Medicine Grand Rounds
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Postpartum period: an opportunity to improve maternal metabolic health

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This is to acknowledge that María A. Ramos-Román, MD has not disclosed any financial interests or other relationships with commercial concerns related directly or indirectly to this program. Dr. Ramos-Román will not be discussing off-label uses in her presentation.

Dr. Ramos-Román is an Assistant Professor in the Division of Endocrinology. She is interested in the hormonal mechanisms by which lactation protects women with a history of gestational diabetes from type 2 diabetes in the postpartum period. A synopsis of her research project *Effect of lactation on ectopic lipid after gestational diabetes* can be found at the UT Southwestern's website under Find a Clinical Trial (FaCT).

Purpose and Overview:
The purpose of this Grand Rounds presentation is to familiarize the audience with the endocrine changes characteristic of lactation. Milk production results from collaboration among multiple systems. Maternal adaptations during lactation and post-lactation recovery may influence long-term maternal metabolic health.

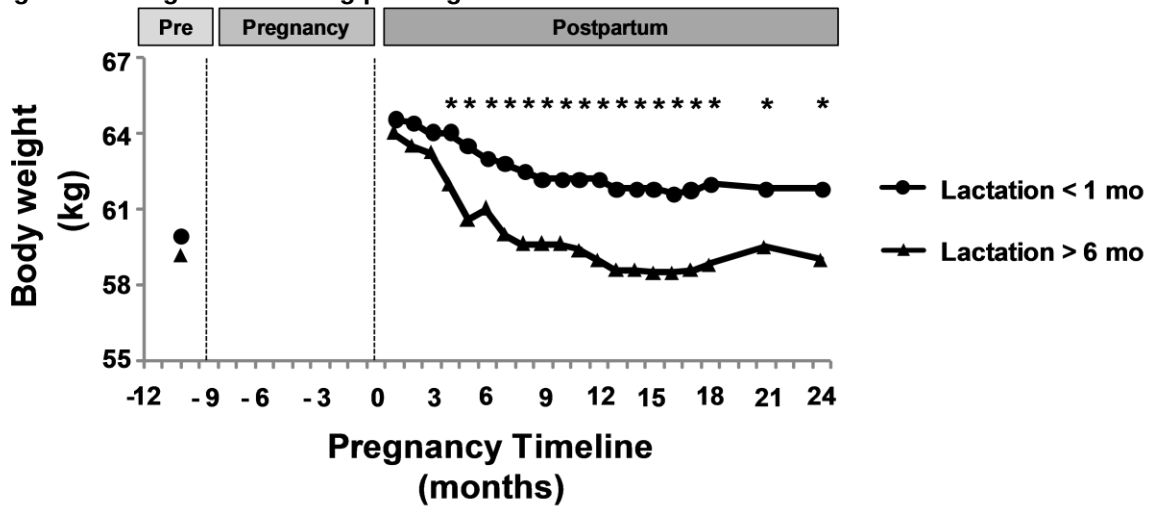
Educational Objectives:

1- Awareness of the endocrine contribution to the communication among the multiple systems that make lactation possible.
2- Identify short-term and long-term alterations in glucose regulation and bone health during lactation and post-lactation recovery.
3- Recognize that postpartum weight loss is not an obligatory trait of lactation.

Pregnancy and postpartum are periods of intense hormonal changes in which maternal metabolism adapts on behalf of her developing offspring. Most pregnancy-induced maternal physiological and anatomical changes return to the non-pregnant state during the 4 to 6 weeks following the delivery of the newborn and the placenta. These early weeks are known as puerperium. As for maternal metabolism, pregnancy ends with the conclusion of lactation (1). This review highlights the implications of postpartum cross-talk among maternal tissues relevant for glucose tolerance and bone health. This multi-system interaction has immediate, delayed, and possibly lasting health consequences. My focus as an internist and endocrinologist will be on the maternal half of a synchronized mother-infant pair. The context of my presentation is the hormonal environment during both lactation and post-lactation recovery in a healthy woman.

