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# Breastfeeding and Gestational Diabetes

*Renata Saucedo, Jorge Valencia, María Isabel Peña-Cano, Enrique Morales-Avila and Arturo Zárate*

## Abstract

Breastfeeding is recommended as the preferred method of feeding for infants for at least 1 year, because of its multiple immediate and long-term benefits for both the mother and child. Among women with a history of gestational diabetes mellitus (GDM), breastfeeding is associated with increased insulin sensitivity, improved insulin secretion, improved glucose tolerance, and a reduced incidence of type 2 diabetes mellitus (T2DM). Lactation has also been associated with postpartum weight loss, reduced long-term obesity risk, a lower prevalence of the metabolic syndrome, hypertension, and cardiovascular disease. The mechanisms underlying the benefits of breastfeeding for the mother are unclear. However, a role of adipose tissue-produced cytokines (adipokines) has been suggested. Lactation appears to mobilize adipose tissue accrued during pregnancy, and some changes in adipokine levels have been reported. Higher lactation intensity has been associated with lower plasma leptin, a peptide mainly associated with appetite regulation and insulin resistance.

**Keywords:** gestational diabetes, breastfeeding, leptin, insulin resistance, type 2 diabetes mellitus

## 1. Introduction

Breastmilk is the physiologic norm for infant nutrition, offering multiple health benefits and protection for babies and mothers [1–4]. WHO recommends that breastfeeding be initiated within 1 hour of birth, that it continue with no other foods or liquids for the first 6 months of life, and that it be continued with complementary feeding (breastfeeding with other age-appropriate foods) until at least 24 months of age. However, global breastfeeding rates remain far below international targets. In most high-income countries, the prevalence of breastfeeding at 12 months is lower than 20%, and it is highest in sub-Saharan Africa, south Asia, and parts of Latin America [5]. In Mexico, rates of breastfeeding are particularly low, 38.3% of Mexican women initiate breastfeeding soon after giving birth, only 14.4% of these women report exclusively breastfeeding at 6 months postpartum, 35.5% report any breastfeeding at 12 months postpartum, and 14.1% report any breastfeeding at 2 years postpartum. Importantly, breastfeeding rates vary by demographic area and are highest in rural over urban area [6].

Breastfeeding has protective effects on maternal health, including a reduced risk of breast cancer and ovarian cancer, obesity, hypertension, stroke, hyperlipidemia, metabolic syndrome, and type 2 diabetes mellitus (T2DM) [7–11].

One of the strongest risk factors for T2DM is a history of gestational diabetes mellitus (GDM). Among women with a history of GDM, the cumulative risk of developing T2DM at 10 years postpartum ranges from 20 to 50% [12]. Infant feeding method is a modifiable risk factor for the development of diabetes; breastfeeding confers short- and long-term benefits on metabolism reducing the risk of developing T2DM.

Despite the important benefits of breastfeeding, there is evidence to suggest that lower rates of breastfeeding occur in women with GDM and that the duration of breastfeeding is shorter compared with that of healthy mothers [13, 14]. The explanations to account for these rates are higher rates of cesarean sections and neonatal intensive care unit admissions, which include increased recovery time for the mother, prolonged separation of mother and baby, and decreased or delayed bonding [15]. Other factors influencing the lower rates of breastfeeding in GDM are insulin therapy during pregnancy and obesity; women with insulin-treated diabetes have less intention to breastfeed and women with high BMI may have different hormonal patterns, delaying onset of milk production [16, 17].

Insulin treatment is related to severity of GDM, and this marked gestational disturbance in insulin and glucose metabolism may interfere with the hormonal pathways for initiation of lactogenesis. Results from a study of gene expression profiles at different stages of lactation suggested that decreased insulin sensitivity may delay milk production as a result of protein tyrosine phosphatase, receptor type F overexpression in the mammary gland [18].

On the other hand, the GDM treatment with oral hypoglycemic agents has not been related to milk production by the mothers [16]. Glyburide and metformin are the two oral hypoglycemic agents most commonly used during pregnancy, and both are safe with breastfeeding [19].

