal serum between the baseline and postpartum samples, while the absolute measure of LDH_2 was unchanged between the measurement time points. In addition, multiple investigators have found that total LDH concentrations in the fetal circulation are typically twice as high as those seen in the maternal blood (Atuk et al., 1961; Fylling, 1961; Hagerman & Wellington, 1959; Konttinen & Pyoeraelae, 1963; Lapan & Friedman, 1959; Meade & Rosalki, 1962; Meade & Rosalki, 1963b; Pulkkinen & Willman, 1968) supporting the conclusion that maternal and fetal enzyme systems are independent from each other due to the placental barrier (Atuk et al., 1961; Fylling, 1961; Lapan & Friedman, 1959). In the present study, findings of relative and absolute increases of LDH_3 and LDH_4 ($p < 0.001$) suggest that the uterine muscle is the most likely contributor to systemically measured LDH in the post-delivery period. This is consistent with the information that these particular isoenzymes are in greatest quantity in the pregnant myometrium (Geyer & Riebschlager, 1974; Hawkins & Whyley, 1966; Meade & Rosalki, 1963a) and because uterine muscle endures the greatest activity and stress during labor.

Future research further investigating potential physiological indicators of preparedness for labor are warranted. In addition, studies aimed at better defining the criteria used to determine active phase labor onset would aid clinicians in minimizing the number of parturients misclassified as being in active labor while simultaneously allowing potentially important physiological events important to

successful parturition to manifest more fully prior to an admission for labor and delivery.

Summary

In summary, among low-risk nulliparous women, total serum LDH levels increased between active phase onset diagnosis and 24-30 hours post-delivery. Moreover, the isoenzymes known to predominate in pregnant uterine muscle were in greatest relative proportions and absolute concentrations in the serum at the post-delivery time point, indicating that systemic measures in the early postpartum period may represent the enzymatic state of uterine muscle immediately prior to active phase onset, during active phase labor, and/or at delivery. Under this assumption, parturients progressing most slowly after a diagnosis of active phase onset had LDH isoenzyme profiles that were less equipped to contend with anaerobic conditions. With the possibility that this profile shift may occur just prior to and even throughout active phase labor, accurately diagnosing active phase onset is seemingly of utmost importance. In cases of uncertainty regarding active labor onset, a longer observation period prior to a diagnosis of active phase labor onset may be warranted.

References

Abramov, Y., Abramov, D., Abrahamov, A., Durst, R., & Schenker, J. (1996). Elevation of serum creatine phosphokinase and its MB isoenzyme during normal labor and early puerperium. *Acta Obstetricia Et Gynecologica Scandinavica, 75*(3), 255-260.

Atuk, N. O., Wax, S. H., Word, B. H., McGaughey, H. S., Corey, E. L., & Wood, J. E. (1961). Observations of the steady state of lactic dehydrogenase activity across the human placental membrane. *American Journal of Obstetrics and Gynecology, 82*, 271-276.

Battellino, L. J., Sabulsky, J., & Blanco, A. (1971). Lactate dehydrogenase isoenzymes in rat uterus: Changes during pregnancy. *Journal of Reproduction and Fertility, 25*(3), 393-399.

Bauer, A., Sward, J., Woyton, J., & Dobryszycka, W. (1970). Lactate dehydrogenase in labour. II. Isoenzymes of placenta and related tissues. *Enzymologia, 39*(3), 177-182.

Benzie, R. J., Doran, T. A., Harkins, J. L., Owen, V. M., & Porter, C. J. (1974). Composition of the amniotic fluid and maternal serum in pregnancy. *American Journal of Obstetrics and Gynecology, 119*(6), 798-810.

Brar, H. S., Platt, L. D., DeVore, G. R., Horenstein, J., & Medearis, A. L. (1988). Qualitative assessment of maternal uterine and fetal umbilical artery blood flow and resistance in laboring patients by Doppler velocimetry. *American Journal of Obstetrics and Gynecology, 158*(4), 952-956.

Brody, S. (1957). Serum lactic dehydrogenase activity during human pregnancy. *Acta Endocrinologica, 25*(1), 101-104.

Burke, R. E., Harris, S. C., & McGuire, W. L. (1978). Lactate dehydrogenase in estrogen-responsive human breast cancer cells. *Cancer Research, 38*(9), 2773-2776.

Castaldo, G., Oriani, G., Cimino, L., Topa, M., Budillon, G., Salvatore, F., et al. (1991). Serum lactate dehydrogenase isoenzyme 4/5 ratio discriminates between hepatocarcinoma and secondary liver neoplasia. *Clinical Chemistry, 37*(8), 1419-1423.

Cohen, J. (1988). *Statistical power analysis for the behavioral sciences.* Hillsdale, New Jersey: Lawrence Erlbaum Associates, Inc.

Cunningham, FG, Leveno, KJ, Bloom, SL, Hauth, JC, Gilstrap, LC, Wenstrom, KD (Ed.). (2005). *Williams obstetrics* (22nd ed.). New York: McGraw-Hill.

Daneshrad, Z., Verdys, M., Birot, O., Troff, F., Bigard, A. X., & Rossi, A. (2003). Chronic hypoxia delays myocardial lactate dehydrogenase maturation in young rats. *Experimental Physiology, 88*(3), 405-413.

Dobryszycka, W., Bauer, A., Woyton, J., & Sward, J. (1970). Lactate dehydrogenase in labour. I. Isoenzymes of serum, cord serum and amniotic fluid. *Enzymologia, 39*(3), 166-176.

Friedman, M. M., & Lapan, B. (1961). Variations of enzyme activities during normal pregnancy. *American Journal of Obstetrics and Gynecology, 82*, 132-137.

Fylling, P. (1961). Serum lactic dehydrogenase activity in umbilical cord, at the end of labor in normal women, and in uncomplicated puerperium. *Scandinavian Journal of Clinical and Laboratory Investigation, 13*, 264-267.

Geyer, H., & Riebschlager, M. (1974). Effect of pregnancy on cytoplasmic and mitochondrial enzymes in human and animal myometrium. *Acta Endocrinologica, 77*(2), 368-379.

Greiss, F. C. J., & Anderson, S. G. (1968). Uterine blood flow during labor. *Clinical Obstetrics and Gynecology, 11*, 96-109.

Hagerman, D. D., & Wellington, F. M. (1959). Serum lactic dehydrogenase activity during pregnancy and in the newborn. *American Journal of Obstetrics and Gynecology, 77*(2), 348-351.

Hawkins, D. F., & Whyley, G. A. (1966). The nature of the lactate dehydrogenase isoenzymes in human placenta and related tissues. *Clinica Chimica Acta; International Journal of Clinical Chemistry, 13*(6), 713-719.

He, S., Bremme, K., Kallner, A., & Blomback, M. (1995). Increased concentrations of lactate dehydrogenase in pregnancy with preeclampsia: A predictor for the birth of small-for-gestational-age infants. *Gynecologic and Obstetric Investigation, 39*(4), 234-238.

Heimback, D. P., & Prezyna, A. P. (1960). Lactic dehydrogenase in pregnancy and the puerperium. *American Journal of Obstetrics and Gynecology, 79*, 108-112.

Jablonsky, G., Leung, F. Y., & Henderson, A. R. (1985). Changes in the ratio of lactate dehydrogenase isoenzymes 1 and 2 during the first day after acute myocardial infarction. *Clinical Chemistry, 31*(10), 1621-1624.

Knutson, R. G., Cornatzer, W. E., Moore, J. H., & Nelson, W. W. (1958). Serum lactic dehydrogenase and glutamic oxalacetic transaminase activites in normal pregnancy. *The Journal of Laboratory and Clinical Medicine, 51*(5), 773-777.

Konttinen, A., & Pyoeraelae, T. (1963). Serum enzyme activity in late pregnancy, at delivery, and during puerperium. *Scandinavian Journal of Clinical and Laboratory Investigation, 15*, 429-435.

Kristensen, S. R., Horder, M., & Pedersen, G. T. (1979). Reference values for six enzymes in plasma from newborns and women at delivery. *Scandinavian Journal of Clinical and Laboratory Investigation, 39*(8), 777-784.

Lapan, B., & Friedman, M. M. (1959). A comparative study of fetal and maternal serum enzyme levels. *The Journal of Laboratory and Clinical Medicine, 54*, 417-426.

Larcombe-McDouall, J., Buttell, N., Harrison, N., & Wray, S. (1999). In vivo pH and metabolite changes during a single contraction in rat uterine smooth muscle. *The Journal of Physiology, 518 (Pt 3)*, 783-790.

Lauzon, L., & Hodnett, E. (2001). Labour assessment programs to delay admission to labour wards. *Cochrane Database of Systematic Reviews (Online),* (3), CD000936.

Linton, E. B., & Miller, E. C. (1959). Serum lactic dehydrogenase in pregnancy. *American Journal of Obstetrics and Gynecology, 78*(1), 11-12.

Little, W. A. (1959). Serum lactic dehydrogenase in pregnancy. *Obstetrics and Gynecology, 13*(2), 152-162.

Lossos, I. S., Intrator, O., Berkman, N., & Breuer, R. (1999). Lactate dehydrogenase isoenzyme analysis for the diagnosis of pleural effusion in haemato-oncological patients. *Respiratory Medicine, 93*(5), 338-341.

