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Cortisol as a Biomarker of Stress in Term Human Labor: Physiological and Methodological Issues

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Abstract

Literature on the use of plasma cortisol to quantify psychophysiological stress in humans is extensive. However, in parturition at term gestation the use of cortisol as a biomarker of stress is particularly complex. Plasma cortisol levels increase as labor progresses. This increase seems to be important for maintenance of maternal/fetal wellbeing and facilitation of normal labor progress. Unique physiological and methodological issues involved in the use of cortisol as a biomarker of stress in labor present challenges for researchers. This review examines these issues, suggests mixed methods and within-subject repeated measures designs, and offers recommendations for assay procedures for parturient sampling. Documentation of clinical interventions and delivery outcomes may elucidate relationships among psychophysiological stressors, cortisol and normal labor progress. With attention to these methodological issues, analysis of plasma cortisol may lead to clinical interventions that support normal labor physiology.

Keywords

cortisol; parturition; labor pain; stress

Labor is a time of psychophysiological stress. To capture the intensity of the labor-induced stress response as well as the physiological response to stress-reduction strategies, researchers have used plasma cortisol level as a biomarker (Jouppila, Hollmen, Jouppila, Kauppila, & Tuimala, 1976; Onur, Ercal, & Karslioglu, 1989; Willcox, Yovich, McColm, &

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Phillips, 1985; Wladimiroff, Lo, de Meijer, Lamberts, & Schalekamp, 1983). It is well established that cortisol levels increase throughout pregnancy and continue to increase with advancing labor. These physiological changes are viewed as a necessity for maintaining maternal/fetal wellbeing and promoting normal labor progression. In this review we present a brief overview of the current understanding of the activity of the hypothalamic-pituitary-adrenal (HPA) axis during late pregnancy and labor and the challenges inherent in measuring cortisol as an indicator of stress during labor.

Both classic studies using radioimmunoassay (RIA) and more current studies utilizing enzyme immunoassay (EIA) and enzyme-linked immunoassay (ELISA; Lequin, 2005) have demonstrated that there is large woman-to-woman variation in pre-labor as well as during-labor cortisol levels. This observation is true for both the percent of free plasma cortisol and the concentration of total and free plasma cortisol at term gestation, in labor and at delivery (Dorr et al., 1989; Predine, Merceron, Barrier, Sureau, & Milgrom, 1979; Willcox et al., 1985). During labor in particular, such variations may be associated with personal differences in anxiety, pain and therapeutic interventions as well as adverse events such as delay in labor progression and fetal distress. From a methodological perspective the accurate comparison of parturient cortisol levels across studies is further challenged by variations in sample characteristics, data collection protocols, and assay procedures. In addition, much of the research on the HPA axis and stress was performed in the 1970s and 1980s, and since that time laboratory techniques have evolved.

Against this backdrop, it is unclear whether researchers can use single or multiple measures of plasma cortisol or other components of the HPA axis as suitable measures of psychophysiological stress during labor or as an outcome measure of stress-reducing interventions. Investigators need to pay special attention to sample collection, person attributes (e.g., stage of labor, pain level), medical interventions, and assay sensitivity.

HPA Axis During Late Pregnancy and Labor

In pregnancy physiological changes in the HPA axis and physiological stress reactivity appear to be attenuated. For example, the cortisol response to standard laboratory stress measures such as a cold pressor test of the hand and white noise via headphones fail to illicit significant cortisol increases in women at 37 and 38 weeks'gestation (Kammerer, Adams, von Castelberg, & Glover, 2002; Hartikainen-Sorri, Kirkinen, Sorri, Anttonen, & Tuimala 1991). Neither is salivary cortisol significantly increased when the Trier Social Stress Test (TSST), a standardized laboratory-based psychosocial stressor, is administered at 31 weeks' gestation (Entringer et al., 2010). Interestingly, in an early study by Schulte et al. (1990), researchers administered a standard corticotropin-releasing hormone (CRH) dose (1μg/kg synthetic human) to 7 pregnant women 1 week before delivery. The dose failed to elicit an increase in adrenocorticotropic hormone (ACTH) or cortisol levels in 6 of the women. Together, these findings suggest decreased responsiveness of the anterior pituitary to CRH in late pregnancy. It is unlikely that researchers will conduct similar CRH-stimulation studies in the future because of ethical considerations.