## **2. Short-term benefits of breastfeeding**

Lactation confers favorable metabolic changes, including lower fasting and postprandial blood glucose, as well as insulin, and triglycerides, and greater insulin sensitivity, and plasma HDL-C [20]. Glucose is diverted for milk production via noninsulin-mediated pathways of uptake by the mammary gland and, thus, lactating women exhibit lower blood glucose [21].

On the other hand, lactation promotes postpartum weight loss [22]; lactogenesis increases maternal total energy expenditure by 15–25% [23]. Prospective studies have reported more rapid weight loss within 6 months postpartum, and lower weight retention at 1 year postpartum [24].

Studies in women with recent GDM report more favorable glucose tolerance and lipid metabolism during 4 months postpartum for lactating compared with non-lactating women [25]. At 6–9 weeks postpartum, the SWIFT cohort in a racially and ethnically diverse group found a dose-response relationship between increasing intensity of lactation and decreasing fasting plasma glucose and both fasting and 2-h insulin, as well as improved insulin sensitivity [26].

In a retrospective cohort among Latinas with recent GDM, Kjos et al. reported 5 mg/dL lower fasting blood glucose for any intensity of lactation versus no lactation, and an improved glucose tolerance determined by the glucose area under the curve from the oral glucose tolerance test (OGTT) [27].

In a recent study of women with previous GDM diagnosed according to the new “International Association of Diabetes and Pregnancy Study Groups” (IADPSG) criteria, that included women with a milder metabolic impairment, breastfeeding for almost 3 months improved the metabolic outcomes, such as fasting and 2 h glycemia at OGTT, an index of insulin resistance (HOMA-IR) and triglycerides [28].

It has been demonstrated that the favorable effects of lactation on glucose metabolism persist after weaning. Chouinard-Castonguay et al., in a cross-sectional study, showed that lactation duration was an independent predictor of fasting insulin concentrations and insulin sensitivity indices up to a mean of 4 years after delivery [29].

### **3. Long-term benefits of breastfeeding**

It has been suggested that a longer duration of breastfeeding is associated with a lower risk of T2DM. However, results in some studies have been inconsistent. Chouinard-Castonguay found that women who reported lactating for >10 months had impaired glucose tolerance less frequently compared with women who lactated for <10 months at 4 years postpartum [29].

In a longitudinal analysis, Buchanan found no difference in the prevalence of diabetes at 11–26 months postpartum [30]. Similarly, Kjos, in a retrospective study, reported that breastfeeding was not associated with the progression to T2DM within a follow-up of 7.5 years after delivery [27], and in a retrospective cohort study, the Nurses’ Health Study, breastfeeding did not affect the risk of diabetes at 14 years [31].

However, of interest, one prospective study that assessed the development of T2DM in women with GDM for up to 20 years after delivery found that breastfeeding reduced the risk of diabetes by 46%; median time to postpartum diabetes was 12.3 years for women who breastfed versus 2.3 years for women who did not breastfeed, independently of maternal BMI and insulin use during pregnancy [32]. Moreover, women who breastfed for >3 months had lower risk of diabetes than women who breastfed for  $\leq 3$  months ( $P = 0.029$ ).

Also, the positive metabolic impact of breastfeeding has been reported in women with mild forms of GDM. A recent study showed that women with glucose intolerance in early postpartum breastfed less often than women with a normal OGTT (69.5 vs. 84.2%,  $p = 0.041$ ) [33].

The discrepancy among the different studies could be a result of the differences in the design of the study, the severity of GDM, diagnosis of T2DM, breastfeeding assessment, follow-up time postpartum sample size, lifestyle behaviors, ethnic characteristics, and, finally, the use of oral contraceptives. Birth control with progestin-only oral contraceptive pills has been associated with an increased risk of T2DM during the first 2 years of use. Kjos reported a threefold increase in the risk of T2DM at 7.5 years postpartum in breastfeeding women with recent GDM. By contrast, use of low dose progestin/estrogen combination oral contraceptive pills during breastfeeding does not increase the risk of T2DM [27].

