

Peripartum prolactin and cortisol level changes. A prospective pilot study

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ABSTRACT

Objectives: Although the role of prolactin and cortisol in the human lactation process seems to be undisputed, the changes in postpartum serum concentrations in mothers make data interpretation difficult.

Material and methods: To determine the factors that possibly influence these hormones, we examined a group of patients who were admitted to the Gynecology-Obstetrics Clinical Hospital in Poznań for labor induction and/or in the active phase of the first labor period. The serum levels of cortisol and prolactin were assessed in these full-term pregnant women during admission to labor, in the third stage of labor, and on the second day postpartum. The prolactin and cortisol levels were also measured in the umbilical cord for the assessment of newborn babies.

Results: The results showed a significant relationship between maternal age and the level of prolactin measured before childbirth and fluctuations in cortisol level with respect to labor duration. In addition, we observed a strong correlation between the level of prolactin assessed before childbirth and the pH and base excess of the umbilical cord artery. Most importantly, a correlation was noted between breastfeeding within 2 hours after the labor and the level of cortisol measured after childbirth.

Conclusions: We observed a significant correlation between a summarized labor duration and maternal and umbilical cord cortisol levels measured right after the labor. The fact of breastfeeding within 2 hours after the labor strongly correlated with lower levels of maternal cortisol as well as a cortisol level in umbilical cord blood and it suggests that immediate initiation of breastfeeding reduces stress level for both, mother and newborn.

Key words: lactation; breastfeeding; prolactin, cortisol; skin-to-skin contact; augmentation of labor

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INTRODUCTION

The role of prolactin in human lactation process seems to be undisputed; however, the variable postpartum serum concentrations in mothers make the interpretation of results challenging [1]. After childbirth, prolactin levels begin to decrease, depending on nipple stimulation which allows controlling milk production. After 15 minutes of nipple stimulation, the serum levels of prolactin in mothers reach 100–200 ng/mL in the first seven days postpartum [2], but the peak levels remain higher and reach 350 ng/mL after 45 minutes of nipple stimulation at the first month after childbirth [1]. Oxytocin,

a hormone synthesized by large cellular neurons in supraoptic and paraventricular hypothalamic nuclei, is transported along with neurophysins in axons in the form of neurogenic granules to the posterior pituitary lobe, where it is stored. In the hypothalamus, the hormone is present in the form of an inactive precursor. The inactive precursor gradually hydrolyses into smaller fragments and relocates along axons to the posterior pituitary lobe in an active form [3], after which it is released by the stimulation of receptors located in the nipples, vagina, and cervix [4]. Natural oxytocin decreases the activity of the hypothalamic–pituitary–adrenal axis (HPA), which in turn leads to

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a decrease in the level of adrenocorticotrophic hormone and cortisol [5]. At the other end of the spectrum, both perinatally and postnatally, the HPA axis acts as a crucial determinant of fetal and neonatal physiological outcomes in stress adaptation [6]. During pregnancy, maternal hypothalamus releases corticotropin-releasing hormone (CRH) which stimulates the release of cortisol from the maternal adrenal cortex, among other steroids [7]. CRH is also abundant in the placental tissue, and the secretion of placental corticotropin-releasing hormone (pCRH) is dependent on the maternal cortisol level which is responsible for the positive feedback loop that maintains high cortisol levels throughout the prenatal period [6]. pCRH is particularly expressed in the third trimester [8], during which maternal serum cortisol concentration is 1000-fold higher compared to prepregnancy levels [9]. CRH and pCRH seem to be important elements of the childbirth induction process, as well as preterm birth [6,10]. Evidence also suggests that pCRH modulates glucose transporter in placental tissue which is linked with fetal growth [7].

Objectives

This study aimed to assess the influence of the dose of intravenous synthetic oxytocin infusions administered for induction, augmentation, and active management of labor on the maternal serum levels of prolactin and cortisol during admission to labor, in the third stage of labor, and on the second day postpartum, and the levels of prolactin and cortisol in the umbilical cord.

