

# Maternal prepregnancy obesity and insulin treatment during pregnancy are independently associated with delayed lactogenesis in women with recent gestational diabetes mellitus<sup>1–4</sup>

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## ABSTRACT

**Background:** The timely onset of stage II lactogenesis (OL) is important for successful breastfeeding and newborn health. Several risk factors for delayed OL are common in women with a history of gestational diabetes mellitus (GDM), which may affect their chances for successful breastfeeding outcomes.

**Objective:** We investigated the prevalence and risk factors associated with delayed OL in a racially and ethnically diverse cohort of postpartum women with recent GDM.

**Design:** We analyzed data collected in the Study of Women, Infant Feeding and Type 2 Diabetes After GDM Pregnancy (SWIFT), which is a prospective cohort of women diagnosed with GDM who delivered at Kaiser Permanente Northern California hospitals from 2008 to 2011. At 6–9 wk postpartum, delayed OL was assessed by maternal report of breast fullness and defined as occurring after 72 h postpartum. We obtained data on prenatal course and postdelivery infant feeding practices from electronic medical records and in-person surveys. We used multivariable logistic regression models to estimate associations of delayed OL with prenatal, delivery, and postnatal characteristics.

**Results:** The analysis included 883 SWIFT participants who initiated breastfeeding and did not have diabetes at 6–9 wk postpartum. Delayed OL was reported by 33% of women and was associated with prepregnancy obesity (OR: 1.56; 95% CI: 1.07, 2.29), older maternal age (OR: 1.05; 95% CI: 1.01, 1.08), insulin GDM treatment (OR: 3.11; 95% CI: 1.37, 7.05), and suboptimal in-hospital breastfeeding (OR: 1.65; 95% CI: 1.20, 2.26). A higher gestational age was associated with decreased odds of delayed OL but only in multiparous mothers (OR: 0.79; 95% CI: 0.67, 0.94).

**Conclusions:** One-third of women with recent GDM experienced delayed OL. Maternal obesity, insulin treatment, and suboptimal in-hospital breastfeeding were key risk factors for delayed OL. Early breastfeeding support for GDM women with these risk factors may be needed to ensure successful lactation. This trial was registered at [clinicaltrials.gov](http://clinicaltrials.gov) as NCT01967030. *Am J Clin Nutr* 2014; 99:115–21.

## INTRODUCTION

The timing of the onset of copious milk production is important for successful breastfeeding and newborn health. However, few studies have examined whether abnormal maternal glucose metabolism during pregnancy delays milk production in the first days postpartum. Stage I lactogenesis occurs during pregnancy when the mammary gland starts producing small

quantities of colostrum (1). Later, during the first few days postpartum, the onset of copious milk secretion, which is known as stage II lactogenesis, takes place. The production of milk during the first day postpartum is low (<100 mL/d), but a substantial increase in milk volume normally occurs between 36 and 92 h postpartum, which is typically noticed by the mother and is the hallmark of stage II lactogenesis (2).

Delayed onset of stage II lactogenesis (OL)<sup>5</sup> is usually defined as OL after 72 h (3 d) postpartum, and its incidence in the US is high (23–44%) (3–5). Factors associated with an increased risk of delayed OL in developed countries include primiparity (5–9), maternal overweight and obesity (4, 5, 10, 11), prolonged stage II labor (4, 5), use of labor pain medications (7), cesarean delivery (5, 7, 8), particularly an urgent one (4), stress during labor and delivery (6, 12), flat or inverted nipples (5) or lack of nipple discomfort (11), infant birth weight (4, 11), nonoptimal infant breastfeeding behavior (11), milk-based preonset supplementation (4), maternal insulin-dependent type 1 diabetes (13), and, more recently, gestational diabetes mellitus (GDM) (14). Several of these risk factors are more common in women with a history of GDM [eg, prepregnancy overweight and obesity (15, 16) and cesarean delivery (17)]. The provision of supplemental formula feedings as medical management of neonatal hypoglycemia ([primarily in large-for-gestational-age babies (17)] may also

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<sup>5</sup> Abbreviations used: GDM, gestational diabetes mellitus; OL, onset of stage II lactogenesis; SWIFT, Study of Women, Infant Feeding and Type 2 Diabetes After GDM Pregnancy.

