Corticotropin-releasing hormone and progesterone plasma levels association with the onset and progression of labor

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Summary

Purpose of Investigation: To examine the relationship between maternal plasma progesterone along with corticotropin- releasing hormone (CRH) plasma levels and the progression of labor. *Materials and Methods:* Maternal serum CRH and progesterone were measured during the latent phase of labor, active labor, and 24 hours postpartum in women who went into spontaneous labor and delivered vaginally at term. Progesterone (P) levels in women delivered by an elective cesarean section at term were also measured as baseline. *Results:* Mean maternal plasma P was 18% higher in the active phase than in the latent phase of labor ($p < 0.01$), and declined significantly by 24 hours postpartum ($p < 0.001$). Mean level of serum CRH was 24% higher in the active phase than in the latent phase of labor ($p < 0.01$), and subsequently declined significantly by 24 hours postpartum ($p < 0.001$). *Conclusions:* As labor progresses, P and CRH increase and subsequently decrease precipitously in the immediate postpartal period. P levels tend to drop in women who are in early labor compared with non-laboring full-term women.

Key words: CRH; Progesterone; Phases of labor; Term labor; Latent phase of labor; Active labor; Postpartum.

Introduction

Human pregnancy is maintained by a complex endocrine balance involving autocrine and paracrine signaling [1]. Although the precise mechanisms that control the onset of labor have not as yet been fully explained, accumulating data suggest that progesterone and corticotropin-releasing hormone (CRH) play substantial roles.

Progesterone (P) maintains pregnancy by promoting myometrial relaxation and quiescence [2]. It is thought to actively block myometrial contractility and its withdrawal converts the myometrium to the laboring state. Meanwhile, maternal plasma CRH is closely linked to the timing of parturition in human pregnancies [3]. Placental CRH is synthesized by human trophoblast, amnion, chorion, and decidual cells [4] and is secreted in maternal and fetal plasma [5]. It plays a key role in the initiation of parturition and in regulating the cascade of events involved in the birthing process [4, 6]. In addition, CRH may interact with the declining P levels which leads to the onset of labor [7], although this has not as yet been studied in detail.

The authors aimed to examine the relationship between maternal plasma P and CRH levels and the onset and progression of labor. Hypothesizing that the onset of labor is associated with a rise in CRH accompanied by a drop in P levels, P and CRH maternal serum levels were compared in the latent phase, active labor, and postpartal period spontaneously laboring women at term. Additionally, serum P from third-trimester non-laboring women was measured as baseline. Studies undertaking further examination of the fluctuation occurring in the plasma levels of CRH and P during labor and postpartum will shed additional light on the mechanisms of normal labor, while the conclusions of this study could be applied in the ongoing research of preterm labor.

Materials and Methods

Fourteen women at term were included in the study: nine of them presented in spontaneous early labor and delivered vaginally and the remaining five were admitted for an elective cesarean section by maternal request. None of the subjects was on any medications or had any documented medical or antenatal problems. None of the women who delivered vaginally received epidural anesthesia. Blood samples were taken from all subjects in the latent phase of labor (n = 9), in the active phase of labor (n = 9), and prior to the elective cesarean section (n = 5), and postpartum. Gestational age was confirmed by a first-trimester dating ultrasound. All subjects gave informed consent for participation in the study. The study was approved by the Ethics Review Board of the hospital.

Collection of blood samples

Ten milliliters of venous blood was collected from each participant by venipuncture of the antecubital vein. Blood samples were centrifuged at 1,600 rpm for 15 min at 0°C. Plasma was collected in duplicate aliquots. Plasma was frozen at -80°C and each aliquot was thawed on the day of the assay quantification.