MATERIAL AND METHODS

The study group included patients who were admitted to the Gynecology-Obstetrics Clinical Hospital in Poznan for labor induction and/or in the active phase of the first labor period. The inclusion criteria were as follows: single pregnancy, no contraindications to natural childbirth at the time of qualification, gestational age between 37 and 42 weeks, and no fetal anomalies. Among the patients who were approached for the study, 78 provided written informed consent for participation in the study. The procedures used for patient recruitment and for collection and storage of the research material were approved by the Poznan University of Medical Sciences Bioethics Committee (No. 869/19; specifically approved for this study on 12 September 2019).

The serum concentrations of cortisol and prolactin were assessed among the full-term pregnant women: during admission to labor, in the third stage of labor (before infusion with oxytocin, among women who gave birth naturally), and on the second day postpartum. The levels of prolactin and cortisol were also measured in the umbilical cord for the assessment of newborn babies (Fig. 1).

Blood sample was collected from a venous vessel (or umbilical vein) using Sarstedt S-Monovette (9 mL) closed

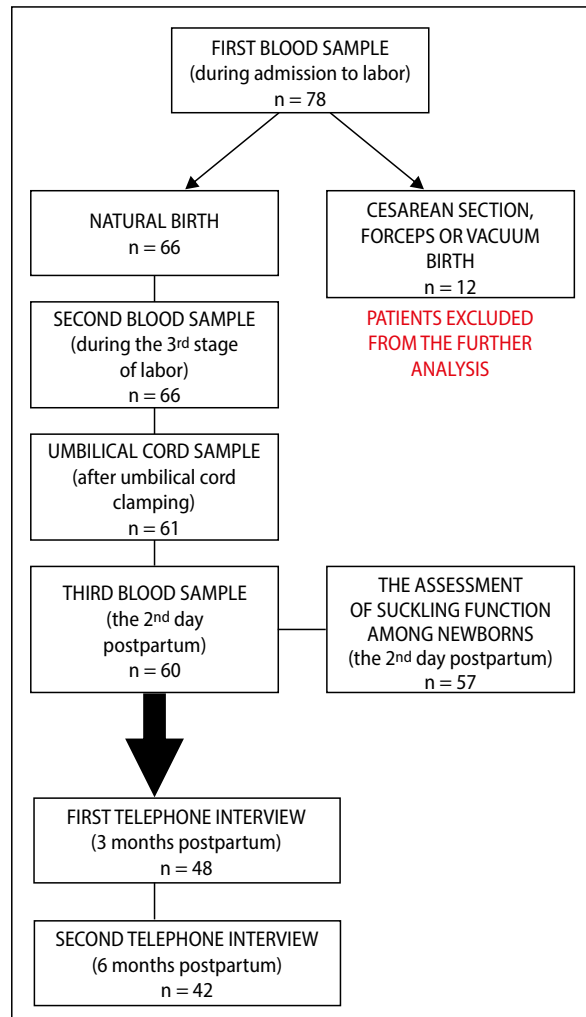


Figure 1. Schematic representation of patient selection and examination

aspiration and vacuum set, containing a clotting activator (silicate). The collected sample was labeled with the date and time of collection and was transferred to the laboratory, where cortisol and prolactin levels were measured by electrochemiluminescence using Cobas 6000 apparatus. Considering daily fluctuations in serum cortisol levels, the first sample was collected in the morning. Before starting the cortisol analysis, the hourly range, corresponding to the hours of sampling, was marked in relation to the cortisol test (6–10 and 16–20). For high concentrations of hormone, reassessment was performed after diluting the sample.