### **4. Mechanisms in the protective effects of breastfeeding**

The potential mechanisms involved in the protective effects of breastfeeding on glucose metabolism include breastfeeding-related hormones such as prolactin and estrogen [34]. Prolactin levels are elevated and estradiol is lower in breastfeeding

women than in non-lactating women. In vitro experiments of rat pancreatic islets cultured with prolactin have shown enhanced stimulated insulin secretion through stimulation of  $\beta$ -cell proliferation by downregulating the expression of menin [35, 36]. Also, prolactin modulates the transcription factors STAT5 and PPAR $\gamma$ , and the expression of lipoprotein lipase, which are co-expressed in breast, adipose tissue, and skeletal muscle [37].

On the other hand, it has been suggested that lactation improves insulin sensitivity by mobilizing lipids derived from liver and muscle for lactogenesis rather than by redirecting lipids into adipocytes [34].

Another mechanism is the influence of lactation on regional fat tissue metabolism; some studies have reported enhanced fat mass mobilization from the trunk and thighs for lactating women [38, 39]. In keeping with this, another study reported that lactation history is associated with a smaller visceral fat area in women who reported they lactated for at least 3 months [40].

There is also evidence that leptin, which is an adipokine positively associated with body adiposity and insulin resistance, is modified in breastfeeding women with previous GDM [41]. Leptin directly affects whole-body insulin sensitivity by regulating the efficiency of insulin-mediated glucose metabolism by skeletal muscle and by hepatic regulation of gluconeogenesis through its action on gene expression of phosphoenolpyruvate carboxykinase [42, 43]. Moreover, it exerts an acute inhibitory effect on insulin secretion, and upregulates inflammatory mediators like TNF $\alpha$  and interleukin-6, which contribute to excessive insulin resistance both at the level of the whole body and in specific organs, including in the liver, muscle, and brain [44].

Leptin is predominantly produced by adipocytes, but is also produced by non-adipose tissues such as stomach, intestine, ovaries, and in particular, the placenta [45]. Maternal leptin levels increase two- to threefold in pregnancy, with a peak occurring around 28 weeks of gestation and decreasing to pre-pregnancy concentrations after delivery [46]. It has been suggested that the rise in maternal leptin concentration during pregnancy may result from an upregulation of adipocyte leptin synthesis in the presence of increasing insulin resistance and hyperinsulinemia in the second half of pregnancy [47]. However, there is strong evidence that the placenta, rather than maternal adipose tissue, contributes to the increase of maternal leptin concentrations during pregnancy [48]. Leptin induces human chorionic gonadotropin production, regulates placental growth, angiogenesis, trophoblast invasion, and nutrient transfer [49]. Leptin enhances the mobilization of maternal fat stores to increase availability and to support transplacental transfer of lipid substrates [50]. Moreover, leptin upregulates placental System A amino acid transport, to increase fetal nutrient availability [51]. Leptin serves as a mitogen for a growing number of cell types, including endothelial cells, hemopoietic cells, lung epithelial cells, and pancreatic  $\beta$ -cells in vitro [52]. Leptin could therefore be stimulating growth of tissues in the developing fetus.

Leptin contributes to the pathophysiologic relationship between GDM and subsequent T2DM. In our previous study, we found that women with previous GDM persisted with insulin resistance in the postpartum period, in association with higher leptin levels compared with the control group [53]. It is possible that postpartum insulin resistance may be contributing to these elevated levels. A positive association between leptinemia and insulinemia has been reported in numerous studies of obese and non-obese humans [54, 55]. Experimentally, increased insulin levels may stimulate leptin production in adipocytes, and vice versa, an increase in leptin levels may lead to insulin resistance and alter  $\beta$ -cell secretory capacity [56, 57]. Interestingly, we recently reported that breastfeeding was associated with better metabolic profile in the early postpartum period in women with previous

GDM, showing that women with longer duration of lactation had greater weight loss at postpartum and lower leptin levels compared with women who lactated for a short period. This difference remained statistically significant after adjustment for weight [58]. Similarly, a previous study with a large cohort of women with recent GDM that utilized a quantitative measure of lactation intensity found that mean leptin concentrations were inversely associated with lactation intensity (lower by 15–21%) independent of maternal pre-pregnancy obesity, race, weight loss, sociodemographics, and postpartum insulin resistance [41]. It has been suggested that during lactation, prolactin suppresses leptin secretion [59].

