Does Insulin Explain the Relation between Maternal Obesity and Poor Lactation Outcomes? An Overview of the Literature[1–4]

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ABSTRACT

It is well established that obese women are at increased risk of delayed lactogenesis and short breastfeeding duration, but the underlying causal contributors remain unclear. This review summarizes the literature examining the role of insulin in lactation outcomes. Maternal obesity is a strong risk factor for insulin resistance and prediabetes, but until recently a direct role for insulin in milk production had not been elucidated. Over the past 6 y, studies in both animal models and humans have shown insulin-sensitive gene expression to be dramatically upregulated specifically during the lactation cycle. Insulin is now considered to play a direct role in lactation, including essential roles in secretory differentiation, secretory activation, and mature milk production. At the same time, emerging clinical research suggests an important association between suboptimal glucose tolerance and lactation difficulty. To develop effective interventions to support lactation success in obese women further research is needed to identify how, when, and for whom maternal insulin secretion and sensitivity affect lactation ability. *Adv Nutr* 2016;7:407–14.

Keywords: lactation, breastfeeding, obesity, maternal, insulin, diabetes, impaired glucose tolerance, insulin resistance

Introduction

The health benefits of breastfeeding, which are conferred to both the recipient infant and lactating mother, are evident not only in disadvantaged populations (1) but also in developed countries (2–6). As a result, the WHO and the American Academy of Pediatrics recommend exclusive breastfeeding to age 6 mo, with continued breastfeeding plus complementary foods through the first 1 (7) to 2 (8) y of life. Even after adjusting for sociodemographic variation, obese women are particularly at risk of delayed onset of lactogenesis (9) and shortened duration of any and exclusive breastfeeding (10–13). A wide range of mediators, such as cesarean delivery (14), difficulty positioning the infant at the breast (15), and aberrations in maternal physiology (16, 17), may underlie these associations.

Although it is well established that obesity is a strong risk factor for insulin resistance and impaired insulin secretion, a direct role for insulin in milk synthesis is only recently gaining recognition. Thus, the focus of this review is on what is known with regard to the contribution of insulin secretion and insulin sensitivity to lactation outcomes. Considering that 23% of reproductive-aged women in the United States are prediabetic (18), suboptimal insulin dynamics could be an unrecognized impediment to improving exclusive breastfeeding rates in the United States.

Current Status of Knowledge

Is there a physiologic basis for the link between maternal obesity and shortened breastfeeding duration? Even after adjusting for socioeconomic variables, a statistically significant relation between maternal obesity and shortened breastfeeding duration has been reported for nation-level cohorts in the United States (10), Australia (12), Denmark (11), and Norway (13). In addition, nearly all smaller cohort studies reached similar findings, as recently reviewed elsewhere (19). These results possibly are in part biased by an unmeasured factor covarying with obesity, such as weaker breastfeeding intention. On the other hand, there is evidence in support of an underlying physiologic factor

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driving the relation. First, all of the nation-level studies found that the risk of shortened breastfeeding duration increases with increasing BMI class (dose-response relation) (10–13). Second, the strength of the relation was strongest in Norway, where there is widespread social support for breastfeeding, substantial maternity leave, and nearly universal breastfeeding initiation (and thus less sociocultural confounding by obesity). Specifically, in the Norwegian Mother and Child Cohort Study (n = 49,669), breastfeeding initiation varied only slightly, from 99.6% among normal-weight women [BMI (in kg/m^2) <25.0] to 97.4% among very obese women (BMI ≥35.9; $P < 0.001$), but sustaining full breastfeeding to at least 4 mo markedly declined from a high of 62.9% among normal-weight women to a low of 37.8% among very obese women ($P < 0.001$) (13).

Further evidence for a biological basis comes from a recent mediation analysis. With the use of data from the CDC's Infant Feeding Practices II survey, O'Sullivan et al. (20) examined if early breastfeeding problems mediated the relation between obesity and short breastfeeding duration. Their analysis revealed obesity to be a risk factor for not exclusively breastfeeding at 1 mo and the factor "insufficient milk" was a statistically significant mediator of this relation in both primiparous and multiparous women.