The primary challenge involved in the study of the HPA axis during labor is that, during this time, maternal cortisol levels are influenced by two physiological mechanisms: the feed-forward loop of feto-uteroplacental corticosteroids and the traditional negative feedback loop of the HPA-axis stress response. Free plasma cortisol levels in women with early spontaneous labor are almost 3-fold higher than pre-induction levels from women at term gestation. With each unit increase of maternal plasma cortisol (μg/dl) there is an associated 34 pg/ml increase in CRH (Sandman et al., 2006). At term gestation, the fetus, uterus and placenta all contribute to increases in maternal cortisol levels. Although we have an

incomplete understanding of the mechanism, we do know that in the feed-forward loop, increases in cortisol increase CRH rather than decreasing it as in the typical stress negative feedback system. It is the balance of both the negative feedback system and the feed-forward system that gives rise to the levels of plasma cortisol seen in maternal samples during late pregnancy and labor. We have listed factors that contribute to increasing plasma cortisol levels in laboring women in Table 1.

Despite the inherent challenges in interpreting cortisol findings, it is important to consider the essential role that the HPA-axis hormones (CRH, ACTH, cortisol) and corticosteroid-binding globulin (CBG) play in mediating the physiological changes necessary for normal labor progression and delivery. Testing strategies to manipulate (reduce) cortisol levels during this period may not be entirely justified without consideration of its role during labor.

Metabolism

A primary function of cortisol is to maintain glucose equilibrium. Increases in cortisol serve primarily to prevent hypoglycemia during acute and prolonged stress through influence on metabolic activities that provide energy. During labor, fetal glucose is supplied via transplacental transfer down the maternal/fetal concentration gradient (Barta & Drugan, 2010; Bon et al., 2007). Glucose is also the principal nutritive metabolite for the pregnant myometrium (Steingrimsdottir, Ronquist, Ulmsten, & Waldenstrom, 1995).

At term, plasma glucose levels of healthy fasting women in spontaneous labor increase significantly and progressively above late pregnancy levels when measured at cervical dilations of 2–4 cm and 6–8 cm and immediately prior to delivery (Holst, Jenssen, Burhol, Jorde, & Maltau, 1986). Insulin levels decrease as labor progresses, while plasma glucagon levels increase (Maheux et al., 1996). Blood glucose is the energy substrate used during low-intensity effort such as early labor (3–6 cm), while muscle glycogen is used during high-intensity effort, such as transition (7–10 cm) and expulsion (10 cm to delivery). Cortisol is essential to maintaining glucose levels when glycogen stores are depleted with fasting or with a long labor and difficult second stage. High levels of cortisol maximize glucose availability for the fetus and myometrium. Documentation of oral intake prior to and during labor, intravenous fluids, as well as the duration and number of expulsive efforts provide a context for interpretation of changes in plasma cortisol level secondary to metabolic demands. Thus, in nonlaboring states, high levels of cortisol may reflect intermittent or acute stress, while during labor, high levels of cortisol may be adaptive. But how high and for how long cortisol increases should be considered within normal range or adaptive is unclear. Furthermore, the effects on labor progress of cortisol-altering interventions are virtually unknown. Both questions are worthy of further exploration.

Inflammation

During labor circulating neutrophils, monocytes and natural killer cell levels increase, and the chemotactic migratory response of neutrophils is heightened (Yuan, Jordan, McInnes, Harnett, & Norman, 2009). This leukocytosis does not occur at term when labor is absent (Delgado, Neubert, & Dudenhausen, 1994). Spontaneous human labor at term is considered an inflammatory process “characterized by a molecular signature consistent with over-expression of genes involved in inflammation and leukocyte chemotaxis” (Mittal et al., 2010, p. 623). With labor there is local infiltration of the myometrium and cervix by neutrophils and macrophages (Osman et al., 2003; Thomson et al., 1999), decidual (fetal–maternal interface) macrophage numbers increase 4-fold (Hamilton et al., 2012), and placental tissue shows significant increases in 11β-HSD1 (an enzyme that converts cortisone to cortisol) activity (Murphy & Clifton, 2003). At the same time, the increased production of pro-inflammatory cytokines and chemokines and changes in gene expression of the

chorioamniotic membranes without accompanying changes in systemic or membrane histological inflammation all support the view of labor as an inflammatory process (Haddad et al., 2006; Romero et al., 2006).