Radioimmunoassay assessment of hormone levels

Plasma was extracted and processed for radioimmunoassay (RIA) by using a conventional RIA Kit according to the manufacturer's instructions. CRH was extracted from three ml of plasma with Sep-Pak C-18 cartridges and eluted with Buffer B (60% acetonitrile, 1% TFA, and 39% distilled water). The extracts

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were evaporated, reconstituted in assay buffer, and assayed for CRH immunoreactivity. The RIA kit had a detection rate ranging from 0.1 to 67 pg/tube. A CRH-specific rabbit antiserum was used as the probe. CRH iodinated with I^{125} served as the tracer. Serum P was similarly assayed by a conventional RIA kit.

Statistical analysis

Data were distributed normally and are presented as means ± standard deviation. Mean maternal plasma P and CRH concentrations in the latent phase of labor (cervical dilation < four cm), in the active phase of labor (cervical dilation ≥ four cm), and 24 hours postpartum were compared in the women (n = 9) who delivered vaginally at term (over 37 weeks of gestation) by two-way analysis of variance (ANOVA). The sources of difference underlying effects revealed by ANOVA were detected by Fisher's *post hoc* analysis. Mean plasma concentrations of P during the latent phase of labor in the above women were compared with the levels of P in the women (n = 5) who were delivered by an elective cesarean section at term by student t-test. A $p < 0.05$ was considered as level of statistical significance.

Table 1. — *Progesterone (ng/ml) and CRH (pg/ml) levels (mean ± SD) in full term mothers during latent labor, active labor and post delivery.*

	Latent phase	Active phase	Post delivery	F-test	Effect of time
Progesterone	103.2 ± 17.6	121.8 ± 11.3[a]	12.2 ± 8.2[b]	221.2	$p < 0.001$
CRH	778.9 ± 226.6	968.9 ± 240.3[a]	28.5 ± 16.3[b]	118.1	$p < 0.001$

[a]$p < 0.01$ vs latent phase, [b]$p < 0.001$ vs active phase.

Table 2. — *Progesterone (ng/ml) levels (mean ± SD) in full term women in latent phase of labor (n = 9) compared with full term women not in labor (n = 5).*

	Latent labor	Not in labor	t-test	Statistical significance
Progesterone	103.2 ± 17.6	123.2 ± 19.4	1,965t	$p < 0.10$ (Prob = 0.073)

Results

P and CRH level changes during progression of labor

Table 1 and Figure 1A demonstrate a significant effect of labor phase (latent, active, postpartum) on P levels ($p < 0.001$). Specifically, the mean maternal plasma concentration during active labor was 18% higher than the mean level during the latent phase of labor ($p < 0.01$). A steep decline in P levels was observed following delivery: mean maternal plasma P concentration at 24 hours postpartum was significantly lower than active labor mean level ($p < 0.001$).

Likewise, there was a significant effect of labor phase (latent, active, postpartum) on CRH level (Table 1 and Figure 1B). Mean maternal plasma CRH concentration during active labor was 24% higher than that during the latent phase of labor ($p < 0.01$). Similarly to the pattern observed in P levels, there was a precipitous decline in CRH levels following delivery. Mean maternal plasma CRH concentration 24 hours postpartum was roughly $1/34^{th}$ of active labor mean level ($p < 0.001$).

P levels elevated with spontaneous occurrence of labor

Table 2 illustrates that mean P concentrations in women who were at term and in early labor differed from those who were full term but not in labor ($p < 0.10$). Although this does not reach statistically significant levels, there is a trend showing that the mean maternal plasma concentration of P in the non-laboring group was higher than in the latent phase laboring group, a determination likely to be further confirmed with a larger number of participants.

Discussion

The fluctuation of maternal CRH and P levels during different stages of labor was examined in this study. P levels were lower in full-term pregnant women who labored spontaneously compared to gestation-matched women who did not labor, suggesting that a drop in P levels is linked to the initiation of labor. In addition, there was a parallel increase in P and CRH levels as women progressed from the latent to the active phase of labor. Both hormones subsequently dropped rapidly to non-pregnant levels as compared to standard laboratory values of non-pregnant women by day one after delivery (Figure 1).