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occur more frequently in this population. Each of these issues may contribute to increased risk of delayed OL in GDM women as observed by Nommsen-Rivers et al (14). The identification of risk factors for delayed OL in this population could help to prevent a shorter breastfeeding duration (18, 19) and excess neonatal weight loss (defined as  $\geq 10\%$  of birth weight by day 3 postpartum) (5) and would also enable GDM women who intend to breastfeed to experience benefits of lactation for their own future health and that of their offspring (20–22).

Thus, by using data from the Study of Women, Infant Feeding and Type 2 Diabetes after GDM Pregnancy (SWIFT), we conducted the current study to 1) estimate the incidence of delayed OL in women with a history of GDM, 2) assess the independent relations of maternal prepregnancy weight status and severity of GDM to risk of delayed OL, and 3) identify other potential risk factors for this outcome in GDM women.

## SUBJECTS AND METHODS

The SWIFT is a prospective cohort study that enrolled women with recent GDM at 6–9 wk postpartum and assessed glucose tolerance via the 2-h 75-g oral-glucose-tolerance test at baseline and annually thereafter. The study was designed to test the hypothesis that a longer duration of lactation reduces the risk of type 2 diabetes in the first 2 y postpartum in this high-risk population. A detailed description of the SWIFT study design and methods has been previously published (23).

### Study population

Briefly, the SWIFT cohort includes 1035 women enrolled between September 2008 and December 2011 who had been diagnosed with GDM via the 3-h 100-g oral-glucose-tolerance test by using the criteria of Carpenter and Coustan (24) before 32 wk gestation. The SWIFT cohort is racially and ethnically diverse with  $\sim 35.3\%$  Asian, 7.6% African American, 31.0% Latina, 23.1% white, and 1.9% of other racial and ethnic groups. The SWIFT inclusion criteria were as follows: 1) prenatal care and delivery of a singleton, live birth  $\geq 35$  wk gestation within the Kaiser Permanente Northern California system; 2) mothers who were 18–42 y old at delivery and free of serious medical conditions; 3) signed informed consent and completed study questionnaires for the baseline visit; 4) not taking medications that inhibit lactation postdelivery or affect glucose tolerance; and 5) a reported intention to breastfeed. Additional inclusion criteria for this particular study included 1) initiated breastfeeding and 2) data available on the outcome variable.

### Data collection and data sources

SWIFT data were collected through in-person interviews and assessments, telephone calls, electronic medical records, and laboratory tests as described elsewhere (23). Lactogenesis II was assessed by maternal perception of the onset of lactation, which is considered a valid clinical indicator of lactogenesis II (25, 26) and is widely used in this research arena (5, 19, 27, 28); this indicator has shown reasonable degrees of sensitivity and specificity (71.4% and 79.3%, respectively) compared with those with repeated test weighing, which is the gold-standard measurement of lactogenesis II (25). Thus, SWIFT participants were asked to indicate on what day postpartum (by using 24-h in-

crements) they first felt that their breasts were noticeably fuller than before giving birth. Breast fullness is a common symptom reported by women as a cue for OL (26, 28).

In addition, data from the Kaiser Permanente in-patient records, perinatal databases, and electronic medical records (known as Health Connect) were extracted for participants. Specifically, the prepregnancy medical history, pregnancy course, labor and delivery, perinatal outcomes, and newborn and in-hospital infant feeding information were obtained from SWIFT study in-person interviews and the Kaiser Permanente electronic medical records.

### Definition of variables

The main outcome of the study (ie, delayed OL) was defined as the onset of breast fullness that occurred after 72 h postpartum. Of exposure variables, we calculated pregravid BMI (in  $\text{kg}/\text{m}^2$ ) and classified women by 2009 Institute of Medicine BMI categories (underweight:  $< 18.5$ ; normal:  $\geq 18.5$  to  $< 25.0$ ; overweight:  $\geq 25.0$  to  $< 30.0$ , and obese  $\geq 30.0$ ) at conception or early pregnancy; however, because of a very small number of subjects in the underweight category, we combined underweight and normal categories for the analysis. An excessive gestational weight gain was defined by using BMI and according to 2009 Institute of Medicine recommendations (underweight: 28–40 lb or 12.7–18.1 kg; normal: 25–35 lb or 11.3–15.9 kg; overweight 15–25 lb or 6.8–11.3 kg; and obese: 11–20 lb or 5.0–9.1 kg). We also calculated the percentage of recommended pregnancy weight gain, whereby values  $< 100$  indicated gaining less weight than the lower end of the recommended range, whereas values  $> 100$  indicated gaining more than the upper end of the recommended range. We grouped race and ethnicity into the following 5 categories: non-Hispanic white, non-Hispanic black, Hispanic, Asian, and other; however, for a multivariate analysis we combined blacks, Asians, and subjects in the other category into a non-Hispanic, nonwhite category.