Maggiulli, M. J., Gustafson, J. C., Rector, W. D., & Hilf, R. (1977). Enzyme activities in human endometrium, myometrium and leiomyomas of the uterus. *Enzyme, 22*(1), 13-18.

Makkonen, M. (1977). Myometrial energy metabolism during pregnancy and normal and dysfunctional labor. *Acta Obstetricia Et Gynecologica Scandinavica.Supplement, 71*, 1-68.

Makkonen, M., Penttila, I. M., & Castren, O. (1980). Serum lactic acid dehydrogenase and isoenzymes during pregnancy and labor. *Acta Obstetricia Et Gynecologica Scandinavica, 59*, 97-102.

Makkonen, M., Puhakainen, E., Hanninen, O., & Castren, O. (1982). Lactate dehydrogenase isoenzymes in human myometrium during pregnancy and labor. *Acta Obstetricia Et Gynecologica Scandinavica, 61*(1), 35-37.

McNiven, P. S., Williams, J. I., Hodnett, E., Kaufman, K., & Hannah, M. E. (1998). An early labor assessment program: A randomized, controlled trial. *Birth (Berkeley, Calif.), 25*(1), 5-10.

Meade, B. W., & Rosalki, S. B. (1962). Lactic dehydrogenase isoenzymes in pregnancy. *Lancet, 1*, 1407.

Meade, B. W., & Rosalki, S. B. (1963a). The origin of increased maternal serum enzyme activity in pregnancy and labour. *The Journal of Obstetrics and Gynaecology of the British Commonwealth, 70*, 862-868.

Meade, B. W., & Rosalki, S. B. (1963b). Serum enzyme activity in normal pregnancy and the newborn. *The Journal of Obstetrics and Gynaecology of the British Commonwealth, 70*, 693-700.

Miotti, A. B., Alter, A. A., Moltz, A., & Sabb, F. (1973). Serum and amniotic fluid lactic dehydrogenase in pregnant women. *American Journal of Obstetrics and Gynecology, 117*(8), 1129-1136.

Monir-Bishty, E., Pierce, S. J., Kupittayanant, S., Shmygol, A., & Wray, S. (2003). The effects of metabolic inhibition on intracellular calcium and contractility of human myometrium. *BJOG: An International Journal of Obstetrics and Gynaecology, 110*(12), 1050-1056.

Nagy, I., Hirka, G., Kurcz, M., Anda, E., & Baranyai, P. (1978). The role of estrogens in the regulation of lactate dehydrogenase activity and its submolecular organization in rat anterior pituitary. *Endokrinologie, 71*(1), 1-12.

Nagy, I., Hirka, G., Kurcz, M., & Baranyai, P. (1978). Changes of lactic dehydrogenase activity and combination of its subunits in rat anterior

pituitary during puberty and in maturity, as well as during estrous cycle on the actue effect of estradiol and after castration. *Endokrinologie, 71*(1), 13-24.

Paavonen, T., Liippo, K., Aronen, H., & Kiistala, U. (1991). Lactate dehydrogenase, creatine kinase, and their isoenzymes in pleural effusions. *Clinical Chemistry, 37*(11), 1909-1912.

Parratt, J. R., Taggart, M. J., & Wray, S. (1995). Functional effects of intracellular pH alteration in the human uterus: Simultaneous measurements of pH and force. *Journal of Reproduction and Fertility, 105*(1), 71-75.

Parratt, J., Taggart, M., & Wray, S. (1994). Abolition of contractions in the myometrium by acidification in vitro. *Lancet, 344*(8924), 717-718.

Peisner, D. B., & Rosen, M. G. (1986). Transition from latent to active labor. *Obstetrics and Gynecology, 68*(4), 448-451.

Pierce, S. J., Kupittayanant, S., Shmygol, T., & Wray, S. (2003). The effects of pH change on Ca(++) signaling and force in pregnant human myometrium. *American Journal of Obstetrics and Gynecology, 188*(4), 1031-1038.

Pulkkinen, M. O., & Willman, K. (1968). Enzymes and isoenzymes in maternal and foetal sera. A study on lactate and isocitrate dehydrogenases, alkaline phosphatases and beta-glucuronidase. *Acta Obstetricia Et Gynecologica Scandinavica, 47*(3), 273-291.

Rahnama, P., Ziaei, S., & Faghihzadeh, S. (2006). Impact of early admission in labor on method of delivery. *International Journal of Gynaecology and Obstetrics: The Official Organ of the International Federation of Gynaecology and Obstetrics, 92*(3), 217-220.

Richards, A. H., & Hilf, R. (1972). Effect of estrogen administration on glucose 6-phosphate dehydrogenase and lactate dehydrogenase isoenzymes in rodent mammary tumors and normal mammary glands. *Cancer Research, 32*(3), 611-616.

Richterich, R., Schafroth, P., & Aebi, H. (1963). A study of lactic dehydrogenase isoenzyme pattern of human tissues by adsorption-elution on sephadex-DEAE. *Clinica Chimica Acta; International Journal of Clinical Chemistry, 8*, 178-192.

Roman, W. (1969). Quantitative estimation of lactate dehydrogenase isoenzymes in serum. I. Review of methods and distribution in human tissues. *Enzymologia, 36*(4), 189-219.

Rotenberg, Z., Davidson, E., Weinberger, I., Fuchs, J., Sperling, O., & Agmon, J. (1988). The efficiency of lactate dehydrogenase isoenzyme determination for the diagnosis of acute myocardial infarction. *Archives of Pathology & Laboratory Medicine, 112*(9), 895-897.

Rotenberg, Z., Weinberger, I., Davidson, E., Fuchs, J., Harell, D., & Agmon, J. (1989). Lactate dehydrogenase isoenzyme patterns in serum of patients with metastatic liver disease. *Clinical Chemistry, 35*(5), 871-873.

Schneider, D., Halperin, R., Langer, R., Bukovsky, I., & Herman, A. (1997). Peritoneal fluid lactate dehydrogenase in ovarian cancer. *Gynecologic Oncology, 66*(3), 399-404.

Smith, J. J., Schwartz, E. D., & Schwartz, M. K. (1959). Lactic acid dehydrogenase during pregnancy and puerperium. *Obstetrics and Gynecology, 13*(2), 163-165.

Society of Obstetricians and Gynaecologists of Canada. (1995). *Policy statement number 40: Dystocia*

Stone, M. L., Lending, M., Slobody, L. B., & Mestern, J. (1960). Glutamic oxalacetic transaminase and lactic dehydrogenase in pregnancy. *American Journal of Obstetrics and Gynecology, 80*, 104-107.

Sward, J., Woyton, J., Dobryszycka, W., & Bauer, A. (1972). The influence of parturition on some serum enzyme activities. *Archivum Immunologiae Et Therapiae Experimentalis, 20*(2), 273-275.

Tsoi, S. C., Zheng, J., Xu, F., & Kay, H. H. (2001). Differential expression of lactate dehydrogenase isozymes (LDH) in human placenta with high expression of LDH-A(4) isozyme in the endothelial cells of pre-eclampsia villi. *Placenta, 22*(4), 317-322.

Vergnon, J. M., Guidollet, J., Gateau, O., Ripoll, J. P., Collet, P., Louisot, P., et al. (1984). Lactic dehydrogenase isoenzyme electrophoretic patterns in the diagnosis of pleural effusion. *Cancer, 54*(3), 507-511.

von Eyben, F E, Blaabjerg, O., Hyltoft-Petersen, P., Madsen, E. L., Amato, R., Liu, F., et al. (2001). Serum lactate dehydrogenase isoenzyme 1 and

prediction of death in patients with metastatic testicular germ cell tumors. *Clinical Chemistry and Laboratory Medicine : CCLM / FESCC, 39*(1), 38-44.

von Eyben, F E, Blaabjerg, O., Petersen, P. H., Horder, M., Nielsen, H. V., Kruse-Andersen, S., et al. (1988). Serum lactate dehydrogenase isoenzyme 1 as a marker of testicular germ cell tumor. *The Journal of Urology, 140*(5), 986-990.

von Eyben, F E, Madsen, E. L., Blaabjerg, O., Petersen, P. H., von der Maase, H, Jacobsen, G. K., et al. (2001). Serum lactate dehydrogenase isoenzyme 1 and relapse in patients with nonseminomatous testicular germ cell tumors clinical stage I. *Acta Oncologica (Stockholm, Sweden), 40*(4), 536-540.

Weiner, H. (2006). Enzymes: classification, kinetics, and control. In T.M. Devlin (Ed.), *Textbook of biochemistry with clinical indications* (6th ed.). Hoboken, NJ: Wiley-Liss.

West, M., & Zimmerman, H. J. (1958). Lactic dehydrogenase and glutamic oxaloacetic transaminase in normal pregnant women and newborn children. *The American Journal of the Medical Sciences, 235*(4), 443-447.

Wieme, R. J., & Van Maercke, Y. (1961). The fifth (electrophoretically slowest) serum lactic dehydrogenase as an index of liver injury. *Annals of the New York Academy of Sciences, 94*, 898-911.

Wroblewski, F., & Gregory, K. F. (1961). Lactic dehydrogenase isozymes and their distribution in normal tissues and plasma and in disease states. *Annals of the New York Academy of Sciences, 94*, 912-932.

Wroblewski, F., Ross, C., & Gregory, K. (1960). Isoenzymes and myocardial infarction. *The New England Journal of Medicine, 263*, 531-536.

