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The relationship between serum levels of prolactin and growth hormone in the early postnatal period

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BACKGROUND: In the neonatal period, the pituitary hormones including prolactin (PRL) and human growth hormone (hGH) are secreted in high amounts due to immature feedback mechanisms. As both hormones are secreted in part by the same somatomammotrophic cells, we investigated their relationship in newborns with respect to sex, gestational week, method of delivery, and anthropometric data.

METHODS: The serum levels of PRL and hGH were measured in blood drawn from 225 newborns. The newborn data were extracted from medical records.

RESULTS: A positive correlation was found between log-transformations of PRL and hGH ($r = 0.17$; $P = 0.01$; $n = 225$), with a stronger correlation in newborns whose blood samples were taken more than 2 days after birth ($r = 0.42$; $P < 0.001$; $n = 130$). Log-transformations of the PRL/hGH ratio demonstrated a positive correlation with the gestational week ($r = 0.39$; $P < 0.001$; $n = 200$). Multiple regression analysis showed that 15% of the variance in the logarithm of this ratio is attributed to the gestational week.

CONCLUSION: In newborns, serum PRL and hGH levels show a positive correlation that can be explained by common regulatory factors or a drift phenomenon. A higher gestational week is associated with a higher PRL/hGH ratio. Further studies are needed to look for possible confounders and to determine the PRL–hGH relationship in different conditions.

Prolactin (PRL) and human growth hormone (hGH) are pituitary hormones that affect proliferation and growth, high levels of which are known to be the risk factors for malignancy (1,2). Fetal serum PRL levels rise gradually during pregnancy (3) and later decline in the first year of life. hGH is the main growth-stimulating hormone after birth (4). Prenatally, two of its variants, hGH-V and human placental lactogen (hPL), produced by placental syncytiotrophoblasts, regulate fetal development together with fetal pituitary hGH and insulin-like growth factor-1 (IGF-1) (5,6). Serum hGH levels are higher in preterm newborns than in the full-term infants (7). In the early postnatal period (0–28 days of life), pituitary hormones including PRL and hGH are secreted in large amounts, probably due to a delay in the maturation of the negative-feedback mechanisms (8). Pituitary somatomammotrophic cells that co-secrete PRL and hGH are already recognizable in the anterior pituitary early in fetal development (9,10) and contain secretory granules that can be either mono- or bi-hormonal (11,12). It has been suggested that somatomammotrophs function as an intermediate in the process of transdifferentiation between somatotrophs and lactotrophs (13). PRL and hGH share several stimulatory factors (e.g., thyrotropin-releasing hormone, hypoglycemia, and physical stress) and inhibitory factors (e.g., dopamine, somatostatin, and obesity) (4,14–16). Likewise, some molecules have a different effect on the two hormones (e.g., IGF-1). Publications on the relationship between the secretion of PRL and hGH in different conditions are scant. Concomitant measurements of both hormones were performed in patients with acromegaly (17), prolactinomas (18), pituitary adenomas that secrete both hormones (19), Parkinson's disease (20), obesity (21), and Laron syndrome (22). Few studies report simultaneous measurements of these hormones in the postnatal period (23,24). The aim of this study was to investigate the PRL–hGH relationship in a large number of newborns with respect to sex, length of gestation, method of delivery, and anthropometric data.

METHODS

This study was approved by the Institutional Review Board at Rabin Medical Center (Petach Tikva, Israel).

Subjects

A total of randomly selected 225 infants aged 0–27 days (mean ± SD = 2.43 ± 3.84) born in the Helen Schneider Hospital for Women (Petach Tikva, Israel) between June 2015 and July 2016 were included in this study. These infants were admitted to the Neonatal Intensive Care Unit at Schneider Children's Medical Center (Petach Tikva, Israel) or to the Newborn Department at Helen Schneider Hospital for Women. The subjects were included regardless of their gestational age (24–42-week gestation). There were no exclusion criteria.

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Measurements

Serum levels of PRL and hGH were measured by means of solid-phase, two-site chemiluminescent immunoassays (Siemens Immulite 2000 Immunoassay System, Erlangen, Germany). The serum samples were taken from the remaining blood collected for a variety of reasons in the neonatal units, and were kept at −20 °C until analyzed. Whenever available, the following clinical and anthropometric data were extracted from medical records in the hospitalizing unit: sex, gestational week, method of delivery, birth weight, length and head circumference, birth of a twin sibling, and known medical diagnoses of the newborn and its mother.

Data Analysis

The values of PRL and hGH, as well as PRL/hGH ratios, were log-transformed to achieve a Gaussian distribution for further analysis. Pearson's correlation coefficients were calculated to determine the correlations between continuous values such as the logarithms of hGH and PRL. One-way ANOVA and Tukey's *post hoc* test were performed to determine differences between the mean values of the PRL/hGH ratio logarithm among different categorical subgroups. A stepwise multiple regression analysis was performed with the PRL/hGH ratio logarithm as a dependent variable to determine the possible predictors of this ratio. Statistical tests were performed using IBM SPSS Statistics (Version 23, Armonk, NY, USA).