In summary, the consistency of the epidemiologic evidence, the dose-response nature of the relation, countries with strong social support for breastfeeding showing the largest disparity, and evidence of "insufficient milk" being a mediator all support the possibility of a physiologic causal factor underlying the relation between obesity and short breastfeeding duration.

Obese women are more likely to experience delayed onset of lactogenesis. A key factor in the successful establishment of breastfeeding is the timely onset of copious milk production after childbirth. This was previously described as "stage 2 lactogenesis" (21), but contemporary terms for this phenomenon are "secretory activation" or, simply, "lactogenesis" (22). Maternal perception of lactogenesis is proven to be strongly correlated with milk transfer (23–25) and biochemical (26, 27) measures. Obesity and large breast size do not bias perception of lactogenesis (9).

Lactogenesis is considered delayed if signs or symptoms of copious milk production do not occur within the first 72 h postpartum (28). Delayed lactogenesis is associated with short- and long-term negative sequelae. For example, the RR of excess neonatal weight loss (≥10% of birth weight) was found to be 7 times greater in exclusively breastfed infants if there was delayed lactogenesis compared with timely lactogenesis (40.4% compared with 5.7%; $P < 0.0001$) (23). On a longer-term basis, women experiencing delayed lactogenesis are at greater risk of shorter breastfeeding duration (28–30).

Delayed lactogenesis is highly prevalent among women in the United States (9, 17, 23, 31), especially compared with women in less developed settings (24, 32, 33) (**Figure 1**). The prevalence of delayed lactogenesis was 22% in a community-based cohort in Davis, California, despite the strong motivation to exclusively breastfeed and intensive lactation support (23). In contrast, among rural Ghanaian mothers, the prevalence of delayed lactogenesis is reported to be 4% (24). This disparity is consistent with the observation that the Ghanaian newborns were already above birth weight by day 4 of life (24), whereas exclusively breastfed infants in the United States are an average of 7–8% below birth weight at day 4 of life (34).

Several risk factors are associated with delayed lactogenesis, with the strongest factor being primiparity (23, 27, 31, 35–37). Other noted risks include cesarean delivery (23, 28, 35–38), ineffective or infrequent breast emptying (9, 27), and elevated cortisol concentrations in both the mother (27, 35) and umbilical cord serum (27). However, even after adjusting for confounding variables, there is a consistent association between maternal obesity and delayed lactogenesis (9, 23, 29, 31, 36, 37, 39, 40), although the association did not reach significance in Scott et al. (37). Given the high prevalence of obesity in the United States (35% in 2014) (41), it may be contributing to our higher prevalence of delayed lactogenesis in comparison to less industrialized settings (24, 32, 33).

Why obese women have a greater risk of delayed lactogenesis is poorly understood. To date, only a few small clinical studies have examined potential mechanisms in humans. In a study by Rasmussen and Kjolhede (16), serum concentrations of progesterone, basal prolactin, estradiol, and insulin at ~48 h and 7 d postpartum were not significantly different in lactating obese (n = 17) compared with normal-weight (n = 23) women. The authors did find a significant difference in prolactin in response to a suckling episode at 48 h ($P < 0.05$) but not at 7 d postpartum. Timing of onset of lactogenesis or other breastfeeding outcomes were not reported. Repetition of these findings in a larger sample is needed to confirm this finding and elucidate clinical consequences.

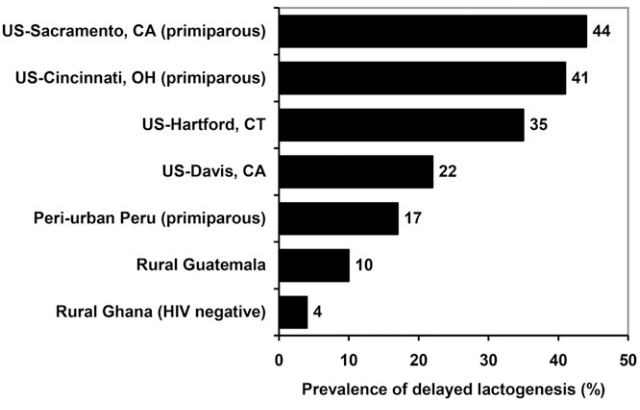

FIGURE 1 Prevalence of delayed lactogenesis (defined as lack of copious milk production symptoms by 72 h postpartum). Sources: rural Ghana (24); rural Guatemala (32); peri-urban Lima, Peru (33); Davis, California (23); Hartford, Connecticut (31); Sacramento, California (9); and Cincinnati, Ohio (17).