Maternal age (yrs)	24.87 (4.77)	Range: 18-36
Gestational age at delivery (days)	276.07 (7.09)	Range: 259-290
Hispanic		
Yes	5 (5.5%)	
No	86 (94.5%)	
Race		
White	66 (72.5%)	
Black	18 (19.8%)	
Other	7 (7.7%)	
Marital status		
Married	41 (45.1%)	
Not married	50 (54.9%)	
Gravidity	1.33 (0.70)	Range: 1-5
Maternal body mass index	29.88 (4.59)	Range: 18.0-41.7
Cervical dilatation at active phase onset diagnosis (cm)	3.56 (0.52)	Range: 3.0-5.0
Cervical effacement at active phase onset diagnosis		
60-79%	11 (12.1%)	
≥ 80%	80 (87.9%)	
Fetal station at active phase onset diagnosis		
-3 or above	1 (1.1%)	
-2	51 (56.0%)	
-1	31 (34.1%)	
0	6 (6.6%)	
Not reported	2 (2.2%)	
Mode of delivery		
Spontaneous vaginal	63 (69.2%)	
Instrumented vaginal (i.e., vacuum / forceps)	18 (19.8%)	
Cesarean	10 (11.0%)	
Amniotomy		
No	33 (36.3%)	
Yes (at < 6 cm)	42 (46.2%)	
Yes (at ≥ 6 cm)	16 (17.6%)	
Oxytocin augmentation		
No	33 (36.3%)	
Yes (at < 6 cm)	40 (44.0%)	
Yes (at ≥ 6 cm)	18 (19.8%)	

Table 3.1 Demographic and labor variables describing study sample (n = 91)

(continued)

Table 3.1 continued

Epidural use		
No	5 (5.5%)	
Yes (at < 6 cm)	77 (84.6%)	
Yes (at ≥ 6 cm)	9 (9.9%)	
Active phase labor duration (min)	452.75 (205.37)	Range: 121-1186
Second stage labor duration (min)	86.12 (67.83)	Range: 8-283
Total labor duration (min)	533.86 (222.01)	Range: 166-1253
Infant weight (g)	3392.78 (460.91)	Range: 2329-4722
Infant length (cm)	49.54 (2.21)	Range: 44.0-54.5
Infant gender		
Male	46 (50.5%)	
Female	45 (49.5%)	

For continuous variables, mean (SD) provided.
For categorical variables, n (%) provided.

	Total (U/L)	Isoenzyme (%)					H-subunit	M-subunit	Ratio H/M
		1	2	3	4	5			
Active phase of labor onset diagnosis	147.59 (22.81)	29.66 (3.13)	30.33 (3.17)	19.21 (2.36)	8.74 (2.18)	12.07 (3.88)	94.59 (14.86)	53.00 (10.82)	1.82 (0.30)
24-30 hrs post-delivery	173.35 (30.92)	23.89 (3.57)	26.00 (3.30)	27.45 (3.17)	13.62 (3.52)	9.05 (2.43)	104.46 (16.60)	68.91 (16.38)	1.55 (0.23)
t test value	7.491 *	14.186 *	14.055 *	28.898 *	14.851 *	7.898 *	5.335 *	8.739 *	8.572 *

Table 3.2 Maternal serum LDH paired-sample *t* tests between active phase labor onset diagnosis and post-delivery samples (n = 75) [Mean (SD)]

Note: Each measure was normally distributed per the Kolmogorov-Smirnov test ($p > 0.05$). Bonferroni correction for multiple tests was $p < 0.005$ (i.e., $p = .05/9$).

* $p < 0.001$ (2-tailed).

	24-30 hrs post-vaginal delivery LDH measures								
	Total	Isoenzyme (%)					H-	M-	Ratio
	(U/L)	1	2	3	4	5	subunit	subunit	H/M
Dilation rates (cm/hr) at 4 hrs post-active phase onset diagnosis †	.199	-.275 *	-.087	.289 **	.282 *	-.137	.196	.209	-.128
Active phase duration (min)	-.141	.194	.125	-.275 *	-.170	.157	-.120	-.145	.119
Labor duration (total) (min)	-.096	.155	.169	-.292 **	-.130	.119	-.077	-.104	.114

Table 3.3 Correlation coefficients between post-vaginal delivery LDH measures and labor parameters among all parturients (n = 79)

* *p < 0.05 (2-tailed). **p ≤ 0.01 (2-tailed).

† Variable not normally distributed per the Kolmogorov-Smirnov test (p < 0.05), thus, Spearman's rho non-parametric test of correlation used.

Groups	n	Total (U/L)	24-30 hrs post-vaginal delivery LDH measures Isoenzyme (%)					Subunit		
			1	2	3	4	5	H	M	H/M
Active Phase Labor Onset										
Correctly Classified	40	177.6	23.4	25.7	28.0	14.0	8.9	106.4	71.2	1.53
		(32.8)	(3.6)	(3.0)	(3.2)	(3.1)	(2.0)	(18.2)	(16.7)	(0.22)
Misclassified	39	165.9	24.6	26.6	26.7	13.0	9.3	100.8	65.1	1.59
		(28.2)	(3.4)	(3.5)	(3.0)	(3.9)	(2.7)	(14.5)	(15.6)	(0.24)
t test value		1.706	1.556	1.212	1.960	1.351	.588	1.527	1.674	1.214
Augmented (oxytocin)										
No	30	174.1	23.0	25.6	28.8	13.9	8.8	104.2	69.9	1.52
		(29.3)	(3.4)	(3.5)	(3.0)	(3.5)	(1.8)	(16.7)	(15.2)	(0.20)
Yes	49	170.4	24.6	26.4	26.5	13.3	9.3	103.3	67.2	1.58
		(32.2)	(3.5)	(3.1)	(2.9)	(3.5)	(2.7)	(16.8)	(17.1)	(0.25)
t test value		.514	2.026 *	1.031	3.280 **	.744	.822	.246	.725	1.308
Augmented (oxytocin)										
No or at ≥ 6 cm	46	176.7	23.1	25.5	28.1	14.1	9.1	105.5	71.2	1.51
		(31.9)	(3.5)	(3.3)	(3.1)	(3.6)	(2.1)	(17.5)	(16.7)	(0.21)
At < 6 cm	33	165.0	25.1	26.9	26.3	12.6	9.2	101.0	64.0	1.62
		(28.8)	(3.3)	(3.2)	(3.0)	(3.2)	(2.8)	(15.2)	(15.1)	(0.24)
t test value		1.670	2.495 *	1.817	2.692 **	1.958	.223	1.174	1.979	2.118 *

Table 3.4 Maternal serum LDH total and isoenzyme relative distribution group comparisons across four conditions / events

(continued)

Table 3.4 continued

Perineal Outcome										
< 2º laceration	25	172.2 (32.9)	23.6 (3.5)	25.7 (4.0)	28.0 (3.6)	13.8 (3.9)	8.9 (2.6)	103.2 (17.6)	68.9 (18.0)	1.54 (0.25)
≥ 2º episiotomy / laceration	54	171.6 (30.4)	24.1 (3.5)	26.3 (2.9)	27.1 (2.9)	13.3 (3.3)	9.2 (2.3)	103.8 (16.3)	67.9 (15.7)	1.56 (0.22)
t test value		.070	.688	.807	1.275	.567	.451	.154	.273	.426

Mean (SD)

* *p < 0.05 (2-tailed). **p < 0.01 (2-tailed).