Cortisol is well known for its anti-inflammatory properties, which allow it to block inflammation before it begins, and for its role in the resolution of inflammation (Hall & Guyton, 2011). The fact that these inflammatory changes occur at a time of rising cortisol levels suggests that the sensitivity to cortisol, the availability of free cortisol and/or other factors may be contributing to the lack of anti-inflammatory effects normally attributed to high levels of plasma cortisol. This reduced anti-inflammation, too, may be considered adaptive to labor and delivery. Of interest would be concurrent plasma measurement of peripheral leukocytes, cytokines and chemokines and indicators of the HPA axis during labor.

Women who are nulliparous with prolonged labor or rupture of membranes or who experience multiple vaginal examinations (above the standard every-2-hr examination) or internal monitoring are at increased risk for intrapartal intra-amniotic infection (Newton, Prihoda, & Gibbs, 1989) and increased maternal and fetal stress. When studying the HPA indicators during labor, investigators need to consider whether women with chorioamnionitis should be excluded from study entry or whether the presence of chorioamnionitis should be controlled for at the time of data analyses (Redline, 2012).

Corticotropin Releasing Hormone (CRH) and CRH-Binding Protein (CRHbp) in Labor

As maternal cortisol increases during labor, other elements of the HPA axis also change immediately before and during labor. In addition to the hypothalamic source, the placenta of women at term gestation expresses CRHbp prior to labor (Mayor-Lynn, Toloubeydokhti, Cruz, & Chegini, 2011). Plasma CRHbp decreases markedly (by approximately half) from term to delivery (Perkins, Eben, Wolfe, Schulte, & Linton, 1993). As a result, during labor more bioactive CRH is available in the maternal circulation. When measured hourly, plasma CRH levels increase progressively during spontaneous labor in healthy primigravidas at term gestation (Petraglia et al., 1990).

Researchers have found higher plasma levels of CRH at term in women with spontaneous labor (physiological readiness) than in those induced for postdate delivery (inadequate physiological readiness; Ochedalski, Zylinska, Laudanski, & Lachowicz, 2001). At the same time, women at term who go into spontaneous labor have lower levels of CRHbp. Following delivery CRH levels decrease (Florio et al., 2007). Changes in CRH and CRHbp are important in the preparation for and onset of spontaneous labor at term and in normal labor progression. Indeed, in early studies, women with higher plasma concentrations of CRH had shorter labors and greater uterine myometrial contractility during oxytocin induction than those with lower CRH levels (McLean, Thompson, Zhang, Brinsmead, & Smith, 1994; Stalla et al., 1989). CRH and CRHbp are part of the cortisol feed-forward loop. Thus, these normal preparatory and necessary parturition changes cast doubt on whether CRH or CRHbp can be used as indicators of psychophysiological stress during labor.

ACTH in Labor

Plasma levels of ACTH are higher in all stages of labor than in late pregnancy (Carr, Parker, Madden, MacDonald, & Porter, 1981), and they increase with spontaneous advancing labor (Harbach et al., 2008). Yet, unlike the strong association of ACTH to cortisol in nonpregnant women, the relationship of ACTH to cortisol in labor and the stress of labor are unclear. Although data are limited, in one study ($N = 28$), investigators found no correlation between ACTH and cortisol levels during labor (Odagiri et al., 1982), while in a second

study there was a weak positive correlation (r = .37, N = 50) between ACTH and cortisol levels (Bergant et al., 1998). However, variables such as the point in labor when data were collected were not consistent between these two studies.

The utility of using ACTH as a sole measure of psychophysiological stress during labor is not clear. Factors such as oxytocin infusion influence ACTH levels. In one study ACTH levels were higher in women who received oxytocin for labor induction as compared to those who experienced spontaneous labor (Ochedalski et al., 2001). It is uncertain whether it is the exogenous oxytocin in concert with CRH or increased contractility and pain that result in increased ACTH levels (Conell-Price, Evans, Hong, Shafer, & Flood, 2008). Examination of maternal ACTH in concert with CRH, CRHbp, and cortisol may provide clues as to the sensitivity of the HPA-axis components during labor and whether those relationships can be manipulated through therapeutic interventions to decrease psychophysiological stress during labor. Investigators using ACTH as a marker of psychophysiological stress or as an endpoint for stress-reducing interventions should consider variables such as oxytocin therapy, including timing and dosing, as covariates (Conell-Price et al., 2008).