The average maternal weight gain at 40 weeks of gestation is 12.5 kg. Twenty eight percent (3.3 kg) of that weight gain corresponds to fat stores intended to subsidize the energy costs of lactation (2). Several factors influencing postpartum weight change include duration and intensity of lactation, pre-pregnancy weight, gestational weight gain, postpartum diet, physical activity, and age (3). Overall, the literature is inconsistent about the magnitude and direction of the weight change attributed to lactation. In clinical practice some mothers will report ease to lose weight, while others will maintain weight stability and some will even gain weight (4). **Figure 1** shows an example of significant weight loss during prolonged lactation.

Figure 1. Weight loss during prolonged lactation.



If the energy content of human milk is 700 kcal/L and established milk production averages 700 mL/day, then the estimated caloric intake to support lactation approximates 500 kcal/day (5). Two major nutritional components in milk are triglycerides and lactose. Milk triglycerides have fatty acids derived from diet, very low-density lipoproteins from liver, fatty acids newly-made in the mammary gland from glucose, and those derived from adipose tissue lipolysis (maternal fat stores) (6). In a society with easy access to food, milk triglycerides are primarily sourced by diet and endogenous lipid synthesis (de novo lipogenesis or DNL). The utilization of adipose stores is spared for use as an emergency resource. The lactating mammary gland also requires between 50 grams and 75 grams of glucose per day (7). A substantial proportion of this glucose requirement is destined to make lactose.

Lactation affects the plasma insulin concentration and insulin action in the mother. Mammary glucose uptake is an insulin-independent process that lowers blood glucose concentrations,

lessens the secretory demands on the endocrine pancreas, and results in the low circulating insulin characteristic of lactation (8). The hormonal control of lactation ensures that insulin resistance in non-mammary tissues allows for uptake of nutrients by the mammary gland (9). This compensatory mechanism between mammary and non-mammary tissues makes healthy lactating women appear as insulin sensitive as healthy women who have not had a recent pregnancy. Studies on circulating hormones and adipose tissue specimens provide support for the concept that insulin resistance occurs in non-mammary tissues at the onset of lactation. Specifically, the reciprocal relationship between the concentrations of pituitary prolactin and adipose adiponectin has implications for the physiology of lactation (10).

Milk production involves many maternal adaptations that take place concurrently or sequentially. These maternal adaptations are under hormonal control and involve a variety of tissues and organs: pituitary, mammary gland, ovaries, pancreas, skeletal muscle, liver, adipose tissue, and bone. The main hormones discussed today are prolactin, adiponectin, insulin, estrogen, and parathyroid hormone-related protein (PTHrP).

Pituitary prolactin is responsible for initiation and maintenance of lactation. Prolactin signals through prolactin receptors found in tissues important in metabolism such as β-cells of the pancreas, hepatocytes, adipocytes, macrophages, and skeletal myocytes. The magnitude of the prolactin response to suckling decreases with time postpartum (11,12). Prolactin has lipolytic activity at the high concentrations present during late pregnancy and early lactation (13). Prolactin also induces ovarian refractoriness, which means that the ovaries do not respond to gonadotropin stimulation in the presence of increased prolactin (14). This results in lack of ovulation and lactational amenorrhea of variable duration.

Adipose tissue adiponectin decreases after the third trimester of pregnancy and reaches its maximum suppression during the postpartum period despite what appears to be a return to pre-pregnancy insulin sensitivity (15). Low adiponectin concentrations have been reported until 6 months postpartum with recovery back to pre-pregnancy concentrations by 12 months postpartum (16). However, these reports did not disclose lactation status, duration/intensity of lactation or time relative to cessation of lactation. Higher adiponectin concentrations are associated with a lower risk of type 2 diabetes and lower bone mineral density (17). Adiponectin concentrations are inversely related to adipose tissue mass determined by size and number of adipocytes. The occurrence of low adiponectin during lactation is consistent with insulin resistance in adipose tissue during this period (rather than insulin sensitivity).

Pancreatic insulin concentrations decrease during lactation. In this low insulin environment, high concentrations of prolactin increase the activity of lipoprotein lipase in the mammary epithelium and decrease the activity of this enzyme in adipose tissue (18,19). These changes contribute to the routing of fatty acids towards milk in both the fasting and the fed states. The low insulin concentration during lactation could be a fail-safe mechanism that supports lipolysis and milk lipid when dietary intake is restricted.

Placental estrogen will clear from the maternal circulation within 7 days of placental delivery. Ovarian production will remain low for a variable period of time depending on duration/intensity of lactation, prolactin concentration, and ovarian refractoriness to gonadotropin stimulation. An environment low in estrogen will synergize with high production of PTHrP to promote bone resorption in favor of calcium availability for milk (20).