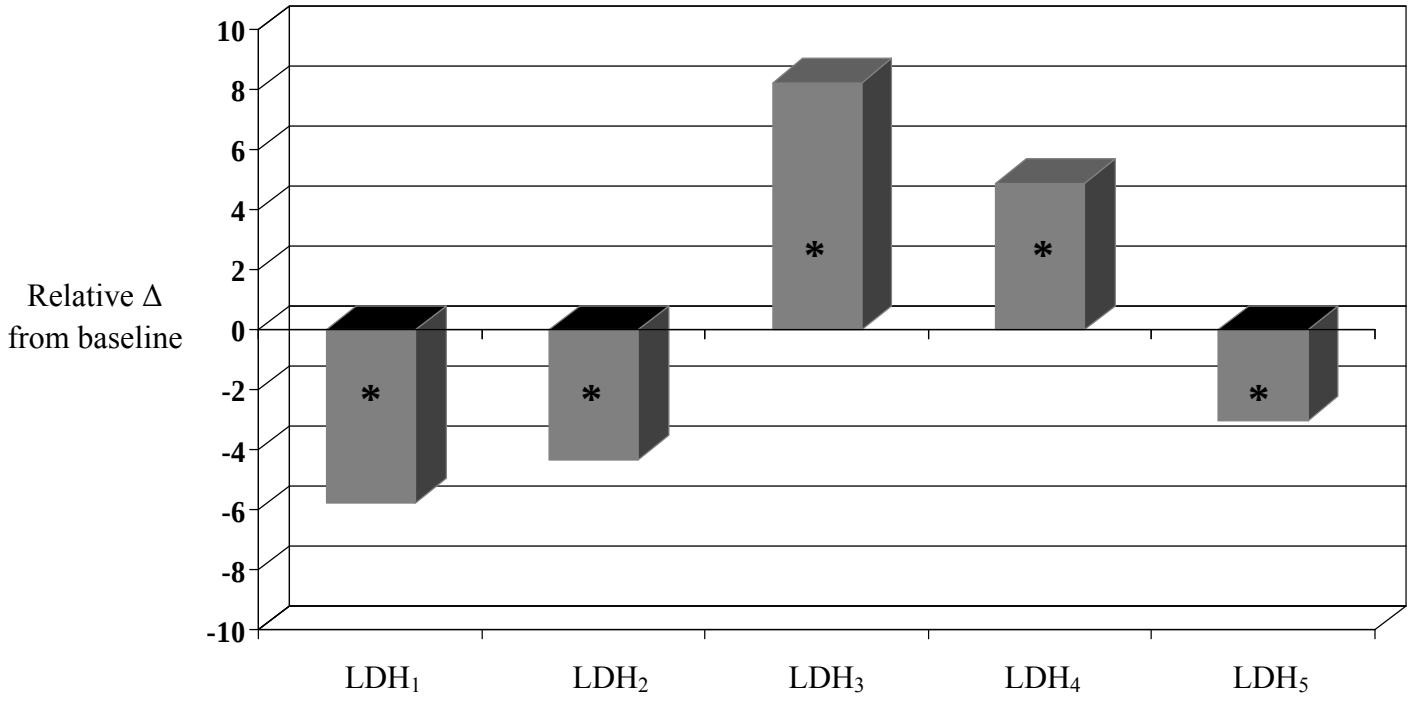


Figure 3.1 LDH isoenzyme paired-sample differences (24-30 hrs post-delivery % minus baseline %) (n = 75)

* $p < 0.001$ (2-tailed).

BIBLIOGRAPHY

Abramov, Y., Abramov, D., Abrahamov, A., Durst, R., & Schenker, J. (1996). Elevation of serum creatine phosphokinase and its MB isoenzyme during normal labor and early puerperium. *Acta Obstetricia Et Gynecologica Scandinavica, 75*(3), 255-260.

Althabe, F. & Belizán, J. M. (2006). Caesarean section: the paradox. *Lancet, 368*, 1472-1473.

American College of Obstetricians and Gynecologists. (2003). ACOG Practice Bulletin Number 49, December 2003: Dystocia and augmentation of labor. *Obstetrics and gynecology*, *102*(6), 1445-1454.

Akoury, H. A., Brodie, G., Caddick, R., McLaughin, V. D., & Pugh, P. A. (1988). Active management of labor and operative delivery in nulliparous women. *American Journal of Obstetrics and Gynecology, 158*, 255-258.

Albers, L. L. (1999). The duration of labor in healthy women. *Journal of Perinatology: Official Journal of the California Perinatal Association, 19*(2), 114-119.

Albers, L. L., Schiff, M., & Gorwoda, J. G. (1996). The length of active labor in normal pregnancies. *Obstetrics and Gynecology, 87*, 355-359.

Alexander, J. M., Lucas, M. J., Ramin, S. M., McIntire, D. D., & Leveno, K. J. (1998). The course of labor with and without epidural analgesia. *American Journal of Obstetrics and Gynecology, 178*(3), 516-520.

Alexander, J. M., Sharma, S. K., McIntire, D. D., & Leveno, K. J. (2002). Epidural analgesia lengthens the Friedman active phase of labor. *Obstetrics and Gynecology, 100*(1), 46-50.

Amann, M., Romer, L. M., Pegelow, D. F., Jacques, A. J., Hess, C. J., & Dempsey, J. A. (2006). Effects of arterial oxygen content on peripheral locomotor muscle fatigue. *Journal of Applied Physiology (Bethesda, Md.: 1985), 101*(1), 119-127.

Atuk, N. O., Wax, S. H., Word, B. H., McGaughey, H. S., Corey, E. L., & Wood, J. E. (1961). Observations of the steady state of lactic dehydrogenase activity across the human placental membrane. *American Journal of Obstetrics and Gynecology, 82*, 271-276.

Barr, S. I., Costill, D. L., & Fink, W. J. (1991). Fluid replacement during prolonged exercise: Effects of water, saline, or no fluid. *Medicine and Science in Sports and Exercise, 23*(7), 811-817.

Battellino, L. J., Sabulsky, J., & Blanco, A. (1971). Lactate dehydrogenase isoenzymes in rat uterus: Changes during pregnancy. *Journal of Reproduction and Fertility, 25*(3), 393-399.

Bauer, A., Sward, J., Woyton, J., & Dobryszycka, W. (1970). Lactate dehydrogenase in labour. II. Isoenzymes of placenta and related tissues. *Enzymologia, 39*(3), 177-182.

Bencini, F. X., & Symonds, E. M. (1972). Ketone bodies in fetal and maternal blood during parturition. *The Australian & New Zealand Journal of Obstetrics & Gynaecology, 12*(3), 176-178.

Benzie, R. J., Doran, T. A., Harkins, J. L., Owen, V. M., & Porter, C. J. (1974). Composition of the amniotic fluid and maternal serum in pregnancy. *American Journal of Obstetrics and Gynecology, 119*(6), 798-810.

Bergholt, T., Lim, L. K., Jorgensen, J. S., & Robson, M. S. (2007). Maternal body mass index in the first trimester and risk of cesarean delivery in nulliparous women in spontaneous labor. *American Journal of Obstetrics and Gynecology, 196*(2), 163.e1-163.e5.

Bieniarz, J., Burd, L., Motew, M., & Scommegna, A. (1971). Inhibition of uterine contractility in labor. *American Journal of Obstetrics and Gynecology, 111*(7), 874-879.

Bofill, J. A., Vincent, R. D., Ross, E. L., Martin, R. W., Norman, P. F., Werhan, C. F., et al. (1997). Nulliparous active labor, epidural analgesia, and cesarean delivery for dystocia. *American Journal of Obstetrics and Gynecology, 177*(6), 1465-1470.

Brar, H. S., Platt, L. D., DeVore, G. R., Horenstein, J., & Medearis, A. L. (1988). Qualitative assessment of maternal uterine and fetal umbilical artery blood flow and resistance in laboring patients by Doppler velocimetry. *American Journal of Obstetrics and Gynecology, 158*(4), 952-956.

Brisson-Carroll, G., Fraser, W., Breart, G., Krauss, I., & Thornton, J. (1996). The effect of routine early amniotomy on spontaneous labor: A meta-analysis. *Obstetrics and Gynecology, 87*(5), 891-896.

Brody, S. (1957). Serum lactic dehydrogenase activity during human pregnancy. *Acta Endocrinologica, 25*(1), 101-104.

Bulbring, E., & Tomita, T. (1987). Catecholamine action on smooth muscle. *Pharmacological Reviews, 39*, 49-96.

Burke, R. E., Harris, S. C., & McGuire, W. L. (1978). Lactate dehydrogenase in estrogen-responsive human breast cancer cells. *Cancer Research, 38*(9), 2773-2776.

Callow, M., Morton, A., & Guppy, M. (1986). Marathon fatigue: The role of plasma fatty acids, muscle glycogen and blood glucose. *European Journal of Applied Physiology and Occupational Physiology, 55*(6), 654-661.

Cammu, H., Clasen, K., Van Wettere, L., & Derde, M. P. (1994). 'To bathe or not to bathe' during the first stage of labor. *Acta Obstetricia Et Gynecologica Scandinavica, 73*(6), 468-472.

Cammu, H., & Van Eeckhout, E. (1996). A randomised controlled trial of early versus delayed use of amniotomy and oxytocin infusion in nulliparous labour. *British Journal of Obstetrics and Gynaecology, 103*(4), 313-318.

Castaldo, G., Oriani, G., Cimino, L., Topa, M., Budillon, G., Salvatore, F., et al. (1991). Serum lactate dehydrogenase isoenzyme 4/5 ratio discriminates between hepatocarcinoma and secondary liver neoplasia. *Clinical Chemistry, 37*(8), 1419-1423.

Chang, M., Wang, S., & Chen, C. (2002). Effects of massage on pain and anxiety during labour: A randomized controlled trial in Taiwan. *Journal of Advanced Nursing, 38*(1), 68-73.

Clark, A., Carr, D., Loyd, G., Cook, V., & Spinnato, J. (1998). The influence of epidural analgesia on cesarean delivery rates: A randomized, prospective clinical trial. *American Journal of Obstetrics and Gynecology, 179*(6), 1527-1533.

Cluett, E. R., Pickering, R. M., Getliffe, K., & St George Saunders, N.J. (2004). Randomised controlled trial of labouring in water compared with standard of

augmentation for management of dystocia in first stage of labour. *BMJ (Clinical Research Ed.), 328*(7435), 314.

Cohen, J. (1988). *Statistical power analysis for the behavioral sciences.* Hillsdale, New Jersey: Lawrence Erlbaum Associates, Inc.

Cunningham, FG, Leveno, KJ, Bloom, SL, Hauth, JC, Gilstrap, LC, Wenstrom, KD (Ed.). (2005). *Williams obstetrics* (22nd ed.). New York: McGraw-Hill.

Daneshrad, Z., Verdys, M., Birot, O., Troff, F., Bigard, A. X., & Rossi, A. (2003). Chronic hypoxia delays myocardial lactate dehydrogenase maturation in young rats. *Experimental Physiology, 88*(3), 405-413.

