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Annals of Pregnancy and Care

Short Communication

Colostral Metabolites as Indicators of Lactogenesis II in Women with Gestational Diabetes Mellitus

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Submitted: 02 March 2017

Accepted: 27 March 2017

Published: 31 March 2017

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Keywords

- Breastfeeding
- Colostrum
- Gestational diabetes mellitus
- Lactation

Abstract

Background: Breastfeeding is beneficial for maternal-infant dyads affected by gestational diabetes, although women with gestational diabetes often have lower breastfeeding rates and face more challenges with early breastfeeding than non-diabetic women. Metabolite concentration shifts of lactose and citrate indicate the transition to secretory activation and increased milk production of lactogenesis II.

Objectives: To compare differences in specific colostral metabolite levels, including lactose and citrate concentrations, of women with and without gestational diabetes.

Methods: Prospective case-control composition analysis of colostrum of 19 postpartum women with gestational diabetes and 31 postpartum non-diabetic women.

Results: Composition analyses revealed significantly lower concentrations of specific metabolites at 72 hours postpartum in colostral samples of women with gestational diabetes compared to non-diabetic women: mean (SD) glucose μM (5.8(0.6) versus 6.3(0.8), 95% CI 0.06, 0.88),mean (SD) lactose mM (142.4(49.8) versus 176.7(38.9), 95% CI 0.88, 55.96),mean (SD) glucose-6-phosphate μM (4.2(0.6) versus 4.5(0.5), 95% CI 0.02, 0.72), and median (IQR) citrate mM (3.4(2.1) versus 5.5(2.5), 95% CI 1.00, 4.47).

Conclusions: Compared to non-diabetic women, lower levels of specific colostral metabolites within 72 hours of delivery may indicate delayed secretory activation among women with gestational diabetes, suggesting a biological mechanism associated with lower exclusive breastfeeding rates among women with gestational diabetes.

ABBREVIATIONS

GDM: Gestational Diabetes Mellitus

INTRODUCTION

Prevalence rates of gestational diabetes mellitus (GDM) have been increasing globally, elevating the urgency to address lactation among maternal-infant dyads affected by GDM. Research has suggested that benefits of early, frequent, and longer duration of breastfeeding in women with GDM includes reduced risk of maternal type 2 diabetes [1,2] and reduced risk of infant hypoglycemia [3]. Exclusive breastfeeding for the first six months of life is recommended based on evidence from research around the world [4]. However, epidemiologic research has found that women with GDM have lower exclusive breastfeeding rates than non-diabetic women [5].

The transition to secretory activation, also known as lactogenesis II, involves a shift in the milk production process. Following placental expulsion, progesterone levels decrease and prolactin levels increase [6]. Secretory activation is characterized by the initiation of copious milk production along with milk component concentration shifts [6]. During transition, milk production volume increases from approximately 30 mL on the first postpartum day to approximately 500 mL by day four and is perceived by women as their milk "coming in" [6,7]. According to maternal self-report, lactating women typically experience an increase in breast fullness at 36 to 96 hours postpartum [7], with

72 hours considered the cutoff for delayed lactogenesis II [8,9].

Biochemical markers in milk indicate the initiation of secretory activation through decreasing sodium, chloride, and total nitrogen levels and increasing lactose, glucose, and citrate levels [7,10,11]. Mammary glucose uptake is essential in lactose synthesis which is critical in milk production. Glucose is phosphorylated to glucose-6-phosphate prior to conversion to uridine diphosphate galactose; thereafter both glucose and uridine diphosphate galactose are used to synthesize lactose in the Golgi membrane [12]. Lower concentrations of glucose and glucose-6-phosphate in milk of women with GDM are consistent with lower milk lactose concentrations. As an osmolyte, lactose draws water into the alveoli thereby increasing milk volume [13]. Increased serum insulin levels relative to serum glucose levels associated with glucose tolerance were associated with maternal report of breast fullness, suggesting an earlier shift to secretory activation based on metabolic status of primipara women [14]. Hormonally, milk prolactin levels of diabetic women were significantly lower within the first week postpartum compared to non-diabetic women [15]. Confounding factors and co-morbidities negatively associated with breastfeeding should also be considered in delayed transition to secretory activation among diabetic women [16].

Research on timing of lactation-related breast fullness and diabetes has been primarily conducted with pregestational diabetic women. Compared to non-diabetic women, women with type 1 diabetes have a higher incidence of delayed lactogenesis by approximately a day [10,11]. In a retrospective observational study of 883 women with GDM, 33% reported delayed lactogenesis based on perceived breast fullness with a higher likelihood among those who were obese, older, required insulin, and had suboptimal early breastfeeding. Since there was no non-diabetic control group for comparison, 72 hours served as the proxy for normal versus delayed lactogenesis [9]. Similarly, a qualitative study of postpartum women who had GDM reported perceived a delay in their milk "coming in" [17].