Cortisol and Corticosteroid Binding Globulin (CBG) in Labor

Cortisol is the HPA-axis hormone most frequently studied. Total and free plasma cortisol levels increase dramatically with spontaneous labor and then increase continuously throughout labor and delivery at term (Dorr et al., 1989; Predine et al., 1979; Willcox et al., 1985; Yuan et al., 2009). In labor, maternal cortisol levels appear to be affected by acute stress. In one study total cortisol measured at 1 min postdelivery in 30 women with spontaneous uncomplicated labor and delivery was 49.74 ± 2.60 ug/dl, and the free cortisol level was 4.86 ± 0.40 ug/dl (Van Cauwenberge et al., 1987). However, in a group of 21 parturients experiencing acute labor stress due to terminal fetal bradycardia and instrumental delivery (forceps or vacuum), total cortisol was 81.9 ± 3.79 ug/dl and free cortisol was 12.52 ± 1.12 ug/ dl at the same timepoint. These markedly increased levels suggest that cortisol levels may be linked to the physical and emotional stress associated with delivery complications.

It is unlikely that the maternal cortisol increase associated with stress and labor progression comes from the fetus. Fetuses have an independent cortisol response to stress, as determined through intrauterine needling of the intrahepatic vein. Gitau, Fisk, Teixeira, Cameron, and Glover (2001) reported that basal fetal cortisol levels at 17–35 weeks of gestation were 13-fold lower than maternal levels. In a more recent study, maternal cortisol levels were 28 times higher than the level in amniotic fluid (proxy for fetal level) between 15 and 37 weeks' gestation, though the levels were positively correlated (r = .32, p < .001; Glover, Bergman, Sarkar, & O'Connor, 2009). However, gestational ages ranged widely in both studies, and neither study included women at term gestation, when fetal cortisol levels increase. Thus, while measures of maternal plasma cortisol are elevated with acute stress and probably reflect maternal rather than fetal sources, the increases in cortisol driven by ACTH may be overshadowed by additional feto–uteroplacental contributions.

With labor, the ratio of CBG (the specific plasma transport glycoprotein for cortisol) to cortisol substantially decreases (Batra & Grundsell, 1978), likely due to a decrease in CBG levels, which begins prior to labor onset (Ho et al., 2007). Changes in the levels of CBG have direct consequences for the bioavailability of cortisol.

During labor CBG plays a dual role in the stress response and parturition, doing more than simply controlling free plasma cortisol (Breuner & Orchinik, 2002; Dhillo et al., 2002). Sivukhina, Jirikowski, Bernstein, Lewis, and Herbert (2006) found CBG to be partially co-localized with oxytocin and vasopressin (stress-related hormones and uterine contractile

agents) in the paraventricular and supraoptic nuclei of the human hypothalamus, suggesting that it may be involved in the HPA stress reaction. It could be hypothesized that, when stress during labor is excessive, CBG levels increase, resulting in increased binding of cortisol and less free cortisol available to act. But at this time, CBG's effect on labor remains theoretical.

Methodological Issues

Consideration of methodological issues such as overall study design, variables and specific assay techniques may improve data quality, reveal limits for cortisol levels and help clarify physiological mechanisms of parturition. Table 2 lists methodological issues that affect the use of plasma cortisol as a biomarker of stress in labor.

When studied under laboratory conditions, the magnitude of cortisol increase in response to stress differs depending on the characteristics of the individual and the type of stressor (Dickerson & Kemeny, 2004), and similar differences are likely to exist in uncontrolled clinical settings. Pain is frequently identified as the major or only stressor in labor, and therefore cortisol levels are sometimes viewed as a surrogate measure of pain. In addition, investigators often use plasma cortisol levels as an indicator of the effectiveness of interventions for pain relief, including intravenous narcotics, epidural analgesia and hydrotherapy (Benfield et al., 2010; Jouppila et al., 1976; Neumark, Hammerle, & Biegelmayer, 1985; Scull et al., 1998; Stocche, Klamt, Antunes-Rodrigues, Garcia, & Moreira, 2001).

As an example, we measured the cortisol response to a pain-reducing intervention in healthy, term spontaneously laboring parturients ($N = 11$) before and during hydrotherapy (immersion to the chest in 37°C water). We found no significant differences between groups pre-immersion and post-immersion in pain or cortisol levels. However, at 15 min of hydrotherapy, women with high pre-immersion pain evidenced a greater decrease in pain than women with low pre-immersion pain levels. This decrease in pain was accompanied by a 2-fold decrease in plasma cortisol (Benfield et al., 2010). These results, albeit in a small sample, suggest that examination of pre-and post-testing cortisol levels across women may be inadequate. Rather, exploring intra-individual changes in cortisol linked to symptom (anxiety, pain) severity may be more fruitful in demonstrating cortisol's potential as a biomarker of stress reduction.