Davis, J. D. (1999). Management of injuries to the urinary and gastrointestinal tract during cesarean section. *Obstetrics and Gynecology Clinics of North America, 26*(3), 469-480.

Dobryszycka, W., Bauer, A., Woyton, J., & Sward, J. (1970). Lactate dehydrogenase in labour. I. Isoenzymes of serum, cord serum and amniotic fluid. *Enzymologia, 39*(3), 166-176.

Dumoulin, J. G., & Foulkes, J. E. (1984). Ketonuria during labour. *British Journal of Obstetrics and Gynaecology, 91*(2), 97-98.

Eisenkop, S. M., Richman, R., Platt, L. D., & Paul, R. H. (1982). Urinary tract injury during cesarean section. *Obstetrics and Gynecology, 60*(5), 591-596.

Elkins, G., Staniunas, R., Rajab, M. H., Marcus, J., & Snyder, T. (2004). Use of a numeric visual analog anxiety scale among patients undergoing colorectal surgery. *Clinical Nursing Research, 13*(3), 237-244.

Enoka, R. M., & Duchateau, J. (2008). Muscle fatigue: What, why and how it influences muscle function. *The Journal of Physiology, 586*(1), 11-23.

Evaluation of cesarean delivery / [developed under the direction of the task force on cesarean delivery rates, roger K. freeman ... et al.](2000). In Freeman R. K. (Ed.). Washington, D.C.: American College of Obstetricians and Gynecologists.

Fontaine, P., & Adam, P. (2000). Intrathecal narcotics are associated with prolonged second-stage labor and increased oxytocin use. *The Journal of Family Practice, 49*(6), 515-520.

Foulkes, J., & Dumoulin, J. G. (1985). The effects of ketonuria in labour. *The British Journal of Clinical Practice, 39*(2), 59-62.

Fraser, W. D., Marcoux, S., Moutquin, J. M., & Christen, A. (1993). Effect of early amniotomy on the risk of dystocia in nulliparous women. The Canadian early amniotomy study group. *The New England Journal of Medicine, 328*(16), 1145-1149.

Fraser, W. D., Turcot, L., Krauss, I., & Brisson-Carrol, G. (2000). Amniotomy for shortening spontaneous labour. *Cochrane Database of Systematic Reviews (Online),* (2), CD000015.

Fraser, W., Vendittelli, F., Krauss, I., & Breart, G. (1998). Effects of early augmentation of labour with amniotomy and oxytocin in nulliparous women: A meta-analysis. *British Journal of Obstetrics and Gynaecology, 105*(2), 189-194.

Frentzen, B. H., Johnson, J. W., & Simpson, S. (1987). Nutrition and hydration: Relationship to preterm myometrial contractility. *Obstetrics and Gynecology, 70*(6), 887-891.

Friedman, E. A. (Ed.). (1978). *Labor: Clinical evaluation and management* (2nd ed.). New York: Appleton-Century-Crofts.

Friedman, E. A., & Kroll, B. H. (1969). Computer analysis of labour progression. *The Journal of Obstetrics and Gynaecology of the British Commonwealth, 76*(12), 1075-1079.

Friedman, E. (1954). The graphic analysis of labor. *American Journal of Obstetrics and Gynecology, 68*(6), 1568-1575.

Friedman, E. A. (1955). Primigravid labor: A graphicostatistical analysis. *Obstetrics and Gynecology, 6*(6), 567-589.

Friedman, E. A., & Kroll, B. H. (1971). Computer analysis of labor progression. III. Pattern variations by parity. *The Journal of Reproductive Medicine, 6*(4), 179-183.

Friedman, M. M., & Lapan, B. (1961). Variations of enzyme activities during normal pregnancy. *American Journal of Obstetrics and Gynecology, 82*, 132-137.

Frigoletto, F. D. J., Lieberman, E., Lang, J. M., Cohen, A., Barss, V., Ringer, S., et al. (1995). A clinical trial of active management of labor. *The New England Journal of Medicine, 333*, 745-750.

Fylling, P. (1961). Serum lactic dehydrogenase activity in umbilical cord, at the end of labor in normal women, and in uncomplicated puerperium. *Scandinavian Journal of Clinical and Laboratory Investigation, 13*, 264-267.

Gallagher, E. J., Bijur, P. E., Latimer, C., & Silver, W. (2002). Reliability and validity of a visual analog scale for acute abdominal pain in the ED. *The American Journal of Emergency Medicine, 20*(4), 287-290.

Garite, T. J., Porto, M., Carlson, N. J., Rumney, P. J., & Reimbold, P. A. (1993). The influence of elective amniotomy on fetal heart rate patterns and the course of labor in term patients: A randomized study. *American Journal of Obstetrics and Gynecology, 168*(6), 1827-31; discussion 1831-2.

Garite, T. J., Weeks, J., Peters-Phair, K., Pattillo, C., & Brewster, W. R. (2000). A randomized controlled trial of the effect of increased intravenous hydration on the course of labor in nulliparous women. *American Journal of Obstetrics & Gynecology, 183*(6), 1544-1548.

Gaston-Johansson, F. (1996). Measurement of pain: The psychometric properties of the pain-O-meter, a simple, inexpensive pain assessment tool that could change health care practices. *Journal of Pain and Symptom Management, 12*(3), 172-181.

Gaston-Johansson, F., Franco, T., & Zimmerman, L. (1992). Pain and psychological distress in patients undergoing autologous bone marrow transplantation. *Oncology Nursing Forum, 19*(1), 41-48.

Gaston-Johansson, F., Fridh, G., & Turner-Norvell, K. (1988). Progression of labor pain in primiparas and multiparas. *Nursing Research, 37*(2), 86-90.

Gaston-Johansson, F., Hofgren, C., Watson, P., & Herlitz, J. (1991). Myocardial infarction pain: Systematic description and analysis. *Intensive Care Nursing, 7*(1), 3-10.

Geyer, H., & Riebschlager, M. (1974). Effect of pregnancy on cytoplasmic and mitochondrial enzymes in human and animal myometrium. *Acta Endocrinologica, 77*(2), 368-379.

Goffinet, F., Fraser, W., Marcoux, S., Breart, G., Moutquin, J. M., & Daris, M. (1997). Early amniotomy increases the frequency of fetal heart rate abnormalities. Amniotomy study group. *British Journal of Obstetrics and Gynaecology, 104*(5), 548-553.

Goodlin, R. C., Quaife, M. A., & Dirksen, J. W. (1981). The significance, diagnosis, and treatment of maternal hypovolemia as associated with fetal/maternal illness. *Seminars in Perinatology, 5*(2), 163-174.

Greiss, F. C. J., & Anderson, S. G. (1968). Uterine blood flow during labor. *Clinical Obstetrics and Gynecology, 11*, 96-109.

Grossman, S. A., Sheidler, V. R., McGuire, D. B., Geer, C., Santor, D., & Piantadosi, S. (1992). A comparison of the Hopkins pain rating instrument with standard visual analogue and verbal descriptor scales in patients with cancer pain. *Journal of Pain and Symptom Management, 7*(4), 196-203.

Guyton, A. C., & Hall, J. E. (Eds.). (2006). *Textbook of medical physiology* (11th ed.). Philadelphia: Elsevier/Saunders.

Hagerman, D. D., & Wellington, F. M. (1959). Serum lactic dehydrogenase activity during pregnancy and in the newborn. *American Journal of Obstetrics and Gynecology, 77*(2), 348-351.

Hales, K. A., Morgan, M. A., & Thurnau, G. R. (1993). Influence of labor and route of delivery on the frequency of respiratory morbidity in term neonates. *International Journal of Gynaecology and Obstetrics, 43*(1), 35-40.

Hamilton, B. E., Martin, J. A., & Ventura, S. J. (2007). Births: Preliminary data for 2006. *National Vital Statistics Reports: From the Centers for Disease Control and Prevention, National Center for Health Statistics, National Vital Statistics System, 56*(7), 1-18.

Hawkins, D. F., & Whyley, G. A. (1966). The nature of the lactate dehydrogenase isoenzymes in human placenta and related tissues. *Clinica Chimica Acta; International Journal of Clinical Chemistry, 13*(6), 713-719.

He, S., Bremme, K., Kallner, A., & Blomback, M. (1995). Increased concentrations of lactate dehydrogenase in pregnancy with preeclampsia: A predictor for the birth of small-for-gestational-age infants. *Gynecologic and Obstetric Investigation, 39*(4), 234-238.

Heimback, D. P., & Prezyna, A. P. (1960). Lactic dehydrogenase in pregnancy and the puerperium. *American Journal of Obstetrics and Gynecology, 79*, 108-112.

Henderson, E., & Love, E. J. (1995). Incidence of hospital-acquired infections associated with caesarean section. *The Journal of Hospital Infection, 29*(4), 245-255.

Henry, J. P., Gauer, O. H., & Reeves, J. L. (1956). Evidence of the atrial location of receptors influencing urine flow. *Circulation Research, 4*(1), 85-90.

Hepple, R. T. (2002). The role of O2 supply in muscle fatigue. *Canadian Journal of Applied Physiology = Revue Canadienne De Physiologie Appliquee, 27*(1), 56-69.

Hultman, E., & Greenhaff, P. L. (1991). Skeletal muscle energy metabolism and fatigue during intense exercise in man. *Science Progress, 75*(3-4), 361-370.