While maternal reports suggest that women with GDM experience perceived delay in their milk "coming in" and breast fullness, there is a lack of biochemical research validating these subjective self-reports. A primary objective was to examine and compare colostral metabolite levels of women with and without GDM within the first 72 hours postpartum and to link compositional changes to possible metabolic events in the mammary gland which may explain differences in the timing of perceived milk "coming in" among women with GDM.

MATERIALS AND METHODS

The current study involves metabolite analysis of a subset of participants from a larger prospective case-control study of 67 GDM and non-diabetic postpartum breastfeeding women. Based on inclusion and exclusion criteria of the current study, women who expressed milk after 72 hours (n=13) or had insufficient colostral samples (n=4) were excluded, thereby resulting in the final sample of 50 women, 19 with GDM and 31 without diabetes. The women had delivered a singleton, term (>37 weeks' gestation) infant in an Israeli medical center and were fluent in English, Hebrew, or Arabic. Potential participants were identified by the medical, nursing, or lactation staff on the postpartum unit with identification of women with GDM based on hospital records of GDM diagnosis according to prenatal results of 75-gram oral glucose challenge test of >153 mg/dL plasma glucose at two hours or >180 mg/dL plasma glucose at one hour. Maternal biometric, maternal metabolic data, infant assessment parameters, and feeding patterns were collected from the medical records; sociodemographic, lactation experience, and lactation perception were collected from maternal report using questionnaires. Colostrum samples of approximately 5 ml were collected by postpartum women with guidance by a lactation consultant using hand expression or pumping within an average time of 1.8 days (range 0.79 to 3.0) and were stored in a -70^{0}C freezer in the hospital until transport on dry ice to the affiliated university laboratory for enzymatic analysis.

The metabolites measured using enzymatic reactions included citrate, L-lactate, malate, glucose, glucose-6-phosphate and β-hydroxybutyrate. The concentrations of citrate, L-lactate, malate, glucose, glucose-6-phosphate and β-hydroxybutyrate were determined in whole milk samples by classical enzymatic reactions using dehydrogenases (NAD^+-depended oxidoreductases) coupled to conversion of NAD^+ into $NADH+H^+$ [18-20]. Statistical analyses were conducted using SPSS version 21 for Windows (SPSS, Chicago, Illinois) and significance level was set at $p < 0.050$. Descriptive analyses were conducted to examine differences in colostral metabolite levels between the two primary groups, women with GDM and non-diabetic women. Log-transformation was necessary to normalize the skewed distribution of certain biochemical variables. Depending on sample size, chi-squared tests or Fisher's exact tests were used to examine differences between proportions in categorical measures and t-tests or Kruskal-Wallis tests were conducted to compare mean differences in the continuous variables of the GDM and non-diabetic women. This study was approved by the medical center's Institutional Review Board and women signed informed consent prior to participation.

RESULTS AND DISCUSSION

Among the 50 samples in the current study, 31 belonged to non-diabetic (62.0%) and 19 belonged to GDM women (38.0%), all of whom delivered a term infant and initiated breastfeeding while in the hospital. Examining significant differences in group characteristics, compared to women without diabetes, GDM women were older by nearly 3 years (p=0.030) and had a higher proportion of perceived delay in their milk "coming in" (p=0.018), while there was no statistically significant difference in mean years of education (16.1 versus 16.7), cesarean delivery (16.1% versus 10.5%), primiparity (3.2% versus 15.8%), and pre pregnancy body mass index (BMI) (24.1 versus 27.3).Only infants born to women with GDM experienced neonatal hypoglycemia (blood glucose levels <45 mg/dL) (p <0.001) and a higher proportion of the infants born to GDM women received formula during the postpartum hospital stay (p=0.050).

Composition analyses revealed significantly lower colostral concentrations of glucose, lactose, glucose-6-phosphate, and citrate within the first 72 hours among GDM compared to non-diabetic women (Table 1). After excluding primipara women to minimize potential confounding, only glucose (5.8(0.6) versus

Table 1: Mean differences in metabolites between non-diabetic (ND) and gestational diabetes mellitus (GDM) women (31 and 19, respectively, except where indicated)

Metabolite (n=ND, n=GDM)	Non-diabetic	GDM	95% CI
	Mean (SD)	Mean (SD)	
Lactose mM (27, 19)	176.7(38.9)	142.4 (49.8)	0.88, 55.96*
Galactose μM (28, 18)	281.5(251.0)	367.7 (311.7)	-247.63, 79.20
Glucose-6-phosphate[1] μM (28, 19)	4.5 (0.5)	4.2 (0.6)	0.02, 0.72*
Glucose[1] μM (28, 19)	6.3 (0.8)	5.8 (0.6)	0.06, 0.88*
	Median (IQR)	Median (IQR)	
β-hydroxybutyrate[2] μM (23, 9)	230.0 (333.0)	510.0 (506.0)	-579.00, 137.00
Lactate[2] μM (22, 7)	643.0 (477.5)	963.0 (311.0)	-436.00, 67.00
Malate[2] μM (17, 5)	766.0 (1475.0)	1598.0 (3331.5)	-2653.00, 275.00
Citrate[2] mM (23, 9)	5.5 (2.5)	3.4 (2.1)	1.00, 4.47*