Adding to the difficulty of planning and implementing study methodologies, findings regarding the effects of traditional pain interventions on plasma cortisol levels of laboring women are not uniform. The few studies that do exist are dated and have dissimilar purposes and methodologies, making a direct comparison of the findings unfeasible. Neumark and colleagues (1985) found that free plasma cortisol levels measured by RIA in 8 healthy nulliparous parturients did not decrease following intramuscular administration of meperidine but continued to rise until delivery regardless of the cm(s) of cervical dilation at the time of administration (Neumark et al., 1985). Therefore, a decrease in pain does not equate with a decrease in plasma cortisol for all interventions. Conversely, in the same study, when 18 healthy parturients received epidural analgesia, individual plasma cortisol levels decreased postintervention in 9, the level remained unchanged in 7, and it increased in 2 (Neumark et al., 1985). This statistically significant finding indicates that following epidural analgesia, a decrease in plasma cortisol is more likely than an increase. However, more studies are needed to explain the variety of findings within the group receiving epidural analgesia. Here the relative importance of influence of study methodology verses that of physiological mechanisms is uncertain.

Samples collected from similar groups of healthy women with no systemic analgesia before receiving equipotent epidural interventions reveal that a postintervention decrease in plasma cortisol level is consistent between studies using repeated measures. Stocche and colleagues (2001) studied women (N = 15) at term gestation in spontaneous labor (≥ 4cm cervical dilation). They noted a significant decrease from pre-intervention epidural analgesia plasma cortisol levels measured by RIA to postintervention levels at 15, 30, 60 and 90 min. Scull and colleagues (1998) had found a similar result in an earlier study of nulliparous women in earlier labor (≤ 5 cm cervical dilation). In that study investigators sampled pre- and post-epidural analgesia cortisol levels every 10 min until up to 60 min post-epidural and assayed the samples by EIA. While findings on changes in maternal plasma cortisol level with pain interventions are scant, the combined knowledge from laboratory and labor intervention studies suggest that the use of repeated measures will capture changes in baseline plasma cortisol level if sampling begins immediately after the intervention and is repeated at intervals through 60 min postintervention.

Another methodological challenge in using cortisol as a biomarker of stress during labor is its own inherent circadian rhythm. The random onset of spontaneous labor makes controlling for the circadian rhythm difficult. As in the nonpregnant state, the peak level of cortisol in pregnant women occurs in the early morning hours, with decreasing values as the day progresses and the lowest values around midnight (Eriksson, Eden, Holst, Lindstedt, & von Schoultz, 1989). However, in late pregnancy, the difference between the concentration of total cortisol in the morning and that in the afternoon is smaller (Meulenberg & Hofman, 1990) as total cortisol levels increase in preparation for labor.

Women (N = 131) at 9 months' gestation, with severely disrupted sleep and less than 6 hr of sleep per night have longer labors and are at higher risk for cesarean delivery (Lee & Gay, 2004). This finding is important because a change in sleep habits also affects the circadian rhythm of cortisol secretion (Balbo, Leproult, & Van Cauter, 2010). The effect of maternal sleep prior to labor on cortisol levels or labor outcomes is currently unknown but should be included as a study variable.

Standardizing sample collection is also difficult because labor is progressive. Even with its inconsistencies, cervical dilation is the best clinical indicator for standardizing measures during parturition unless it is contraindicated (e.g., in cases involving hydrotherapy). Researchers should record cervical dilation before or following an intervention, as per standard clinical practice. They should also consider use of within-subjects, repeated-measures designs to offset between-subject variations, along with documentation of factors known to affect dilation such as parity and membrane status.

Plasma Cortisol the Gold Standard Physiologic Assay of Stress

Salivary cortisol measures, which reliably reflect unbound serum cortisol, can be used during pregnancy (Meulenberg & Hofman, 1990; Vining, McGinley, Maksvytis, & Ho, 1983). However, during labor plasma levels remain the gold standard for measurement. Salivary cortisol may not be a valid measure during labor because of difficulty with specimen collection (Grajeda & Perez-Escamilla, 2002) and a lack of data regarding the relationship between salivary and plasma cortisol levels in parturients (Alehagen, Wijma, Lundberg, Melin, & Wijma, 2001; Alehagen, Wijma, Lundberg, & Wijma, 2005).