Ingemarsson, I. (1976). Effect of terbutaline on premature labor. A double-blind placebo-controlled study. *American Journal of Obstetrics and Gynecology, 125*(4), 520-524.

Jablonsky, G., Leung, F. Y., & Henderson, A. R. (1985). Changes in the ratio of lactate dehydrogenase isoenzymes 1 and 2 during the first day after acute myocardial infarction. *Clinical Chemistry, 31*(10), 1621-1624.

Johnson, N., Lilford, R., Guthrie, K., Thornton, J., Barker, M., & Kelly, M. (1997). Randomised trial comparing a policy of early with selective amniotomy in uncomplicated labour at term. *British Journal of Obstetrics and Gynaecology, 104*(3), 340-346.

Jones, M., & Larson, E. (2003). Length of normal labor in women of Hispanic origin. *Journal of Midwifery & Women's Health, 48*(1), 2-9.

Judelson, D. A., Maresh, C. M., Farrell, M. J., Yamamoto, L. M., Armstrong, L. E., Kraemer, W. J., et al. (2007). Effect of hydration state on strength, power, and resistance exercise performance. *Medicine and Science in Sports and Exercise, 39*(10), 1817-1824.

Karelis, A. D., Peronnet, F., & Gardiner, P. F. (2002). Glucose infusion attenuates muscle fatigue in rat plantaris muscle during prolonged indirect stimulation in situ. *Experimental Physiology, 87*(5), 585-592.

Knutson, R. G., Cornatzer, W. E., Moore, J. H., & Nelson, W. W. (1958). Serum lactic dehydrogenase and glutamic oxalacetic transaminase activites in normal pregnancy. *The Journal of Laboratory and Clinical Medicine, 51*(5), 773-777.

Konttinen, A., & Pyoeraelae, T. (1963). Serum enzyme activity in late pregnancy, at delivery, and during puerperium. *Scandinavian Journal of Clinical and Laboratory Investigation, 15*, 429-435.

Kristensen, S. R., Horder, M., & Pedersen, G. T. (1979). Reference values for six enzymes in plasma from newborns and women at delivery. *Scandinavian Journal of Clinical and Laboratory Investigation, 39*(8), 777-784.

Lapan, B., & Friedman, M. M. (1959). A comparative study of fetal and maternal serum enzyme levels. *The Journal of Laboratory and Clinical Medicine, 54*, 417-426.

Larcombe-McDouall, J., Buttell, N., Harrison, N., & Wray, S. (1999). In vivo pH and metabolite changes during a single contraction in rat uterine smooth muscle. *The Journal of Physiology, 518 (Pt 3)*, 783-790.

Lauzon, L., & Hodnett, E. (2001). Labour assessment programs to delay admission to labour wards. *Cochrane Database of Systematic Reviews (Online),* (3), CD000936.

Lederman, R. P., Lederman, E., Work, B. A. J., & McCann, D. S. (1978). The relationship of maternal anxiety, plasma catecholamines, and plasma cortisol to progress in labor. *American Journal of Obstetrics and Gynecology, 132*, 495-500.

Lederman, R. P., Lederman, E., Work, B. J., & McCann, D. S. (1985). Anxiety and epinephrine in multiparous women in labor: Relationship to duration of labor and fetal heart rate pattern. *American Journal of Obstetrics and Gynecology, 153*, 870-877.

Lederman, R. P., McCann, D. S., Work, B. J., & Huber, M. J. (1977). Endogenous plasma epinephrine and norepinephrine in last-trimester pregnancy and labor. *American Journal of Obstetrics and Gynecology, 129*, 5-8.

Levine, E. M., Ghai, V., Barton, J. J., & Strom, C. M. (2001). Mode of delivery and risk of respiratory diseases in newborns. *Obstetrics and Gynecology, 97*(3), 439-442.

Linton, E. B., & Miller, E. C. (1959). Serum lactic dehydrogenase in pregnancy. *American Journal of Obstetrics and Gynecology, 78*(1), 11-12.

Little, W. A. (1959). Serum lactic dehydrogenase in pregnancy. *Obstetrics and Gynecology, 13*(2), 152-162.

Lopez-Zeno, J. A., Peaceman, A. M., Adashek, J. A., & Socol, M. L. (1992). A controlled trial of a program for the active management of labor. *The New England Journal of Medicine, 326*, 450-454.

Lossos, I. S., Intrator, O., Berkman, N., & Breuer, R. (1999). Lactate dehydrogenase isoenzyme analysis for the diagnosis of pleural effusion in haemato-oncological patients. *Respiratory Medicine, 93*(5), 338-341.

Lyrenas, S. (2002). Labor in the grand multipara. *Gynecologic and Obstetric Investigation, 53*(1), 6-12.

Maggiulli, M. J., Gustafson, J. C., Rector, W. D., & Hilf, R. (1977). Enzyme activities in human endometrium, myometrium and leiomyomas of the uterus. *Enzyme, 22*(1), 13-18.

Makkonen, M. (1977). Myometrial energy metabolism during pregnancy and normal and dysfunctional labor. *Acta Obstetricia Et Gynecologica Scandinavica.Supplement, 71*, 1-68.

Makkonen, M., Penttila, I. M., & Castren, O. (1980). Serum lactic acid dehydrogenase and isoenzymes during pregnancy and labor. *Acta Obstetricia Et Gynecologica Scandinavica, 59*, 97-102.

Makkonen, M., Puhakainen, E., Hanninen, O., & Castren, O. (1982). Lactate dehydrogenase isoenzymes in human myometrium during pregnancy and labor. *Acta Obstetricia Et Gynecologica Scandinavica, 61*(1), 35-37.

Marcil, M., Karelis, A. D., Peronnet, F., & Gardiner, P. F. (2005). Glucose infusion attenuates fatigue without sparing glycogen in rat soleus muscle during prolonged electrical stimulation in situ. *European Journal of Applied Physiology, 93*(5-6), 569-574.

Martin, J. A., Hamilton, B. E., Sutton, P. D., Ventura, S. J., Menacker, F., & Kirmeyer, S. (2006). Births: Final data for 2004. *National Vital Statistics Reports: From the Centers for Disease Control and Prevention, National Center for Health Statistics, National Vital Statistics System, 55*(1), 1-101.

Maughan, R. J. (1992). Fluid balance and exercise. *International Journal of Sports Medicine, 13 Suppl 1*, S132-5.

Maughan, R. J. (2001). Food and fluid intake during exercise. *Canadian Journal of Applied Physiology = Revue Canadienne De Physiologie Appliquee, 26 Suppl*, S71-8.

Maughan, R. J., Bethell, L. R., & Leiper, J. B. (1996). Effects of ingested fluids on exercise capacity and on cardiovascular and metabolic responses to prolonged exercise in man. *Experimental Physiology, 81*(5), 847-859.

McNiven, P. S., Williams, J. I., Hodnett, E., Kaufman, K., & Hannah, M. E. (1998). An early labor assessment program: A randomized, controlled trial. *Birth (Berkeley, Calif.), 25*(1), 5-10.

Meade, B. W., & Rosalki, S. B. (1962). Lactic dehydrogenase isoenzymes in pregnancy. *Lancet, 1*, 1407.

Meade, B. W., & Rosalki, S. B. (1963a). The origin of increased maternal serum enzyme activity in pregnancy and labour. *The Journal of Obstetrics and Gynaecology of the British Commonwealth, 70*, 862-868.

Meade, B. W., & Rosalki, S. B. (1963b). Serum enzyme activity in normal pregnancy and the newborn. *The Journal of Obstetrics and Gynaecology of the British Commonwealth, 70*, 693-700.

Mendelson, C. L. (1946). The aspiration of stomach contents into the lungs during obstetric anesthesia. *American Journal of Obstetrics and Gynecology, 52*, 191.

Metzger, B. E., Ravnikar, V., Vileisis, R. A., & Freinkel, N. (1982). "Accelerated starvation" and the skipped breakfast in late normal pregnancy. *Lancet, 1*(8272), 588-592.

Miotti, A. B., Alter, A. A., Moltz, A., & Sabb, F. (1973). Serum and amniotic fluid lactic dehydrogenase in pregnant women. *American Journal of Obstetrics and Gynecology, 117*(8), 1129-1136.

Monir-Bishty, E., Pierce, S. J., Kupittayanant, S., Shmygol, A., & Wray, S. (2003). The effects of metabolic inhibition on intracellular calcium and contractility of human myometrium. *BJOG: An International Journal of Obstetrics and Gynaecology, 110*(12), 1050-1056.

Morrison, J. J., Rennie, J. M., & Milton, P. J. (1995). Neonatal respiratory morbidity and mode of delivery at term: Influence of timing of elective caesarean section. *British Journal of Obstetrics and Gynaecology, 102*(2), 101-106.

Nagy, I., Hirka, G., Kurcz, M., Anda, E., & Baranyai, P. (1978). The role of estrogens in the regulation of lactate dehydrogenase activity and its submolecular organization in rat anterior pituitary. *Endokrinologie, 71*(1), 1-12.

Nagy, I., Hirka, G., Kurcz, M., & Baranyai, P. (1978). Changes of lactic dehydrogenase activity and combination of its subunits in rat anterior pituitary during puberty and in maturity, as well as during estrous cycle on the actue effect of estradiol and after castration. *Endokrinologie, 71*(1), 13-24.