The Shapiro–Wilk test was used to check the normality of the distribution of the tested variables. For variables that were consistent with the normal distribution, the results were presented as arithmetic mean and standard deviation; on the other hand, for variables not consistent with the normal distribution, the results were presented as median (Me) and the largest (maximum or Max) and smallest (minimum or Min) values. The statistical significance of the studied

| Table 1. Characteristics of the study group | | |
|--|---|--|
| | Description | Comment |
| Age (years) | Min 21, Max 41 | Me = 30 |
| Week of gestation | 37–42 | Me = 40 weeks |
| Maternal BMI [kg/m ²] | Min = 20.83, Max = 37.74 Me = 27.83 | n = 62 (4 patients—no data) |
| Labor method | Natural labor with perineum incision, n = 42 (51.8%) | n = 78 (including all patients who gave their consent for participation in the study). Patients who had vacuum extractor or cesarean section (n = 12) were excluded from further analysis |
| | Natural labor without perineum incision, n = 24 (29.6%) | |
| | Vacuum extractor, n = 9 (11.1%) | |
| | Cesarean section, n = 3 (7.4%) | |
| Parity | Primiparous, n = 21 (32%) | Among the patients who gave birth naturally (n = 66, 100%) |
| | Multiparous, n = 45 (68%) | |
| Maternal disease | Gestational diabetes (G1 and G2), n = 14 (21.2%) | Among other diseases: gestational hypertension, hyperthyroidism, cholestasis of pregnancy |
| | Hypothyroidism, n = 25 (37.8%) | |
| | Other disease, n = 18 (27.3%) | |
| Newborn's Apgar score in the first minute of life (points) | 10, n = 56 (84.8%) | Among the patients who gave birth naturally (n = 66, 100%) |
| | 9, n = 4 (6.1%) | |
| | 8, n = 1 (1.5%) | |
| | 6, n = 1 (1.5%) | |
| | No data, n = 4 (6.1%) | |
| Newborn's sex | Male, n = 39 (59.1%) | Among the patients who gave birth naturally (n = 66, 100%) |
| | Female, n = 27 (40.9%) | |

dependencies and differences was assessed at a significance level (α) of 0.05. Quantitative variables with normality were tested using parametric tests namely Student's *t*-test and analysis of variance, whereas for variables inconsistent with the normal distribution or variables on an ordinal scale non-parametric tests namely Mann–Whitney, Spearman rank correlation coefficient, Kruskal–Wallis test were used. For nominal scale variables, the Fisher Freeman–Halton test was used. Data analysis was performed using Dell Statistica (version 13; Dell Inc., 2016, software.dell.com) and Cytel Studio v.11.1.0.

Some patients were lost from the study due to early discharge with the newborn to home (6 patients) or hospitalization of the newborn in the neonatal unit (1–3 children at different time points).

RESULTS

Characteristics of the study group

Characteristics of the study group are shown in Table 1.

Course of childbirth and puerperium

Course of childbirth and puerperium is shown in Table 2.

Prolactin and cortisol concentrations and correlations

The concentrations of prolactin and cortisol measured in the umbilical cord vein and in mothers during admission to

childbirth, in the third stage of childbirth, and on the second day postpartum are shown in Table 3.

The correlations observed between prolactin and cortisol levels determined in the umbilical cord vein and in mothers during admission to childbirth, in the third stage of childbirth, and on second day postpartum are shown in Table 4.

The statistically significant correlations observed between the first and second stages of labor and particular cortisol values are shown in Table 5. No such correlations were noted between prolactin levels in any case.

DISCUSSION

The levels of maternal and fetal hormones significantly change during the peripartum period [11]. Researchers have shown that many factors may have an influence on the levels of prolactin and cortisol during this period. Since the results are inconsistent, it is necessary to determine physiological hormonal ranges and factors that may negatively influence maternal and neonatal health status in a broad sense. We found statistically significant correlations between the levels of prolactin and cortisol and particular factors, but our findings did not mostly agree with those of other researchers. Rasmussen et al. [12] and other authors [13] showed that maternal body mass index (BMI) has a direct effect on maternal prolactin levels in serum and that lactating women with a BMI > 26 kg/m² had decreased