Disturbances in glucose metabolism may underlie the association between maternal obesity and delayed onset of lactogenesis. To our knowledge, the Early Lactation Success Study is the largest cohort in which the risk factors for delayed lactogenesis were examined to date (9). Among primiparas who initiated breastfeeding, the prevalence of delayed onset of lactogenesis progressively increased across maternal BMI categories, from 31% among women in the normal BMI range, to 43% among women in the overweight BMI range and 52% among women in the obese BMI range ($P = 0.01$). Greater infant birth weight (>3600 g) and older maternal age (≥30 y) were additional risk factors in a model that adjusted for maternal BMI and measures of breast emptying. Cesarean delivery was not a significant predictor once BMI was included in the model. Among women with all 3 risk factors (obesity, older age, greater birth weight infant), 76% experienced delayed lactogenesis. Notably, this model remained valid even when the women with diabetes (gestational and otherwise) were removed. Both older maternal age and higher BMI are known risk factors for impaired glucose intolerance during pregnancy (42–44). Moreover, higher maternal glycemia is a strong predictor of large-for-gestational-age birth weight, even in nondiabetics (42, 43, 45).

As a progression from the above findings, our research team initiated an examination of the association between metabolic biomarkers and time to lactogenesis in a consecutively enrolled sample of expectant primiparas (17). In the final sample of women who delivered at term and initiated breastfeeding ($n = 16$), the prevalences of obesity and gestational diabetes were 31% and 6%, respectively. Prenatal estimates of insulin secretion and insulin sensitivity exhibited a strong linear relation with timing of lactogenesis. Specifically, a weaker relative insulin response to a glucose challenge test (insulin- to-glucose ratio, 1 h post–glucose load) and lower serum adiponectin [a strong correlate of maternal insulin resistance (46)] at 26 wk of gestation together explained 56% of the variation in postpartum hour of onset of lactogenesis ($P < 0.005$). These coefficients remained stable even when maternal BMI and delivery mode were added to the model.

The previous 2 studies suggest that suboptimal maternal glucose tolerance may be a key factor in the relation between obesity and delayed onset of lactogenesis. Glucose tolerance is a function of insulin secretion and insulin sensitivity and exists along a continuum spanning from healthy, to insulin resistant, to impaired glucose tolerance, to prediabetic, to diabetic (47). It is not known at which point along the continuum, if ever, clinically important impairments in lactation are evident. The biomarker study (17) suggests clinically significant impairment in lactation at degrees of glucose intolerance that are less severe than in diabetes. However, this study was based on a small sample and indirect measures of insulin secretion and sensitivity, and thus this remains an important question for future research.

What can we learn from the lactation experience of women with diabetes? More than 2 decades ago, Arthur et al. (26) reported similar concentrations of glucose and lactose in the mature milk of nondiabetic ($n = 29$) and insulin-dependent diabetic ($n = 4$) mothers, but lactogenesis occurred 20 h later among the latter (53 ± 12 compared with 72 ± 13 h, respectively). In a comparison of early milk composition, mean lactose concentration was significantly lower and mean nitrogen significantly higher at day 2 postpartum among 6 insulin-dependent diabetic mothers compared with 14 nondiabetic mothers, indicating less progress toward lactogenesis in the diabetic mothers (48). It is unknown whether these findings would be replicated today, or if the disparity would be mitigated by improvements in glucose monitoring and insulin delivery in the treatment of diabetes. More recently, the breastfeeding experience of women with diabetes has been captured in descriptive research (49, 50), but scant contemporary research is available that compares lactation outcomes between diabetic and nondiabetic women, as exemplified by a recent review (51).