National Institutes of Health. (2006). State of the science conference: Cesarean delivery on maternal request. March 27-29, 2006.

Noakes, T. D. (1993). Fluid replacement during exercise. *Exercise and Sport Sciences Reviews, 21*, 297-330.

Norwitz, E. R., Robinson, J. N., & Repke, J. T. (2002). Labor and delivery. In S. G. Gabbe, J. R. Niebyl & J. L. Simpson (Eds.), *Obstetrics: Normal and problem pregnancies* (4th ed.). Philadelphia: Churchill Livingstone.

Nuthalapaty, F. S., Rouse, D. J., & Owen, J. (2004). The association of maternal weight with cesarean risk, labor duration, and cervical dilation rate during labor induction. *Obstetrics & Gynecology, 103*(3), 452-456.

O'Driscoll, K., Meagher, D., & Boylan, P. (Eds.). (1993). *Active management of labor: The Dublin experience* (3rd ed.). Aylesbury, England: Mosby.

O'Driscoll, K., Jackson, R. J., & Gallagher, J. T. (1969). Prevention of prolonged labour. *British Medical Journal, 2*(5655), 477-480.

O'Driscoll, K., Stronge, J. M., & Minogue, M. (1973). Active management of labour. *British Medical Journal, 3*(5872), 135-137.

Oscarsson, M. E., Amer-Wahlin, I., Rydhstroem, H., & Kallen, K. (2006). Outcome in obstetric care related to oxytocin use. A population-based study. *Acta Obstetricia Et Gynecologica Scandinavica, 85*(9), 1094-1098.

Paavonen, T., Liippo, K., Aronen, H., & Kiistala, U. (1991). Lactate dehydrogenase, creatine kinase, and their isoenzymes in pleural effusions. *Clinical Chemistry, 37*(11), 1909-1912.

Parilla, B. V., Dooley, S. L., Jansen, R. D., & Socol, M. L. (1993). Iatrogenic respiratory distress syndrome following elective repeat cesarean delivery. *Obstetrics and Gynecology, 81*(3), 392-395.

Parratt, J. R., Taggart, M. J., & Wray, S. (1995a). Changes in intracellular pH close to term and their possible significance to labour. *Pflugers Archiv : European Journal of Physiology, 430*(6), 1012-1014.

Parratt, J. R., Taggart, M. J., & Wray, S. (1995b). Functional effects of intracellular pH alteration in the human uterus: Simultaneous measurements of pH and force. *Journal of Reproduction and Fertility, 105*(1), 71-75.

Parratt, J., Taggart, M., & Wray, S. (1994). Abolition of contractions in the myometrium by acidification in vitro. *Lancet, 344*(8924), 717-718.

Peisner, D. B., & Rosen, M. G. (1986). Transition from latent to active labor. *Obstetrics and Gynecology, 68*(4), 448-451.

Perl, F. M., & Hunter, D. J. (1992). What cervical dilatation rate during active labour should be considered abnormal? *European Journal of Obstetrics, Gynecology, and Reproductive Biology, 45*(2), 89-92.

Philpott, R. H. (1972). Graphic records in labour. *British Medical Journal, 4*(5833), 163-165.

Philpott, R. H., & Castle, W. M. (1972a). Cervicographs in the management of labour in primigravidae. I. The alert line for detecting abnormal labour. *The Journal of Obstetrics and Gynaecology of the British Commonwealth, 79*(7), 592-598.

Philpott, R. H., & Castle, W. M. (1972b). Cervicographs in the management of labour in primigravidae. II. The action line and treatment of abnormal labour. *The Journal of Obstetrics and Gynaecology of the British Commonwealth, 79*(7), 599-602.

Pierce, S. J., Kupittayanant, S., Shmygol, T., & Wray, S. (2003). The effects of pH change on Ca(++) signaling and force in pregnant human myometrium. *American Journal of Obstetrics and Gynecology, 188*(4), 1031-1038.

Pircon, R. A., Strassner, H. T., Kirz, D. S., & Towers, C. V. (1989). Controlled trial of hydration and bed rest versus bed rest alone in the evaluation of preterm uterine contractions. *American Journal of Obstetrics and Gynecology, 161*(3), 775-779.

Posner, N. A., & Silverstone, F. A. (1977). Carbohydrate metabolism in pregnancy: Management of the diabetic gravida. *Obstetrics and Gynecology Annual, 6*, 67-125.

Pulkkinen, M. O., & Willman, K. (1968). Enzymes and isoenzymes in maternal and foetal sera. A study on lactate and isocitrate dehydrogenases, alkaline phosphatases and beta-glucuronidase. *Acta Obstetricia Et Gynecologica Scandinavica, 47*(3), 273-291.

Rahnama, P., Ziaei, S., & Faghihzadeh, S. (2006). Impact of early admission in labor on method of delivery. *International Journal of Gynaecology and Obstetrics: The Official Organ of the International Federation of Gynaecology and Obstetrics, 92*(3), 217-220.

Richards, A. H., & Hilf, R. (1972). Effect of estrogen administration on glucose 6-phosphate dehydrogenase and lactate dehydrogenase isoenzymes in rodent mammary tumors and normal mammary glands. *Cancer Research, 32*(3), 611-616.

Richterich, R., Schafroth, P., & Aebi, H. (1963). A study of lactic dehydrogenase isoenzyme pattern of human tissues by adsorption-elution on sephadex-DEAE. *Clinica Chimica Acta; International Journal of Clinical Chemistry, 8*, 178-192.

Rogers, R., Gilson, G., & Kammerer-Doak, D. (1999). Epidural analgesia and active management of labor: Effects on length of labor and mode of delivery. *Obstetrics and Gynecology, 93*(6), 995-998.

Roman, W. (1969). Quantitative estimation of lactate dehydrogenase isoenzymes in serum. I. Review of methods and distribution in human tissues. *Enzymologia, 36*(4), 189-219.

Romer, L. M., Haverkamp, H. C., Lovering, A. T., Pegelow, D. F., & Dempsey, J. A. (2006). Effect of exercise-induced arterial hypoxemia on quadriceps muscle fatigue in healthy humans. *American Journal of Physiology. Regulatory, Integrative and Comparative Physiology, 290*(2), R365-75.

Rotenberg, Z., Davidson, E., Weinberger, I., Fuchs, J., Sperling, O., & Agmon, J. (1988). The efficiency of lactate dehydrogenase isoenzyme determination for the diagnosis of acute myocardial infarction. *Archives of Pathology & Laboratory Medicine, 112*(9), 895-897.

Rotenberg, Z., Weinberger, I., Davidson, E., Fuchs, J., Harell, D., & Agmon, J. (1989). Lactate dehydrogenase isoenzyme patterns in serum of patients with metastatic liver disease. *Clinical Chemistry, 35*(5), 871-873.

Schneider, D., Halperin, R., Langer, R., Bukovsky, I., & Herman, A. (1997). Peritoneal fluid lactate dehydrogenase in ovarian cancer. *Gynecologic Oncology, 66*(3), 399-404.

Segal, S., Csavoy, A. N., & Datta, S. (1998). The tocolytic effect of catecholamines in the gravid rat uterus. *Anesthesia and Analgesia, 87*, 864-869.

Seligman, L. C., Duncan, B. B., Branchtein, L., Gaio, D. S. M., Mengue, S. S., & Schmidt, M. I. (2006). Obesity and gestational weight gain: Cesarean delivery and labor complications. *Revista De Saude Publica, 40*(3), 457-465.

Shirreffs, S. M. (2005). The importance of good hydration for work and exercise performance. *Nutrition Reviews, 63*(6), S14-21.

Sittner, B., Hudson, D. B., Grossman, C. C., & Gaston-Johansson, F. (1998). Adolescents' perceptions of pain during labor. *Clinical Nursing Research, 7*(1), 82-93.

Smith, J. J., Schwartz, E. D., & Schwartz, M. K. (1959). Lactic acid dehydrogenase during pregnancy and puerperium. *Obstetrics and Gynecology, 13*(2), 163-165.

Society of Obstetricians and Gynaecologists of Canada. (1995). *Policy statement number 40: Dystocia*

Stone, M. L., Lending, M., Slobody, L. B., & Mestern, J. (1960). Glutamic oxalacetic transaminase and lactic dehydrogenase in pregnancy. *American Journal of Obstetrics and Gynecology, 80*, 104-107.

Svardby, K., Nordstrom, L., & Sellstrom, E. (2007). Primiparas with or without oxytocin augmentation: A prospective descriptive study. *Journal of Clinical Nursing, 16*(1), 179-184.

Sward, J., Woyton, J., Dobryszycka, W., & Bauer, A. (1972). The influence of parturition on some serum enzyme activities. *Archivum Immunologiae Et Therapiae Experimentalis, 20*(2), 273-275.

Tamiya, N., Araki, S., Ohi, G., Inagaki, K., Urano, N., Hirano, W., et al. (2002). Assessment of pain, depression, and anxiety by visual analogue scale in Japanese women with rheumatoid arthritis. *Scandinavian Journal of Caring Sciences, 16*(2), 137-141.

Tsoi, S. C., Zheng, J., Xu, F., & Kay, H. H. (2001). Differential expression of lactate dehydrogenase isozymes (LDH) in human placenta with high expression of LDH-A(4) isozyme in the endothelial cells of pre-eclampsia villi. *Placenta, 22*(4), 317-322.