Table 2. Course of childbirth and puerperium

| | Description | Comment |
|--|---|--|
| Beginning of labor | Spontaneous contractions, n = 51 (77.3%) | Among the patients who gave birth naturally (n = 66, 100%) |
| | Labor induction, n = 15 (22.7%) | |
| Labor augmentation | During the first stage of labor, n = 8 (12%) | Among the patients who gave birth naturally (n = 66, 100%) |
| | During the second stage of labor, n = 12 (18%) | |
| Active management of the third stage of labor | 5 IU oxytocin, n = 40 (60.6%) | |
| Duration of the first stage of labor (minutes) | From 40 to 1050 | Me = 235 |
| Duration of the second stage of labor (minutes) | From 5 to 275 | Me = 24 |
| Duration of the third stage of labor (minutes) | From 10 to 50 | Me = 10 |
| Amniotic fluid coloration | Clear, n = 59 (89.4%) | Among the patients who gave birth naturally (n = 66, 100%) |
| | Green (with meconium), n = 3 (4.5%) | |
| | No data, n = 4 (6.1%) | |
| Umbilical cord collision | Yes, n = 15 (22.7%) | Among the patients who gave birth naturally (n = 66, 100%) |
| | No, n = 47 (71.2%) | |
| | No data, n = 4 (6.1%) | |
| Analgesics administered to the patients | Nalbupinum (iv* infusion): Yes = 32 (48.5%) No = 30 (45.4%) No data = 4 (6.1%) | Among the patients who gave birth naturally (n = 66, 100%) |
| | Paracetamol (iv* infusion): Yes = 22 (33.3%) No = 40 (60.6%) No data: 4 (6.1%) | |
| | Nitrous dioxide (inhalation): Yes = 28 (42.4%) No = 34 (51.5%) No data = 4 (6.1%) | |
| | Petidin (iv* infusion) — none of the patients | |
| | Epidural anesthesia — none of the patients | |
| | | |
| Breastfeeding within the first 2 hours after labor | Yes, n = 45 (68.2%) | Among the patients who gave birth naturally (n = 66, 100%) |
| | No, n = 14 (21.2%) | |
| | No data, n = 7 (10.6%) | |

Table 3. Min, Max, and Me concentrations of prolactin and cortisol

| | No. of significance (n) | Minimum (ng/mL) | Maximum (ng/mL) | Median (ng/mL) |
|---|-------------------------|-----------------|-----------------|----------------|
| Maternal serum prolactin concentration during admission to childbirth | 78 | 67.24 | 639.60 | 214.90 |
| Maternal serum prolactin concentration in the third stage of childbirth | 65 | 40.75 | 597.20 | 212.60 |
| Maternal serum prolactin concentration on second day postpartum | 60 | 187.80 | 688.30 | 350.75 |
| Umbilical cord prolactin concentration | 61 | 414.800 | 125.90 | 854.40 |
| Maternal serum cortisol concentration during admission to childbirth | 78 | 508.20 | 3116.00 | 1226.00 |
| Maternal serum cortisol concentration in the third stage of childbirth | 65 | 1206.00 | 11169.00 | 1965.00 |
| Maternal serum cortisol concentration on second day postpartum | 60 | 293.40 | 1332.00 | 591.60 |
| Umbilical cord cortisol concentration | 61 | 72.20 | 877.80 | 228.40 |

levels of prolactin 48 hours postpartum than mothers with a lower BMI [12]. We did not observe such a correlation in our study. However, a significant relationship was noted between maternal age and prolactin level measured be-

fore childbirth — the older the woman the higher was her serum prolactin level — which is contradictory to the results of Roelfsema et al. [13]. Sano et al. [14] observed that cortisol and prolactin levels in the cord blood