Sample Analysis

Consideration of the assay limits is essential when studying parturients. The lower limit of the cortisol assay is not problematic because cortisol levels are high due to the expected hypercortisolism of pregnancy and labor. However, the upper limit of sensitivity is of

concern because of high baseline levels. Samples may require dilution prior to assay. In our work, we dilute plasma samples obtained from women during labor four times with diluent A (Proclin 300) to get free cortisol values that fall within the upper range of assay sensitivity.

Conclusion

Labor is a time of psychophysiological stress. It is well established that cortisol levels increase throughout pregnancy and continue to increase with advancing labor at term. These physiological changes are important and may be viewed as a necessity for maintaining maternal/fetal wellbeing and promoting normal labor progression. However, the quantification of cortisol during labor is confounded by two physiological mechanisms: the feed-forward loop of feto–uteroplacental corticosteroids and the traditional negative feedback loop of the HPA-axis stress response. The balance of these two systems gives rise to the plasma cortisol levels seen in maternal samples. Therefore, plasma cortisol may not be the best measure of psychophysiological stress during labor or as an outcome measure of stress-reducing interventions unless researchers take into account normal physiological changes and methodological pitfalls. Oxytocin and vasopressin may be potential alternatives for evaluating stress; however, data are needed to support their roles.

Documentation of clinical interventions and delivery outcomes may elucidate relationships among psychophysiological stressors, cortisol and normal labor progress. With attention to the methodological issues we described above, analysis of plasma cortisol may lead to clinical interventions that support normal labor physiology.

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Table 1

Factors that Contribute to Plasma Cortisol Levels in Laboring Women

HPA Stress Response Negative-Feedback Loop	Feto–Uteroplacental Positive Feed-forward Loop
• Hypothalamic CRH increases	• Placental CRH increases
• Pituitary ACTH increases	• Maternal & fetal cortisol increase
• Cortisol feedback inhibition of ACTH & CRH synthesis	• Cortisol stimulates placental CRH synthesis
• CBG released from hypothalamus	• Plasma CRHbp decreases
• Vasopressin synergism with CRH on ACTH release	• Plasma CBG decreases
• Individual stressors during labor	• Leukocytosis
• Maternal/fetal glucose utilization	• Macrophage infiltration of placenta, cervix & myometrium with local cortisol increase
	• Utero–placental glucose utilization

Note. ACTH = adrenocorticotropic hormone; CBG = corticosteroid binding globulin; CRH = corticotropin-releasing hormone; CRHbp = CRH-binding protein; HPA = hypothalamic-pituitary-adrenal

Table 2

Methodological Issues that Affect the Use of Cortisol as a Biomarker of Stress in Labor and Recommendations

Methodological Issues	Recommendations
Plasma Cortisol Assay Selection & Use	
• Both total and free plasma levels increase • Binding proteins affect free cortisol concentration • High pregnancy plasma cortisol levels increase with advancing labor • Labor is a random event; controlling for time of day is unfeasible	• Measure free cortisol (bioactive) • Analyze binding proteins CRHbp and CBG • Dilute plasma samples before analysis; check upper limit of assay sensitivity • Do not try to control for circadian rhythms
Data Collection with Parturients	
• As labor progresses psychophysiological stress increases • Clinical interventions affect stress hormones and uterine contractility • Cortisol is essential to maintain glucose levels when glycogen stores are depleted with fasting or with a long labor and difficult second stage	• Document the point in labor for specimen collection (e.g.,1st vs 2nd stage); standardize measures by cervical dilation &/or interventions • Document clinical interventions: – Analgesia – Oxytocin – Other (e.g., artificial rupture of membranes, intrauterine pressure catheter) • Monitor uterine contractions • Document PO & IV intake prior to & during labor • Document duration and number of expulsive efforts
Study Design Selection & Measures	
• Large individual variation and type of stressor affect cortisol concentration • Inconsistent results for effects of pain interventions on cortisol concentration • Subjective pain, anxiety, and fear along with neuroendocrine hormones CRH, ACTH, oxytocin, vasopressin affect cortisol	• Use within-subjects design • Use repeated measures through 60 min postintervention to capture changes from baseline • Use psychophysiological mixed methods

Note. ACTH = adrenocorticotropic hormone; CBG = corticosteroid binding globulin; CRH = corticotropin releasing hormone; CRHbp = CRH-binding protein; IV= intravenous; PO = by mouth.