Turner, M. J., Rasmussen, M. J., Turner, J. E., Boylan, P. C., MacDonald, D., & Stronge, J. M. (1990). The influence of birth weight on labor in nulliparas. *Obstetrics and Gynecology, 76*(2), 159-163.

U.S. Department of Health and Human Services. Office of Disease Prevention and Health Promotion. (n.d.). *Healthy people 2010.* Retrieved June 16, 2008, from

Vahratian, A., Zhang, J., Troendle, J. F., Savitz, D. A., & Riz, A. M. (2004). Maternal prepregnancy overweight and obesity and the pattern of labor progression in term nulliparous women. *Obstetrics & Gynecology, 104*(5), 943-951.

van Ham, M A, van Dongen, P W, & Mulder, J. (1997). Maternal consequences of caesarean section. A retrospective study of intra-operative and postoperative maternal complications of caesarean section during a 10-year period. *European Journal of Obstetrics, Gynecology, and Reproductive Biology, 74*(1), 1-6.

Vergnon, J. M., Guidollet, J., Gateau, O., Ripoll, J. P., Collet, P., Louisot, P., et al. (1984). Lactic dehydrogenase isoenzyme electrophoretic patterns in the diagnosis of pleural effusion. *Cancer, 54*(3), 507-511.

von Eyben, F E, Blaabjerg, O., Hyltoft-Petersen, P., Madsen, E. L., Amato, R., Liu, F., et al. (2001). Serum lactate dehydrogenase isoenzyme 1 and prediction of death in patients with metastatic testicular germ cell tumors. *Clinical Chemistry and Laboratory Medicine : CCLM / FESCC, 39*(1), 38-44.

von Eyben, F E, Blaabjerg, O., Petersen, P. H., Horder, M., Nielsen, H. V., Kruse-Andersen, S., et al. (1988). Serum lactate dehydrogenase isoenzyme 1 as a marker of testicular germ cell tumor. *The Journal of Urology, 140*(5), 986-990.

von Eyben, F E, Madsen, E. L., Blaabjerg, O., Petersen, P. H., von der Maase, H, Jacobsen, G. K., et al. (2001). Serum lactate dehydrogenase isoenzyme 1 and relapse in patients with nonseminomatous testicular germ cell tumors clinical stage I. *Acta Oncologica (Stockholm, Sweden), 40*(4), 536-540.

Watanabe, T., Minakami, H., Sakata, Y., Matsubara, S., Tamura, N., Obara, H., et al. (2001). Effect of labor on maternal dehydration, starvation, coagulation, and fibrinolysis. *Journal of Perinatal Medicine, 29*(6), 528-534.

Weiner, H. (2006). Enzymes: classification, kinetics, and control. In T.M. Devlin (Ed.), *Textbook of biochemistry with clinical indications* (6th ed.). Hoboken, NJ: Wiley-Liss.

West, M., & Zimmerman, H. J. (1958). Lactic dehydrogenase and glutamic oxaloacetic transaminase in normal pregnant women and newborn children. *The American Journal of the Medical Sciences, 235*(4), 443-447.

Wieme, R. J., & Van Maercke, Y. (1961). The fifth (electrophoretically slowest) serum lactic dehydrogenase as an index of liver injury. *Annals of the New York Academy of Sciences, 94*, 898-911.

World Health Organization. (1985). Joint interregional conference on appropriate technology for birth. Fortaleza, Brazil, April 22-26, 1985.

World Health Organization. Division of Family Health. Maternal Health and Safe Motherhood Programme. (1994). Partograph in management of labour. *Lancet, 343*(8910), 1399-1404.

World Health Organization. Division of Family Health. Maternal Health and Safe Motherhood Programme. (1994a). *The partograph: The application of the WHO partograph in the management of labour. Report of a WHO multicentre study 1990-1991.* No. WHO/FHE/MSM/94.4). Geneva: World Health Organization.

World Health Organization. Division of Family Health. Maternal Health and Safe Motherhood Programme. (1994b). *Preventing prolonged labour: A practical guide.* No. WHO/FHE/MSM/93.8). Geneva: World Health Organization.

World Health Organization. Division of Reproductive Health. Maternal and Newborn Health/Safe Motherhood. *Care in normal birth: A practical guide. Report of a technical working group.* No. WHO/FRH/MSM/96.24). Geneva: World Health Organization.

Wroblewski, F., & Gregory, K. F. (1961). Lactic dehydrogenase isozymes and their distribution in normal tissues and plasma and in disease states. *Annals of the New York Academy of Sciences, 94*, 912-932.

Wroblewski, F., Ross, C., & Gregory, K. (1960). Isoenzymes and myocardial infarction. *The New England Journal of Medicine, 263*, 531-536.

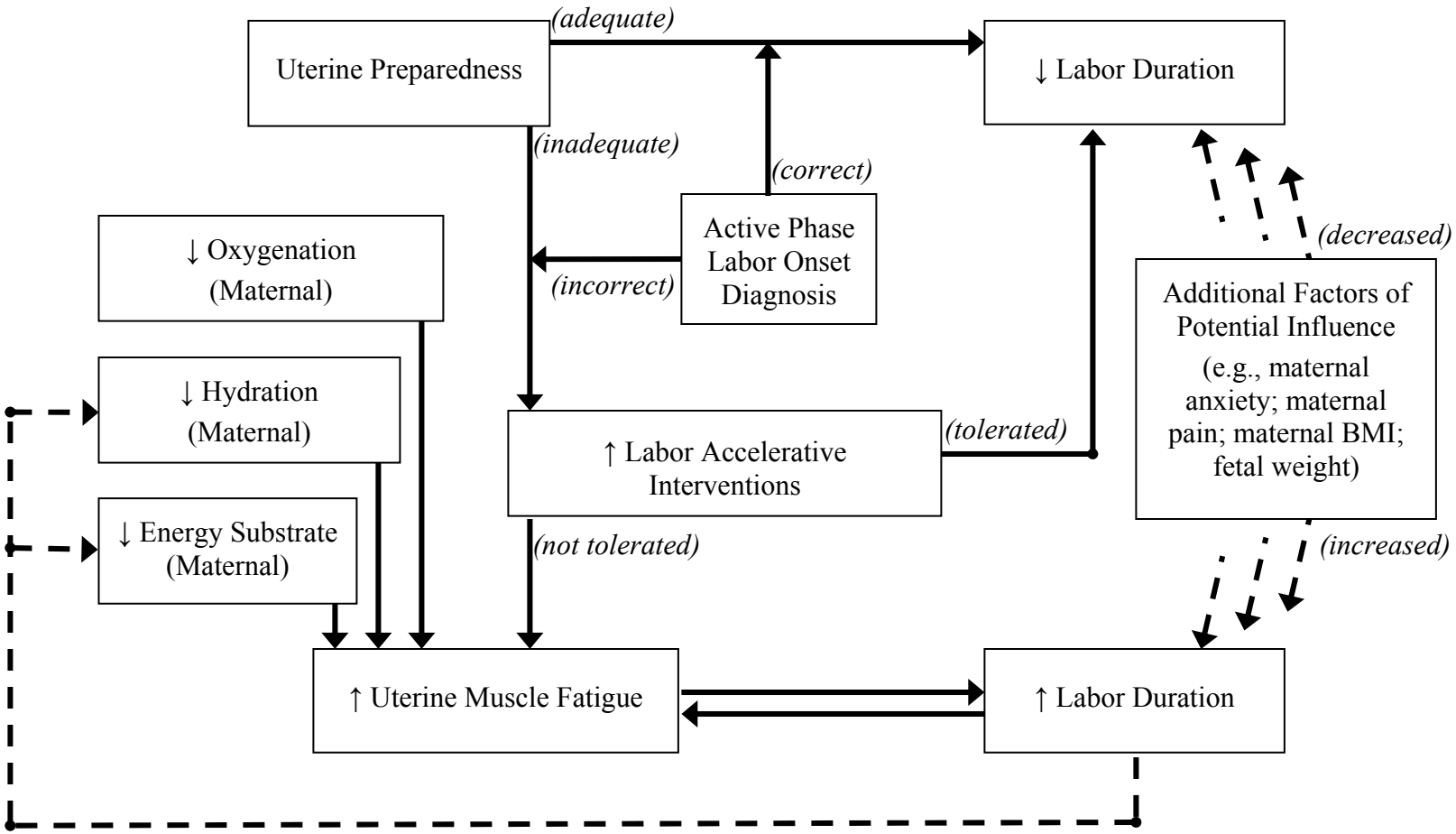
Zeisler, H., Tempfer, C., Mayerhofer, K., Barrada, M., & Husslein, P. (1998). Influence of acupuncture on duration of labor. *Gynecologic and Obstetric Investigation, 46*(1), 22-25.

Zhang, J., Yancey, M. K., Klebanoff, M. A., Schwarz, J., & Schweitzer, D. (2001). Does epidural analgesia prolong labor and increase risk of cesarean delivery? A natural experiment. *American Journal of Obstetrics and Gynecology, 185*(1), 128-134.

Zhang, J., Troendle, J. F., & Yancey, M. K. (2002). Reassessing the labor curve in nulliparous women. *American Journal of Obstetrics and Gynecology, 187*(4), 824-828.

APPENDIX

LABOR DURATION FRAMEWORK



Labor Duration Framework