In contrast, there has been substantial investigation of the opposite relation—that is, the association between a greater "dose" of lactation and decreased risk of developing glucose intolerance or type 2 diabetes (52). For example, in a cohort of 883 women with recent gestational diabetes, there was a significant cross-sectional relation between lactation intensity (i.e., shorter and less exclusive breastfeeding) and glucose tolerance at 6 wk postpartum (52). The authors postulated that lower lactation intensity worsens glucose tolerance in women with recent gestational diabetes. However, the opposite relation cannot be ruled out—i.e., it is glucose intolerance that impeded lactation intensity in the cohort. Evidence for the latter is found in a secondary analysis of the risk factors for delayed lactogenesis in the same cohort. In a model that adjusted for sociodemographic and early breastfeeding variables, significant risk factors for delayed lactogenesis included maternal overweight and obesity, older maternal age, and gestational diabetes treatment with insulin (53). Possibly, these risk factors point to women who are likely to persist with greater postpartum impairment in insulin secretion and sensitivity, which may impede lactation. As a result, by 6 wk postpartum, there will be strong covariance between lactation intensity and glucose intolerance.

To test the hypothesis that maternal glucose intolerance is a risk factor for persistent low milk supply, we conducted a case-control study using electronic medical records from clients attending the Cincinnati Children's Hospital Center for Breastfeeding Medicine outpatient clinic (54). We defined cases as women with a diagnosis of suppressed lactation (low milk supply) in the absence of an infant latch or maternal nipple problem, and we defined controls as women diagnosed with a latch or nipple problem in the absence of low milk supply. We then examined the odds of exposure to diabetes in pregnancy (predominantly gestational diabetes). We found diabetes in pregnancy to increase the odds of low milk supply by 2.6-fold, and this relation persisted even after adjusting for exposure to cesarean delivery, preterm birth, polycystic ovarian syndrome, hypothyroidism, and infertility. Thus, clinically relevant degrees of glucose intolerance may have a persistent effect on lactation capacity.

What is known about the role of insulin in the mammary gland? The association between obesity and impaired milk production was first identified in dairy cows in 1976 (55) and later corroborated in rodents (56). However, the underlying physiologic cause for this association remained elusive. Even though insulin resistance is a predominant feature of obesity, early research on whether insulin acts directly on the mammary gland was contradictory (57–59), with most summaries considering a direct role to be unlikely (60–62). This common conclusion can be traced back to a 1997 review by Neville and Picciano (63), who made the case against a direct role for insulin in milk production. The authors pointed to low plasma insulin values commonly observed during lactation, and they cited glucose clamp studies in both cows (64) and humans (65) that showed no effect of increased plasma insulin or glucose on milk secretion. They also questioned how a hormone that varies with food intake could have an influence on milk production.

Others have dismissed a direct role for insulin in lactation because, even though glucose is an obligate precursor for the synthesis of lactose in the mammary gland, it is well established that glucose transport across the basolateral membrane of the lactocyte is primarily via non–insulin-dependent glucose transport molecules (66). If insulin is not required for glucose entry into the lactocyte, what might its role be in milk synthesis?

Far from being limited to facilitating glucose entry into insulin-dependent tissue, it is now more widely recognized that insulin exerts a powerful influence over other metabolic processes, including synthesis of lipids and proteins, in addition to cell growth and differentiation (67). Given that the lactating mammary gland is literally a biofactory churning out large quantities of lipids, proteins, and carbohydrates from de novo synthesis, it would be reasonable to assume that insulin plays a role in milk biosynthesis. In fact, the more recent in vitro research clearly shows that insulin stimulates the expression of genes directly involved in milk protein synthesis, including increased expression of milk protein transcription and translation factors (68, 69).

