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Authors: Katarzyna M. Wszolek, Karolina Chmaj-Wierzchowska, Malgorzata Piet, Agata Tarka, Marek Chuchracki, Magdalena Muszynska, Blazej Meczekalski, Maciej Wilczak

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Peripartum prolactin and cortisol level changes. A prospective pilot study

Katarzyna M. Wszolek[1, 2], Karolina Chmaj-Wierzchowska[1, 2], Malgorzata Piet[2, 3], Agata Tarka[2, 3], Marek Chuchracki[4], Magdalena Muszynska, Blazej Meczekalski[2, 6], Maciej Wilczak[1, 2]

[1]*Department of Maternal and Child Health, Poznan University of Medical Sciences, Poznan, Poland*

[2]*Gynecology-Obstetrics Clinical Hospital, Poznan University of Medical Sciences, Poznan, Poland*

[3]*Facility of Practical Midwifery Sciences, Poznan University of Medical Sciences, Poznan, Poland*

[4]*Faculty of Health Sciences, Calisia University, Kalisz, Poland*

[6]*Department of Gynecological Endocrinology, Poznan University of Medical Sciences, Poznan, Poland*

Corresponding author:

Katarzyna M. Wszolek

Gynecology-Obstetrics Clinical Hospital, Poznan University of Medical Sciences, 33 Polna St, 60–535 Poznan, Poland

e-mail: katarzyna.wszolek@ump.edu.pl

ABSTRACT

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. 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 Poznan 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. 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 two hours after the labor and the level of cortisol measured after childbirth, which is worth mentioning to emphasize the significance of early maternal–neonatal skin-to-skin contact.
Key words: lactation; breastfeeding; prolactin; cortisol; skin-to-skin contact; augmentation of labor

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 a decrease in the level of adrenocorticotropic 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 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 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 nonparametric 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/m^2 had decreased 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 before 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 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/m^2 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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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**
	Natural labor without perineum incision, n = 24 (29.6%)	
	Vacuum extractor, n = 9 (11.1%)	
	Cesarean section, n = 3 (7.4%)	

		analysis
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%)	

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) F	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

	Green (with meconium), n = 3 (4.5%) No data, n = 4 (6.1%)	patients who gave birth naturally (**n = 66**, 100%)
Umbilical cord collision	Yes, n = 15 (22.7%) No, n = 47 (71.2%) No data, n = 4 (6.1%)	Among the patients who gave birth naturally (**n = 66**, 100%)
Analgesics administered to the patients	**Nalbufinum** (iv* infusion): Yes = 32 (48.5%) No = 30 (45.4%) No data = 4 (6.1%) **Paracetamolum** (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	Among the patients who gave birth naturally (**n = 66**, 100%)
Breastfeeding within the first 2 hours after labor	Yes, n = 45 (68.2%) No, n = 14 (21.2%) No data, n = 7 (10.6%)	Among the patients who gave birth naturally (**n = 66**, 100%)

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	65	40.75	597.20	212.60

third stage of childbirth				
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

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

	No. of significance (n)	**Spearman's coefficient *R***	**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 *R***	**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**

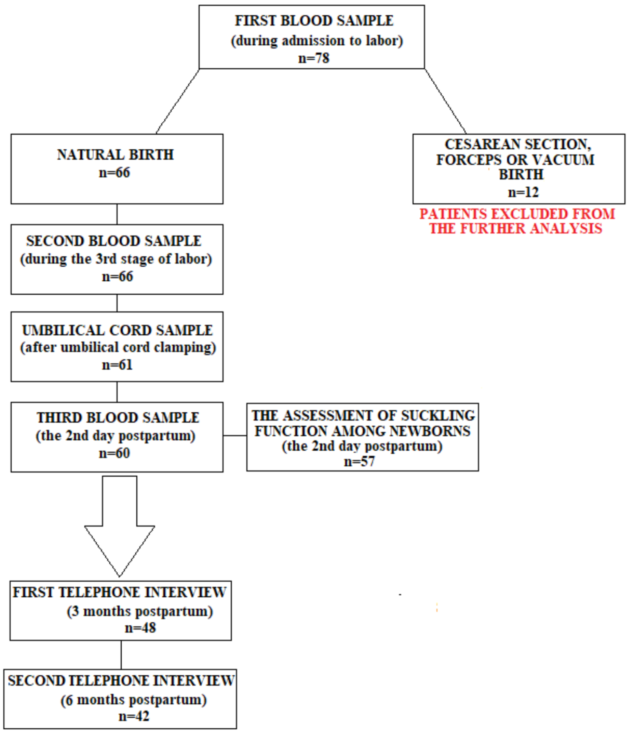

Figure 1. Schematic representation of patient selection and examination