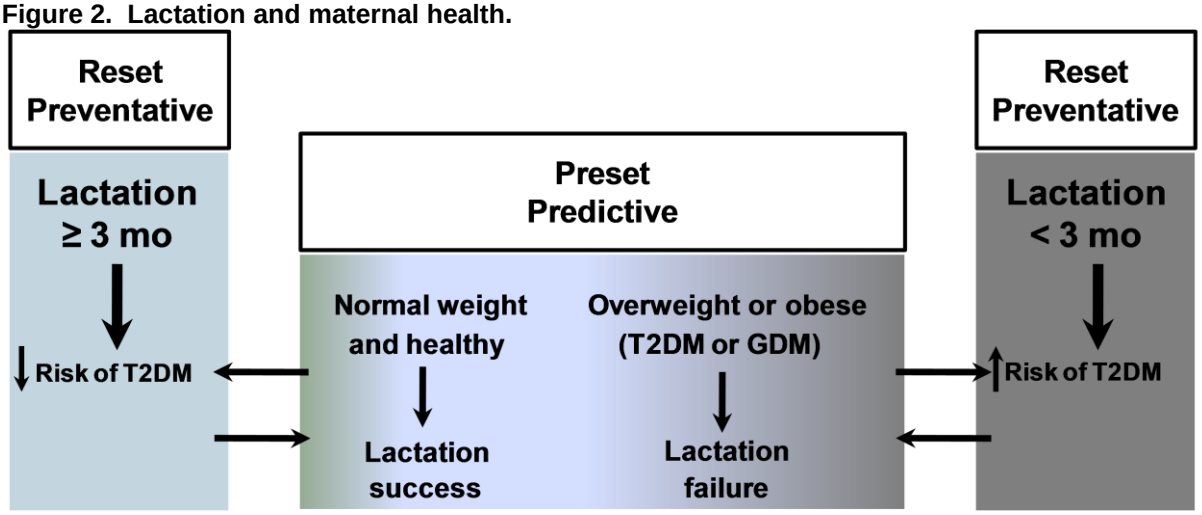
The mammary gland makes PTHrP. Lactation is one of two conditions in which PTHrP circulates (endocrine rather than autocrine or paracrine action) (21). The other condition is

humoral hypercalcemia of malignancy. Mamary PTHrP is secreted into milk and blood. High production of PTHrP during a concurrent hypoestrogenic environment stimulates osteoclast-mediated bone resorption and liberates skeletal calcium stores.

Contribution of lactation to metabolic risk

Two opposing models have been proposed to explain the contribution of lactation to metabolic risk, particularly diabetes risk (**Figure 2**). The reset or preventative model states that factors associated with lactation ≥3 months help women to regain their pre-pregnant weight and metabolic risk status, whereas lactation for <3 months does not (1,22). This 3-month mark appears to be an important turning point during the postpartum period. In contrast, the preset or predictive model argues that a pre-existing abnormal metabolic profile compromises mammary development and the events that allow initiation and maintenance of lactation. In support of this model, overweight and obese women are less likely to initiate lactation and will lactate for a shorter duration than lean women.

Figure 2. Lactation and maternal health.



Gestational diabetes, GDM

What is the significance of the 3-month postpartum mark for the mother?

Major organizations such as the World Health Organization, the American Academy of Pediatrics, and the American College of Obstetrics and Gynecology recommend the practice of exclusive lactation for 6 months followed by partial lactation after introduction of supplemental foods. These organizations recommend extending partial lactation as long as both mother and infant wish to do so. These recommendations take into consideration the growth and development of the infant.

Longitudinal studies including maternal measurements before, during and after the 3-month postpartum mark have identified (a) changes characteristic of the postpartum period common to both lactating and non-lactating mothers, and (b) differences between lactating and non-lactating mothers at or after 3 months postpartum. Bone loss in the lumbar spine occurs in both lactating and non-lactating mothers when tested at 3 months postpartum (23). Weight loss and reduction in adiposity have been consistently reported after 3 months postpartum in lactating mothers. Long-term postpartum risk of type 2 diabetes is lower among mothers with and without a history of gestational diabetes who lactated >3 months (24).