Table 4. Statistically significant relationships between the levels of prolactin and cortisol and the analyzed factors

| | No. of significance (n) | Spearman's coefficient <i>R</i> | p value |
|---|-------------------------|---------------------------------|----------|
| Value of prolactin 1 and age of patients | 65 | 0.2449 | 0.049192 |
| Value of prolactin 1 and cortisol 1 | 78 | -0.482821 | 0.000008 |
| Value of prolactin 1 and cortisol 2 | 65 | -0.307590 | 0.012685 |
| Value of prolactin 1 and 2 | 65 | 0.363549 | 0.002913 |
| Value of prolactin 1 and 3 | 60 | 0.353108 | 0.005651 |
| Value of prolactin 1 and umbilical cord artery pH | 54 | -0.320652 | 0.018081 |
| Value of prolactin 1 and umbilical cord artery BE | 54 | -0.321517 | 0.017754 |
| Value of cortisol 1 and prolactin 1 | 78 | -0.482821 | 0.000008 |
| Value of cortisol 1 and cortisol 2 | 65 | 0.718809 | 0.000000 |
| Value of cortisol 1 and cortisol in umbilical cord blood | 59 | 0.650614 | 0.000000 |
| Value of cortisol 1 and cortisol 3 | 60 | 0.407335 | 0.001237 |
| Value of prolactin 2 and 1 | 65 | 0.363549 | 0.002913 |
| Value of prolactin 2 and 3 | 60 | 0.508683 | 0.000033 |
| Value of prolactin 2 depending on the total dose of synthetic oxytocin given to the mother during labor | 56 | -0.312441 | 0.019059 |
| Value of cortisol 2 and prolactin 1 | 65 | -0.307590 | 0.012685 |
| Value of cortisol 2 and cortisol 1 | 65 | 0.718809 | 0.000000 |
| Value of cortisol 2 and cortisol in umbilical cord blood | 59 | 0.834419 | 0.000000 |
| Value of cortisol 2 and cortisol 3 | 60 | 0.378088 | 0.002897 |
| Value of cortisol in umbilical cord blood and cortisol 1 | 59 | 0.650614 | 0.000000 |
| Value of cortisol in umbilical cord blood and cortisol 2 | 59 | 0.834419 | 0.000000 |
| Value of prolactin 3 and 1 | 60 | 0.353108 | 0.005651 |
| Value of prolactin 3 and 2 | 60 | 0.508683 | 0.000033 |
| Value of cortisol 3 and 1 | 60 | 0.407335 | 0.001237 |
| Value of cortisol 3 and 2 | 60 | 0.378088 | 0.002897 |
| Relationship between the value of prolactin 1 and the fact of breastfeeding within 2 hours after the labor | 60 | N/A | 0.009939 |
| Relationship between the value of cortisol 1 and the fact of breastfeeding within 2 hours after the labor | 60 | N/A | 0.010453 |
| Relationship between the value of cortisol 2 and the fact of breastfeeding within 2 hours after the labor | 60 | N/A | 0.010837 |
| Relationship between the value of cortisol in umbilical cord blood and the fact of breastfeeding within 2 hours after the labor | 60 | N/A | 0.027262 |

Table 5. Statistically significant relationships between the first and second stages of labor and particular cortisol values

| | No. of significance (n) | Spearman's coefficient <i>R</i> | p value |
|---|-------------------------|---------------------------------|----------|
| Relationship between the first stage of labor duration and value of cortisol 2 | 61 | 2.11132 | 0.038991 |
| Relationship between the first stage of labor duration and value of cortisol in umbilical cord blood | 59 | 0.297062 | 0.022325 |
| Relationship between the second stage of labor duration and value of cortisol 2 | 61 | 0.283454 | 0.026852 |
| Relationship between the second stage of labor duration and value of cortisol in umbilical cord blood | 59 | 2.44583 | 0.017562 |

correlated positively with labor duration. In our study, we found a similar relationship but only for cortisol levels. We also observed that the time duration of the first and second stage of labor positively correlated with maternal

cortisol levels measured in the third stage of labor. These findings suggest that the stronger the maternal and fetal stress response, the longer are the first and second stages of labor.

