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C-peptide levels and the duration of lactational amenorrhea

Changes in insulin sensitivity play an important role in directing metabolic energy toward milk production in lactating mammals. In rats, prolactin causes upregulation of insulin receptors in mammary tissue together with an increase in peripheral insulin resistance, leading to a preferential allocation of energy to support milk production (1, 2). In humans, the shift in energy allocation during lactation away from peripheral tissues and toward milk production is correlated with lower insulin levels (2–4).

Insulin also plays an important role in stimulating ovarian steroidogenesis. In vitro studies have demonstrated the effect of insulin in potentiating gonadotropin stimulation of steroid production by both granulosa and theca cells (5–7).

Although insulin is clearly implicated in both the metabolic adaptation to lactation and the stimulation of ovarian function, few studies have examined changes in insulin levels during human lactation, and none have studied the relation of insulin to the postpartum resumption of ovarian function. We report here on a mixed longitudinal study of urinary C-peptide levels (a product of insulin synthesis and hence a biomarker of insulin production) among the Toba of northern Argentina, a population of well-nourished women who practice intensive breastfeeding. The goal of the study is to better understand how the metabolic changes during lactation reflected in insulin production are related to the resumption of ovarian steroidogenesis.

Seventy Toba women from the village of Namqom in northern Argentina participated in the study, representing 90% of all currently breastfeeding, amenorrheic mothers of children younger than 4 months of age in the community. All participating women had a full-term birth (birth weight >2,500 grams, gestational age >37 weeks), were amenorrheic at the beginning of the study, and were not using hormonal contraceptives. Toba women breastfeed their infants with high frequency for 2 to 3 years, or until the second trimester of their next pregnancy. The average (±SE) duration of lactational amenorrhea in this population is 10.2 ± 4.3 months. The protocol for this study was approved by the Harvard University Faculty of Arts and Sciences Standing Committee on the Use of Human Subjects in Research.

First-void morning urine samples were collected weekly from all women until they had experienced three menstrual periods. Samples were aliquoted in triplicate and frozen at −20°C within 2 hours of collection. Urine samples corresponding to the third week of each postpartum month were analyzed for C-peptide. C-peptide levels were estimated using radioimmunoassay kits (I^{125}-labeled DSL-7000; Diagnostic Systems Laboratories, Inc., Webster, TX). Intra-assay and interassay coefficients of variation in C-peptide averaged 5.0% and 7.8%, respectively. Urinary creatinine concentrations were estimated using Taussky's method (8).

Average postpartum C-peptide levels among the women in this study increased quite steadily over time, from 12 ± 3 ng/mg creatinine (mean ± SE) at 1 month to 34 ± 6 ng/mg creatinine at 12 months; after 12 months, the values remained relatively stable. However, the pattern of C-peptide varied by prepregnancy body mass index (BMI). For women with a prepregnancy BMI of ≥26 kg/m^2 (n = 23), the average levels rose from 15 ± 6 ng/mg creatinine at 1 month postpartum to 47 ± 12 ng/mg creatinine at 12 months. For women with a prepregnancy BMI of 23 to 26 kg/m^2 (n = 31), the average levels rose from 12 ± 3 ng/mg creatinine at 1 month postpartum to 34 ± 7 ng/mg creatinine at 12 months. For women with a prepregnancy BMI of <23 kg/m^2 (n = 20), the average levels rose only from 5 ± 2 ng/mg creatinine at 1 month postpartum to 13 ± 4 ng/mg creatinine at 12 months.

The differences apparent in the C-peptide levels according to prepregnancy BMI likely reflect individual differences in insulin sensitivity related to adiposity. To correct for these individual differences, we standardized C-peptide values to each woman's individual mean value after menstrual resumption. To correct for individual variation in the timing of menstrual resumption, individual data were realigned relative to the month of the first postpartum menses. After we normalized and realigned C-peptide values in this way, we could demonstrate a clear pattern of increase from approximately 60% of the postresumption mean value at 12 months before menstrual resumption to 130% at 2 months before menstrual resumption; a decline occurred until stable values were reached on and after the month of menstrual resumption (Fig. 1).

The initially low C-peptide level observed in lactating Toba women is consistent with previous reports (3, 4, 9). However, the full postpartum trajectory of insulin has not been described previously. The initially low insulin levels of insulin production in the early postpartum period likely reflect elevated carbohydrate use for

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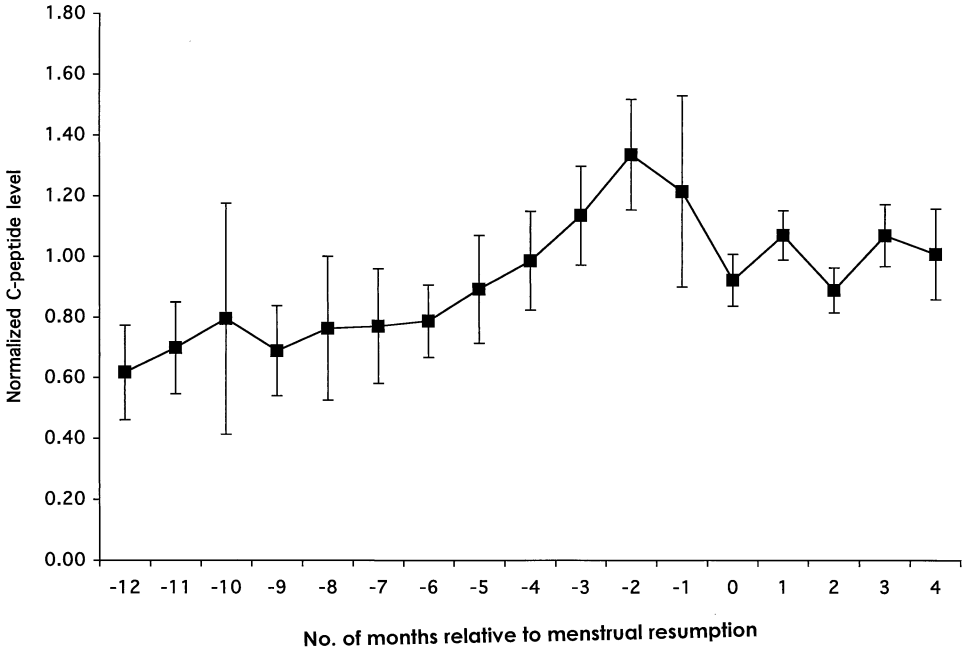
FIGURE 1

Mean (±SE) values of individually normalized C-peptide values relative to month of menstrual resumption for all women in the study. The normalized C-peptide values are expressed as a fraction of each woman's mean value after the resumption of menses.



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milk production in lactating mothers. Rising insulin production over the postpartum time period is consistent with the attenuation of this demand, particularly as supplemental foods are introduced into the infant's diet; also, increased insulin secretion is needed to maintain maternal glucose homeostasis.

The phase of relative insulin resistance preceding menstrual resumption may be associated with a low estrogen milieu affecting glucose oxidation (10). Elevated insulin levels during this period may synergize with gonadotropins to stimulate higher levels of ovarian steroid production, leading to a resumption of menstruation and a resolution of the transient phase of insulin resistance. This sequence and the close temporal correlation between C-peptide changes and menstrual resumption indicate a close coupling between maternal energy metabolism and the postpartum resumption of fecundity.

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