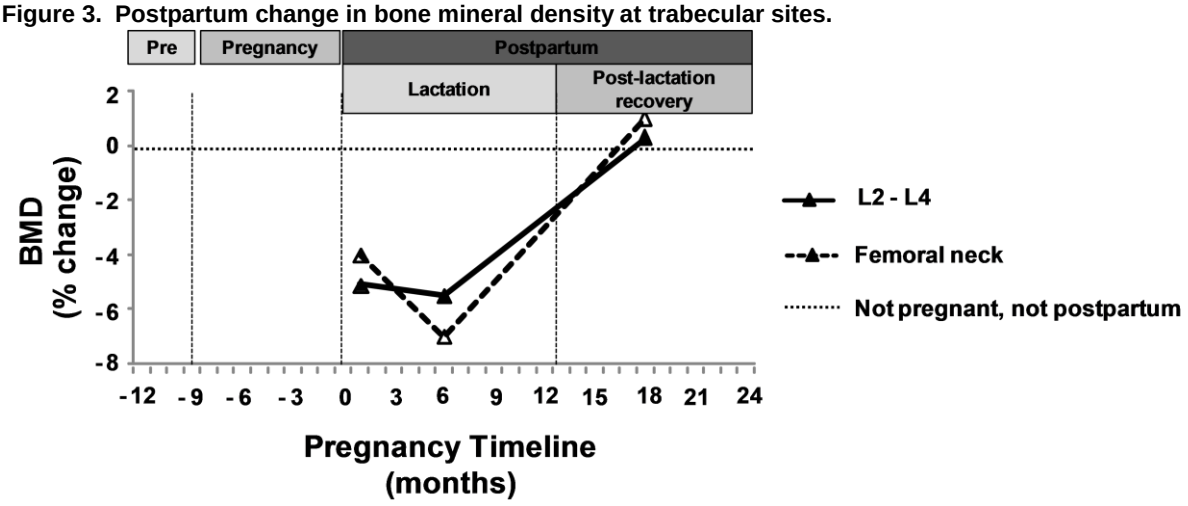
Impact of lactation while it is in progress

Relative to a non-lactating mother, the lactating mother will have lower fasting and postprandial glucose concentrations, lower plasma insulin, and less atherogenic lipids (25). The magnitude of the reduction in risk for metabolic syndrome, cardiovascular disease, and type 2 diabetes will be influenced by the duration and intensity of lactation. It is possible that another benefit of lactation is the covert restoration of functional adipose tissue, resulting in less exposure of non-adipose tissues to excess lipid.

Impact of post-lactation recovery

Bone health has been studied longitudinally from pregnancy to post-lactation recovery (26). An increase in $1,25(OH)_2$Vitamin D is the main adaptation during pregnancy to meet fetal calcium requirements (through increased calcium absorption). During the postpartum period the main source of milk calcium is the maternal skeleton. Bone mineral density falls 3% to 8% at trabecular sites over the first 6 months postpartum (**Figure 3**). Bone loss occurs at an estimated rate of 1-3% per month, which approximates the annual rate of bone loss after menopause (21). Bone mineral density is typically restored spontaneously to non-pregnant levels within 6 to 12 months after cessation of lactation after normal menses return. This rapid period of bone loss and recovery does not increase the risk of postmenopausal osteoporosis or fracture risk later in life. The hormonal environment of post-lactation recovery includes normalization of prolactin and increased circulating estrogen. Circulating PTHrP increases during pregnancy and lactation. However, its trajectory after switching to partial lactation or complete cessation of lactation is not clear. The factors that stimulate bone formation after completion of lactation are not known (27).

Figure 3. Postpartum change in bone mineral density at trabecular sites.



Summary

Lactation is a dynamic process that integrates multiple systems. This integration is under neuro-endocrine control facilitated by a gradual decline in prolactin over time during the postpartum period. This decline in prolactin (a) includes both basal prolactin and stimulated prolactin in response to suckling, and (b) modifies the interaction of prolactin with other hormones relevant to lactation, like adipose adiponectin and ovarian estrogen. It is possible that the concentration of PTHrP is at least partially modified by the concentration of prolactin. Lactation and post-lactation recovery are windows of opportunity to reset maternal metabolic risk and study physiologic adaptations relevant to the prevention of chronic illnesses such as type 2 diabetes and osteoporosis.

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