The observed pattern in P levels complements the findings of Winkler *et al.* [8] who assessed P receptor (PR) concentrations in the human lower uterine segment at different stages of cervical dilatation during parturition at term. They found that PR concentration diminished significantly as women progressed from two to four cm cervical dilatation to four to six cm cervical dilatation and then increased to > six cm cervical dilation.

The finding of the increase in CRH levels as women progressed from latent to active labor followed by a precipitous postpartal decline accords with data from other studies [9, 10]. Beyond the characteristic rise of CRH in the third trimester [11], CRH rises dramatically during the active phase of labor [9] and declines rapidly towards the non-pregnant levels by the first day postpartum [10]. It is interesting to note that the rapid drop in CRH and subsequently in CRH-induced cortisol in the immediate postnatal period is likely to be responsible for the 'baby-blues' commonly observed at postpartum.

CRH, the primary regulator of stress via its management of the hypothalamic-pituitary-adrenal axis (HPA), acts on the fetal pituitary-adrenal axis as well as on the uterus. This multi-sited action possibly maintains a positive feed-back loop between the fetal pituitary-adrenal axis and the placenta, which leads to an up-regulation of fetal secretion of cortisol [12] and dehydroepiandrosterone-sulfate (DHEA-S) [13]. Fetal cortisol, which is essential for the maturation of the fetal lungs [14], sequentially stimulates CRH release from the placenta [8, 11]. Meanwhile, DHEA-S stimulates placental estrogen production, which is also hypothesized to play a major role in the initiation of parturition [15]. CRH receptors exist in the myometrium [16, 17], fetal membranes [18], and placenta [19], indicating that CRH has multiple targets. In addition, placental and fetal membrane secretion of