Moreover, groundbreaking research published in 2009 has demonstrated that mammary gland sensitivity to insulin varies throughout the reproductive cycle due to differential gene expression of the insulin receptor (INSR)[5] isoforms *INSR-A* and *INSR-B* (70, 71). It has been established across a variety of tissues that INSR-A predominates during cell growth and either insulin or insulin-like growth factor II (IGF-II) binding to INSR-A activates the guanosine triphosphatase protein (Ras)-MAPK signaling pathway, which directs cell proliferation (72, 73). In contrast, INSR-B is highly specific for insulin and predominates in metabolically active tissue (e.g., liver, muscle, and adipose). The insulin/INSR-B ligand directs nutrient metabolism through the phosphatidylinositol-3-OH kinase-protein kinase B α (PI3-Akt) signaling pathway (72). Accordingly, it was shown in a murine model that *INSR-A* (along with *INSR-A*) gene expression predominated during early pregnancy (70, 71). Furthermore, Berlato and Doppler (70) showed that gene expression for *INSR-B* increased 2.5-fold specifically during lactation and demonstrated that this isoform is the primary route for stimulating milk protein gene transcription and translation. Thus, Berlato and Doppler's work shows that the mammary gland transitions from being IGF sensitive during early pregnancy when most ductal growth occurs to becoming highly sensitive to insulin specifically during lactation (70).

This work was recently built upon by Neville et al. (74) by using an insulin receptor knockout murine model to block insulin receptor gene expression specifically in the mammary gland. On the basis of her earlier work (63), Neville hypothesized that mammary differentiation into specialized milk-making cells would not be affected by knock down of the insulin receptor specifically in the mammary gland because, rather than insulin, she postulated that IGF pathways direct mammary differentiation. Contrary to their hypothesis, Neville et al. observed that a wide array of genes involved in mammary differentiation and milk synthesis were significantly downregulated in the IRKO mouse, including genes involved in milk lipid synthesis, milk protein synthesis, milk fat globule formation, and milk lactose synthesis. Coming full circle from her earlier work (63), Neville and co-authors recently concluded that the interaction of insulin with its receptor is critical to normal mammary differentiation, and by implication, milk secretion. Perhaps it is not circulating concentrations of insulin or glucose per se that hinders milk production (as examined in the 1980s and 1990s), but instead the combined net effect of insulin resistance and waning insulin secretion on insulin-sensitive signaling directly at the level of the lactocyte that impedes the rate of milk synthesis.

Insulin signaling in the human mammary gland. Human milk fat globules are a rich source of mammary epithelial cell mRNA, providing an opportunity to examine mammary gene expression in the human mammary gland without invasive breast biopsy (75). We recently published the first RNA-sequenced transcriptome analysis of mammary mRNA isolated from human milk during the transition from producing small amounts of colostrum to copious milk production (76). Mirroring the above rodent studies, we observed strong modulation of insulin-sensitive genes across lactation (cluster trajectory analysis, $P < 0.00008$). For example, *INSR* and its downstream metabolic signals [insulin receptor substrate 1 (*IRS1*), protein kinase B α (*AKT1*), and 43 other genes] increased dramatically during the transition to copious milk output, whereas gene expression for the IGF-II receptor (IGF2R) declined. Furthermore, insulin-like growth factor binding protein 2 (IGF2BP2), a known suppressor of IGF-II signaling, was dramatically

[5] Abbreviations used: AKT1, protein kinase B α; IGF-II, insulin-like growth factor II; IGF2BP2, insulin-like growth factor binding protein 2; IGF2R, insulin-like growth factor receptor 2; INSR, insulin receptor; IRS1, insulin receptor substrate 1; PI3-Akt, phosphatidylinositol-3-OH kinase-protein kinase B α; Ras, guanosine triphosphatase protein.

upregulated. Thus, human mammary gene expression patterns portray downregulation of mammary growth and upregulation of mammary metabolism during the onset of lactation, paralleling Berlato and Doppler's (70) results in a murine model.

Will improving insulin action improve milk production? Low milk supply is a frequently cited reason why mothers stop breastfeeding earlier than planned (77, 78), and this is especially true for obese mothers (20). The long-held dogma has been that women's milk supply concerns are a result of maternal misperception rather than true physiologic inability to lactate (79). However, given the current obesity epidemic and emerging evidence of a role for insulin in milk production, physiologic low milk supply may be an increasingly more common reality. Other than advising mothers to increase the frequency and thoroughness of breast emptying, there are no evidence-based strategies for helping mothers to increase milk supply (80).

If insulin plays an important role in milk synthesis, will improving insulin action be an effective strategy for improving milk production? If so, it would open up an entirely new set of strategies for improving milk production in vulnerable women. For example, health-promoting lifestyle interventions such as the Diabetes Prevention Program (81); interventions that lower maternal cortisol (a suppressor of insulin action), such as childbirth support (27) and skin-to-skin care of the newborn (82); and pharmacologic approaches, such as metformin, may offer promise.