[1] Log-transformed variables
[2] Due to small sample size, the 95% CI were calculated using Kruskal-Wallis test
*p<0.05
Abbreviations: ND = non-diabetic; GDM = gestational diabetes mellitus; CI = confidence interval; IQR =interquartile range

6.3(0.8) μM, 95% CI 0.06, 0.95) remained significantly lower.

This novel research examined the differences in colostral metabolite concentrations and maternal report of perceived milk "coming in" based on diabetic status. There were significantly lower levels of colostral lactose, glucose, glucose-6-phosphate, and citrate concentrations among women with GDM compared to non-diabetic women suggesting that GDM is associated with delayed secretory activation, supporting the current findings and previous reports which validate GDM women's perception of a delay in their milk "coming in." A perception of delayed milk "coming in" may increase the risks of poor breastfeeding outcomes and lower exclusive breastfeeding rates in women with GDM. These reduced metabolite concentrations in GDM compared with non-GDM women's colostrum suggest a slower shift in the metabolic pathways associated with onset of lactation, although timing of collection should be considered. Lower lactose levels portend delayed secretory activation among GDM women which suggests a biological mechanism associated with lower breastfeeding rates among GDM women. Glucose uptake by mammary epithelial cells is typically enhanced at the onset of secretory activation which can be utilized by either pentose phosphate shunt to produce reducing agents for lipogenesis, lactose synthesis, or glycolysis [21]. These results show that these pathways were delayed or inhibited with GDM, as manifested by the reduced concentrations of major metabolites in the processes, specifically glucose, glucose-6-phosphate, lactose, and citrate.

Even after primipara women were excluded to minimize potential confounding based on parity, metabolites indicating transition to secretory activation remained lower in women with GDM. Reported maternal perception also suggested delayed transition to lactogenesis II in GDM women, although the biochemical validation requires stricter adherence to collection timing. The study results support previous findings of delayed changes in lactose and citrate levels in women with pregestational insulin dependent diabetes [10] and reports of perceived delayed lactogenesis among women with GDM [9,17]. Lower levels of colostral lactose and citrate concentrations among women with GDM compared to non-diabetic women suggest that GDM is associated with delayed secretory activation which can increase the risks of poor breastfeeding outcomes among maternal-infant dyads affected by GDM.

Delayed secretory activation can be evidenced by early maternal lactation insufficiency, delayed transition to copious milk production, or infant intake insufficiency and is associated with poor breastfeeding outcomes [22]. Women who feel that their infants are unsatisfied after breastfeeding are more likely to supplement with formula and may cease breastfeeding [22]. Resorting to formula contributes to a further decrease in milk production, thereby sabotaging breastfeeding efforts [23]. The regulation of milk production during secretory activation occurs with nutritive sucking or manual milk removal [7]. Thus, maternal-infant separation, late initiation of breastfeeding, and supplementation can negatively impact milk supply and breastfeeding effort.

A study limitation is the variability in timing of the one-time milk collection such that women who expressed milk after 72 hours postpartum were excluded from the analyses for the current study. To overcome this limitation, standardization of collection timing should be employed in future research. Nonetheless, the study findings point to the influence of diabetic status on postpartum timing of metabolite levels and the validation of maternal perception of delayed milk "coming in." Rates of GDM are increasing and addressing the specific issues of this population is important to promote maternal-infant health.

CONCLUSION

It is imperative to identify and address early lactation challenges faced by women with GDM as the prevalence of GDM has been increasing. Lower levels of colostral lactose and citrate concentrations among women with GDM compared to non-diabetic women suggests that GDM is associated with delayed secretory activation, supporting previous reports of GDM women's perception of delayed secretory activation, which can increase the risks of poor breastfeeding outcomes in

women with GDM. Future clinical and biochemical research of human milk should account for timing of collection and further examine factors associated with early lactation in a larger sample of women with GDM to develop approaches to breastfeeding support in this at-risk population.

ACKNOWLEDGEMENTS

The authors thank West Virginia University for financial support and Dr. Smadar Eventov-Friedman and Ms. Lissey Sherby at Hadassah Medical Center for assistance with participant recruitment and data collection.

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Cite this article

Chertok IRA, Haile ZT, Silanikove N, Argov-Argaman N (2017) Colostral Metabolites as Indicators of Lactogenesis II in Women with Gestational Diabetes Mellitus. Ann Pregnancy Care 1(1): 1001.