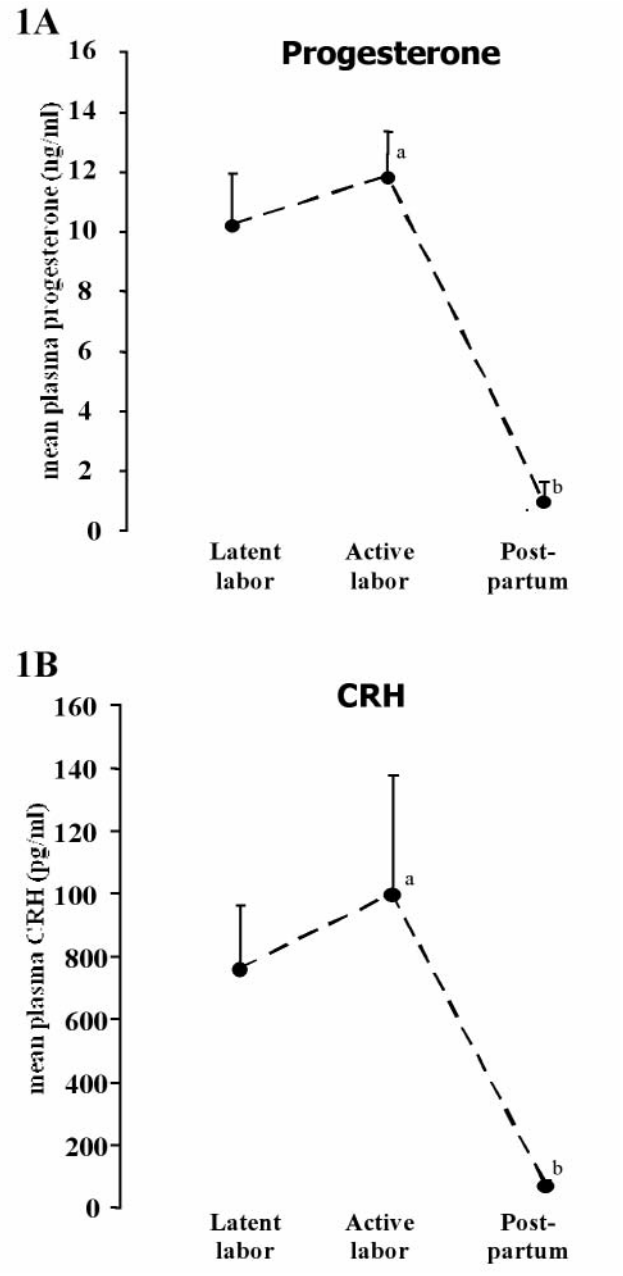

Figure 1. — Progesterone (1A, ng/ml) and CRH (1B, pg/ml) levels in a group of women who delivered vaginally at term during the latent phase of labor, active phase of labor, and 24 hours postpartum. [a]$p < 0.01$ vs latent labor, [b]$p < 0.001$ vs active labor.

prostaglandins E2 and F2a is up-regulated in response to CRH [20, 21]. The ability of CRH to potentiate the action of oxytocin may also contribute to the onset of labor both at term and prematurely [22, 23]. Similarly, the CRH binding protein, which is thought to delay CRH-controlled pituitary-adrenal stimulation by binding and eliminating the free potent CRH, falls rapidly around 20 days prior to spontaneous labor, while placental CRH secretion continues to rise as labor approaches [24].

It becomes apparent that initiation of labor involves complex mechanisms that initiate autonomic and central functions which coordinate myometrial contractility and cervical dilatation. In addition, CRH and its related peptide urocortin 1 increase local metalloproteinase-9 (MMP-9) activity in placenta and fetal membranes, which may trigger the initiation of labor [25]. Studies in second-trimester amniotic fluid from pregnancies that went on to preterm labor revealed raised levels of ADAM-8, a metalloproteinase, and cortisol [26]. This finding further supports the theory of the existence of a 'CRH placental clock' which determines the length of the pregnancy from an early stage [24]. Furthermore, there are accumulating data strongly indicating that CRH and P initiate a cascade of immune responses in the myometrium also contributing to synchronization of the onset of labor [27].

P has an inhibitory effect [7] on the secretion of CRH from the placenta [28], presumably by prohibiting the initiation of a positive feedback loop between CRH, adrenocorticotropic hormone and cortisol [29]. It has been suggested that the inhibitory effect of P is exerted by its binding to glucocorticoid receptors (GRs) on trophoblast cells [30]. At term, CRH-induced high levels of cortisol displace GR-bound P [31], whereby the action of cortisol is initiated. Based on the above, the parallel drop and increase in CRH and P levels and in particular the rise of P levels while labor advances (Figure 1), which was shown in this study, seems a paradoxical finding. A possible explanation for this is that a sequential effect of prostaglandins may take place during labor. Mesiano [32] concluded that functional P withdrawal is mediated by an increase in the myometrial PR-A/PR-B expression ratio. The PR-A isoform opposes P actions mediated by its counterpart, the PR-B isoform. Hence, women with a higher PR-A/PR-B ratio are more likely to deliver earlier than those with lower values. Prostaglandin E2 (PGE2) increases both PR-A and PR-B isoforms without changing the PR-A/PR-B ratio; on the other hand, prostaglandin F2α (PGF2a) selectively induces the expression of PR-A, thereby increasing the PR-A/PR-B ratio [32]. In the present study, the initial diminishing levels of P in women experiencing spontaneous early labor may be a result of a primary PGF2α-mediated increase in the PR-A/PR-B ratio, followed by an increase in PGE2, which does not affect the PR-A/PR-B ratio and may enable the subsequent rise of P levels while labor progresses. Further studies are needed to elucidate the sequential effect of P on the expression and action of various prostaglandins.

The authors conclude that the onset of spontaneous labor is associated with a drop in P levels, which is followed by a parallel rise in the levels of CRH and P while labor progresses. Both hormones decrease rapidly, almost to the pre-pregnancy levels, in the immediate postnatal period. By enhancing an understanding of the mechanisms related to the onset and progression of labor at term, the same principles in preterm labor, one of the main causes of perinatal mortality, and in which area little improvement has been achieved over the last few decades, can be assessed.

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