Interestingly, we found a strong correlation between the level of prolactin 1 (assessed before childbirth) and umbilical cord artery pH and base excess (BE) — the higher the prolactin level was, the lower the pH and BE values in the umbilical cord artery immediately after childbirth were (p-value = 0.018081 and 0.017754, respectively). Similarly, Martinsen et al. [15] determined that higher cortisol levels correlated with a lower pH of umbilical artery blood. They did not find any difference between spontaneous and induced labor.

The fact of breastfeeding within two hours after the labor was strongly correlated with the value of cortisol 2 as well as the level of cortisol measured in umbilical cord blood and cortisol levels were lower if the mother breastfed her newborn at this time (p-value = 0.010837 and 0.027262, respectively). This finding may prompt clinicians to educate mothers about early breastfeeding for their newborn babies. Early breastfeeding ensures early maternal–neonatal skin-to-skin contact, and the first 2 hours after childbirth has been recognized as a “sensitive” [16, 17] or “critical” [18] period. Other researchers have also emphasized the impact of this period on the success of early breastfeeding and maternal and neonatal well-being [19–25] or even early skin-to-skin contact without breastfeeding [26].

The maternal and umbilical cortisol levels measured in our study are consistent with those reported by Neelon et al. [27], although as they also stated, further analysis is required to determine the association between maternal and infant cortisol levels. Ziomkiewicz et al. [28] showed a relationship between maternal cortisol levels and human milk composition, indicating a negative and statistically significant effect of maternal stress on breast milk composition. High cortisol levels were correlated with high fat and low lactose content in milk and with low content of long-chain unsaturated fatty acids [28]. Most importantly, a strong relationship has been shown between cortisol level in maternal plasma and cortisol level in breast milk [29, 30].

In our study, maternal cortisol values were higher than umbilical cord cortisol concentrations, which is contradictory to the results obtained by Bulska et al. [31] who analyzed the influence of the mode of childbirth on the maternal and fetal hormonal stress response. However, a direct comparison between our results and the results of Bulska et al. was not possible since cortisol values may be influenced by many variables and the methodology used in these two studies was different. Bulska et al. [31] indicated that several factors may be responsible for hormonal changes and influence the values of hormones during the perinatal period in mothers and newborn babies, and as researchers we need to consider this bias while planning and scheduling our studies in this field.

A limitation of our study was the small size of the study group, due to which the relationship between the effect of

synthetic oxytocin on selected biochemical parameters in the maternal and umbilical cord serum could not be clearly determined.

Our study was conducted among patients with a single pregnancy, no contraindications to natural childbirth at the time of qualification, gestational age between 37 and 42 weeks, and no fetal anomalies. These criteria allowed to limit factors that may have a possible impact on the obtained results. We found multiple relationships among maternal and umbilical cord levels of cortisol and prolactin which seem interesting for further analysis, but we are aware of the variability in this field.

CONCLUSIONS

1. We did not find any correlation between maternal BMI > 26 kg/m² and maternal prolactin serum levels measured 48 hours postpartum.
2. We found that the older the woman was the higher was her serum prolactin level before the labor.
3. We observed a significant correlation between a summarized labor duration and maternal and umbilical cord cortisol levels measured right after the labor.
4. The fact of breastfeeding within 2 hours after the labor strongly correlated with lower levels of maternal cortisol right after childbirth as well as cortisol level in umbilical cord blood.
5. Lower maternal and neonatal cortisol levels correlated with the fact of breastfeeding within 2 hours after the labor, which suggests reduced stress level for both mother and newborn.

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Institutional review board statement

The study was conducted according to the guidelines of the Declaration of Helsinki, the methods used for patient enrollment and for obtaining the research material and its storage were previously approved by the Poznan University of Medical Sciences Bioethics Committee, No. 869/19 (specifically approved for this study on 12 September 2019).

Informed consent statement

Informed consent was obtained from all subjects involved in the study.

Data availability statement

Data supporting reported results can be found in the Department of Maternal and Child Health, Poznan University of Medical Sciences, Poznan, Polna 33 st.

Conflict of interest

All authors declare no conflict of interest.

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