On the other hand, leptin is a long-term regulator of appetite that serves as an anorexigenic signal when adipose stores are high [60]. It has been detected in breast milk at concentrations of 0.35–4.6 µg/L [61], and the concentration of leptin in breast milk is correlated to indices of maternal adiposity, including body mass index ( $r = 0.65$ ,  $P < 0.02$ ), and fat mass ( $r = 0.65$ ,  $P < 0.02$ ) [62]. This evidence provides an attractive explanation for the ability of breast milk to regulate infant body weight. Bouret has recently suggested that the presence of appetite hormones may permanently affect the appetite-regulating system of the infant by affecting the development of the hypothalamus. These differences in appetite hormone exposure may create permanent changes in the way the brain reacts to appetite hormones and satiety cues [63].

Another adipokine related to abnormal glucose metabolism during pregnancy is adiponectin. It has been suggested that low levels of adiponectin may induce severe insulin resistance prior to the onset of GDM [64]. Gunderson evaluated the relationship between lactation intensity and plasma adiponectin among postpartum women with previous GDM and found that higher lactation intensity was associated with 6% lower adiponectin. This inverse association remained after adjustment for insulin resistance [41]. This observation is consistent with the action of prolactin in suppressing the production and secretion of adiponectin from human adipocytes [13].

## **5. Implications of breastfeeding in the offspring of the GDM mother**

Infants of mothers with GDM are at increased risk of prematurity, macrosomia, hypoglycemia, respiratory distress, hypocalcemia, polycythemia, and hyperbilirubinemia. Breastfeeding has many established benefits for child health; it prevents child morbidity due to diarrhea, respiratory infections, and otitis media [5]. In particular, in the offspring of the GDM mother, lactation has been associated with lower episodes of hypoglycemia [65].

On the other hand, exposure to maternal gestational diabetes has been shown to increase the risk of obesity, childhood-onset type 2 diabetes in offspring, as well as the risk of adult-onset type 2 diabetes and gestational diabetes in those offspring [66]. Breastfeeding confers protection against these medical complications; exclusive breastfeeding decreases the risk of the development of childhood-onset type 2 diabetes and obesity [67].

Benefits of breastfeeding on children's health are likely due to the unique composition of breast milk. Human milk is a source of immunoglobulins, hormones and growth factors including leptin, adiponectin, ghrelin, peptide YY, glucagon-like peptide-1, resistin, and obestatin, which are involved in food intake regulation and energy balance, and may have a role in the regulation of growth and development in the neonatal period and infancy, as well as long-term effects on metabolic programming [68].

## **6. Suggestions for mothers with GDM regarding breastfeeding**

Women whose pregnancy is affected by GDM should be educated early as to the benefits of breastfeeding their offspring. An increase in breastfeeding duration among women with GDM has been demonstrated with prenatal education. Breastfeeding support in the hospital immediately after delivery and during the postpartum period as well as community support that encourages breastfeeding are also essential. Electronic alerts via text message or email, automated letters, and nurse phone contact may increase uptake. This targeted breastfeeding support for women with GDM is feasible and efficacious, and could be integrated into GDM management [69].

Likewise, insulin treatment during pregnancy should be considered a targeting indicator for providing extra skilled breastfeeding support to GDM women who decide to breastfeed [16].

## **7. Conclusions**

Breastfeeding is recommended and encouraged for mothers, as it has multiple benefits for both women and children. Mothers who breastfeed have been shown to have reduced risk of developing subsequent breast cancer and ovarian cancer, obesity, hypertension, stroke, hyperlipidemia, metabolic syndrome, and T2DM. In women with GDM, several studies suggest that breastfeeding is associated with reduced risk of T2DM. Despite this important benefit, there is evidence to suggest that lower rates of breastfeeding occur in women with GDM. Evidence has shown that healthcare provider support of breastfeeding along with patient education has a significant impact on breastfeeding rates. The medical and behavioral communities should be better able to design, implement, and administer public health programs that may promote healthy lifestyle behaviors including breastfeeding among GDM women, and mitigating T2DM risk.

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## **Conflict of interest**

The authors declare that there is no conflict of interests regarding the publication of this chapter.

## **Thanks**

This chapter is dedicated to the memory of Dr. Arturo Zárate (1936–2018), pioneer in the field of Gynecological Endocrinology in Mexico.

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