RESULTS

Demographic Data

The demographic data for newborns included in this study are summarized in **Table 1**.

Overall Analysis

A significant positive correlation was found between logarithms of PRL and hGH in blood samples taken 2–27 days after birth ($r = 0.42$; $P < 0.001$; $n = 130$). A weaker correlation was found when the samples taken in the first 2 days of life were included ($r = 0.17$; $P = 0.01$; $n = 225$) (**Figure 1**). The logarithm of the PRL/hGH ratio had a significant positive correlation with the gestational week ($r = 0.39$; $P < 0.001$; $n = 200$; **Figure 2**). Stepwise multiple regression analysis showed that 15% of the variance in the PRL/hGH ratio logarithm can be attributed to the gestational week (**Table 2**).

The Hormonal Relationship in Different Subgroups

The data collected between 2 and 27 days after birth were further analyzed by dividing the newborns into female and male subgroups, and into preterm (gestational week <37 weeks) and term subgroups. Females demonstrated a stronger correlation between logarithms of PRL and hGH ($r = 0.5$; $P < 0.001$; $n = 63$) than males ($r = 0.39$; $P < 0.001$; $n = 67$) (**Figure 3**). Differences between the preterm ($r = 0.4$; $P = 0.01$; $n = 48$) and term ($r = 0.43$; $P < 0.001$; $n = 66$) infants were not significant.

The Hormonal Ratio in Different Subgroups

Table 3 summarizes the mean values of the PRL/hGH ratio logarithm in different methods of delivery. One-way ANOVA

Table 1. Available demographic data for newborns included in this study

Sex (n)	
Males	118
Females	107
Gestational week[a] (range, mean ± SD)	24–42, 37.66 ± 2.64
Measurements (range, mean ± SD)	
Weight[b] (g)	710–4356, 2956.02 ± 632.76
Length[c] (cm)	42–54, 48.72 ± 2.64
Head circumference[d] (cm)	21.5–37.5, 33.52 ± 2.15
Twins[a] (*n*)	25
Method of delivery[b] (n)	
Vaginal	123
Assisted vaginal	16
Cesarean	62

[a]Data were available for 200 newborns.
[b]Data were available for 201 newborns.
[c]Data were available for 191 newborns.
[d]Data were available for 196 newborns.

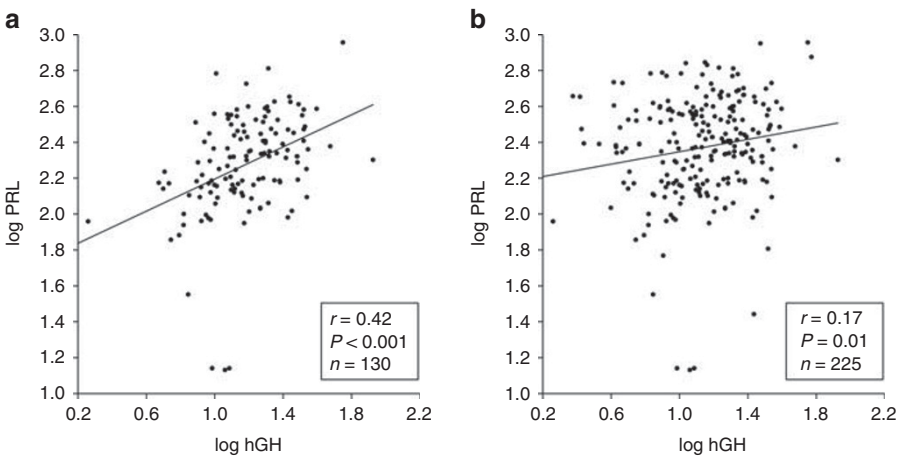

Figure 1. Scatterplots showing the correlation between logarithms of PRL (ng/ml) and hGH (ng/ml) measured during (**a**) 2–27 days after birth and (**b**) 0–27 days after birth. hGH, human growth hormone; PRL, prolactin.

showed a significant difference between the values ($P = 0.02$), and Tukey's *post hoc* test revealed a significant difference between the vaginal delivery group mean value ($n = 123$; mean ± SD = 1.28 ± 0.39) and the cesarean section group mean value ($n = 62$; mean ± SD = 1.15 ± 0.3; $P = 0.04$).

DISCUSSION

Concomitant determination of PRL and hGH in the early postnatal period, during which pituitary hormones are secreted in high amounts, has not been performed before in a large group of infants. Based on the fact that somatomammotrophic cells secrete both hormones, we tried to find out whether they share a common secretory pattern. The stronger correlation between logarithms of PRL and hGH that was calculated when samples from the first 2 days of life were excluded may be partially explained by a PRL surge that occurs in the first day of extra-uterine exposure (25), after which PRL levels decrease during the first postnatal week (26). Thus, the data collected in days 2–27 of life may represent PRL levels that are less affected by the delivery event. As physical stress elevates levels of both PRL and hGH, delivery-related stress may also affect measurements performed immediately after birth. This is demonstrated by our finding that the PRL/hGH ratio logarithm in the vaginal delivery group was significantly higher than that in the cesarean section group, and supports former evidence of significantly higher plasma PRL levels in infants after vaginal delivery than those after elective cesarean delivery (27). The differences in strength between correlations of PRL and hGH logarithms among male vs. female newborns may add further evidence that sex differences in pituitary hormone secretion exist already in the perinatal period. For example, Guyda and Friesen (28) reported significantly lower serum PRL levels in premature female infants when compared with those in the premature male infants, and Schmidt and Schwarz (29) found significant sex differences of luteinizing hormone (LH) and follicle-stimulating hormone (FSH) levels in newborns. The nervous system in the human neonate, in contradistinction to other mammals, continues to mature after birth, and the