It is intriguing to examine traditional galactogogues in this context. The first-line antidiabetic agent metformin was derived from the medicinal plant *Galega oficialis* (83). The name combines the Latin roots for "milk" (*gal*) and "goat" (*ega*), because it was known that feeding this plant would increase milk production in goats and other livestock (common name: goat's rue) (84).

Fenugreek (*Trigonella foenum graecum*) is another interesting case. It is a popular folk remedy for enhancing milk supply (85). High doses of fenugreek also improved glucose tolerance in animal (86, 87) and clinical (88, 89) studies. The latter is perhaps explained by the discovery that fenugreek is a rich source of metformin-like biguanides (83). In Turkish mothers who were randomly assigned to receive fenugreek tea or apple tea during their postpartum stay in the maternity unit, the fenugreek group produced significantly more milk on day 3 (73 ± 54 compared with 39 ± 16 mL/feeding; $P = 0.004$) and their newborns lost less weight ($P < 0.003$) (90). Whether this finding can be confirmed in a larger trial, or in a targeted trial of insulin-resistant women, remains to be explored.

Metformin is a first-line medication prescribed to improve glucose tolerance in type 2 diabetes and is considered compatible with lactation (91), but its effectiveness in improving milk production is not known. Vanky et al. (92) conducted a secondary analysis of predictors of exclusive breastfeeding duration in Norwegian women with polycystic ovary syndrome who were randomly assigned to receive metformin or placebo during pregnancy. Exclusive breastfeeding duration was 4.5 ± 2.8 mo in the metformin group ($n = 98$) and 3.9 ± 2.9 mo in the placebo group ($n = 88$). This small difference was not significant ($P = 0.08$). The researchers, however, did report breast growth during pregnancy to be a strong predictor of exclusive and any breastfeeding duration. Although allocation to the metformin group was not associated with breast size changes, several measures of metabolic health were associated. Women with no increase in breast size during pregnancy were significantly older and had a higher BMI, systolic blood pressure, fasting insulin, and fasting TGs in the first trimester of pregnancy.

An intervention of metformin during pregnancy may not be effective in improving lactation without continued use of metformin into the postpartum period. To examine if metformin might be feasible in boosting milk production in insulin-resistant women already diagnosed with low milk supply, we are currently conducting the MALMS (Metformin to Augment Low Milk Supply) study (clinical trial no. NCT02179788) (93).

Future Directions and Conclusions

Given the long-held dogma that insulin does not play a direct role in lactation, there are critical gaps in our knowledge to be addressed, including elucidating the relative impact of insulin resistance compared with pancreatic β cell function (insulin secretion) and the time point(s) in the lactation cycle most sensitive to intervention. As reviewed here, emerging evidence implicates that impairments in glucose tolerance potentially hinder several stages of lactation, from possibly blunting mammogenesis in early pregnancy (92), impairing the development of differentiated lactocytes during late pregnancy (74), delaying the onset of lactogenesis (9, 17), and impeding the rate of milk production in mature lactation (54, 76).

An impartial review by the Agency for Healthcare Research and Quality on the benefits of breastfeeding to mothers and infants concluded that mothers who lactate have a lower risk of type 2 diabetes, breast cancer, and ovarian cancer (5). Studies published since the Agency for Healthcare Research and Quality report provide further evidence that lactation reduces chronic disease burden in mothers, including lower risk of postpartum weight retention (94, 95), type 2 diabetes (96, 97), metabolic syndrome (98–100), and cardiovascular disease (101–103), and results in a more favorable adipokine profile (104). For these reasons, lactation is promoted as a strategy to improve the life-course health of parous women. Yet, the very women who could stand to most benefit from longer durations of lactation may be the least able to do so. Thus, there is a need to progress beyond current knowledge that obese women are generally at risk of lactation difficulties and move toward more specific characterization of underlying physiologic barriers to lactation. Research in this direction could lead to the discovery of novel interventions to support lactation success in vulnerable women and thereby improve health across 2 generations.

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