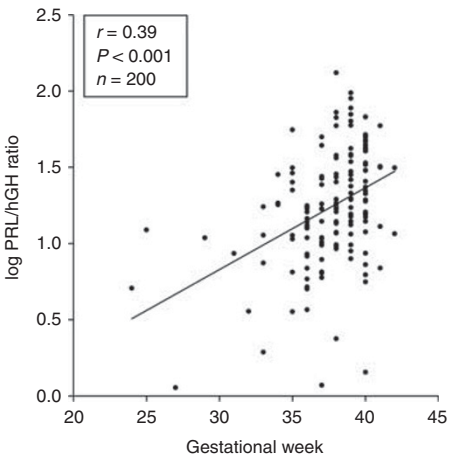

Figure 2. A scatterplot showing the correlation between the logarithm of the PRL (ng/ml)/hGH (ng/ml) ratio and the gestational week. hGH, human growth hormone; PRL, prolactin.

Table 2. Stepwise multiple regression analysis for the logarithm of the PRL/hGH ratio.

	Standardized coefficient (β)	*P*-value
Gestational week	0.39	<0.001
Birth weight	Excluded	Excluded
Birth length	Excluded	Excluded
Birth head circumference	Excluded	Excluded
Overall		
R^2	0.154	—
Adjusted R^2	0.150	—

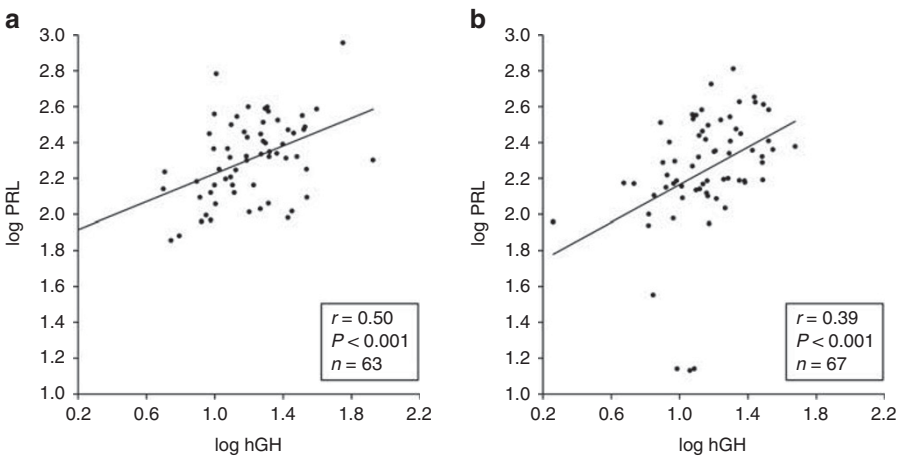

Figure 3. Scatterplots showing the correlation between logarithms of PRL (ng/ml) and hGH (ng/ml) measured 2–27 days after birth in (**a**) female newborns and in (**b**) male newborns. hGH, human growth hormone; PRL, prolactin.

Table 3. Mean logarithms of the PRL (ng/ml)/hGH (ng/ml) ratios in different methods of delivery

Method of delivery	*n*	Mean ± SD
Vaginal	123	1.28 ± 0.39
Assisted vaginal	16	1.38 ± 0.38
Cesarean	62	1.15 ± 0.30

development of the pituitary hormone feedback mechanisms is delayed (30). The bi-hormonal somatomammotrophs may take part in this developmental process. It will be of interest to determine the behavior of PRL during states of hGH deficiency as well as stress in newborns. A possible clinical implication of the postnatal PRL–hGH correlation can be the enhancement of joint actions by both hormones like cell proliferation (4).

CONCLUSIONS

In summary, our findings indicate a significant positive correlation between early postnatal serum PRL and hGH levels that is higher among females, supporting either common regulatory factors or a drift phenomenon involving the somatomammotrophic cells. The postnatal high levels of pituitary hormones can be the result of delivery stress or delay in the maturation of the feedback mechanisms. Of all measured parameters in this study, the gestational week at birth was shown to be the strongest determinant of the PRL/hGH ratio, which was also affected by the method of delivery. Our study may indicate that the preferable time to evaluate PRL and hGH in newborns is after the first 2 postnatal days, when the secretion of both hormones is less affected by the delivery event. Further studies are needed to look for possible confounders and to determine the PRL–hGH relationship in different conditions, in particular the ones in which levels of one hormone are known to be high.

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