We created a variable for the treatment of GDM with 3 categories as follows: only diet treatment, oral hypoglycemic medication, or treatment with insulin; these categories represent the severity of the GDM condition from less to more severe. We assessed infant feeding intentions during pregnancy as described previously (23). The duration of labor was self-reported in hours and dichotomized at the median value for analysis; this categorical variable included a category for women who indicated that they did not go into labor. We also obtained in-hospital breastfeeding scores by using the LATCH scoring system (29) that is widely used in clinical settings mainly because of its simplicity as well as its significant association with breastfeeding duration (30, 31), which makes it a useful tool for targeting early breastfeeding support in a clinical setting. The LATCH scoring system assigns a numerical value (0, 1, or 2) to 5 key areas of breastfeeding identified by the letters of the acronym LATCH; thus, L is for how well the infant latches onto the breast, A is for the amount of audible swallowing noted, T is for the mother's nipple type and condition, C is for the mother's level of comfort, and H is for holding, or the breastfeeding position used by the mother, and the amount of help the mother needs to hold her infant to the breast (29). The total score ranges from 0 to 10, with higher scores representing more successful breastfeeding. For this analysis, we used a composite score by averaging all LATCH scores obtained within the first 24 h after birth; we

dichotomized the average of the LATCH scores at the median value whereby scores below the median value reflected less successful in-hospital breastfeeding.

Newborn variables included gestational age (in wk), birth weight (in g), size at birth (large-, small-, and appropriate-for-gestational-age), Apgar score, and sex. Maternal postpartum characteristics were assessed at 6–9 wk postpartum (enrollment) by in-person interviews, anthropometric measurements, and bioelectrical impedance analysis, as described elsewhere (23).

### Statistical analysis

Descriptive statistics to characterize the sample included frequency distributions for categorical data and means and SDs for all continuous data. We used Pearson's chi-square or Fisher's exact tests to examine bivariate associations between outcome and categorical variables and *t* tests to examine bivariate associations between outcome and continuous variables. We used logistic regression techniques to obtain point and interval estimates of association (ORs) between risk factors of interest and delayed OL. We developed a logistic regression model by adding variables on the basis of a priori hypotheses and significant *P* values from bivariate analyses. We started by entering the main effect of prepregnancy weight status (model 1). We included maternal sociodemographic variables (model 2), and continued to add covariates measuring labor and delivery and newborn and early infant feeding variables (model 3). The variables labor duration and cesarean delivery were entered into the model alternatively because they were highly correlated. Because results were similar with either variable in the model, we presented (model 3) and kept only one of the 2 variables. We further adjusted by GDM treatment (model 4) to determine whether prepregnancy weight status was independently associated with the delayed OL after accounting for GDM severity. Finally, we tested 2-way interaction terms between parity and other covariates by using a cutoff of *P* < 0.10 for statistical significance. The final model (model 5) included all variables in model 4 plus an interaction term for newborn gestational age and parity. Logistic regression models included variables associated with the outcome at a 0.05 significance level. However, we also kept in the models factors that have been consistently associated with delayed OL in the scientific literature regardless of their significance level. We also conducted a sensitivity analysis in a subsample of participants (*n* = 607) that included those with information on infant feeding intentions. With the use of this reduced sample, we ran our final logistic regression model again, first without the infant feeding intentions variable and, then, with that variable in the model. Data were analyzed with SAS software (version 9.3; SAS Institute Inc).

### RESULTS

A total of 883 of 1035 SWIFT participants were included in this analysis. Sample characteristics are shown in **Table 1**. Overall, 77% of women were from minority groups, and the same proportion had some college education or higher (started or completed college or postgraduate degree). Average maternal prepregnancy BMI was  $29.3 \pm 7.0$ ; however, 7 women were underweight (because of the small number of underweight women, they were included in the normal-weight category for

additional analysis). In women who went into labor (*n* = 761), the average duration of labor was  $12.0 \pm 11.5$  h. Newborns were, on average,  $38.7 \pm 1.1$  wk gestational age and weighed  $3400 \pm 484$  kg at birth, and less than 5% of them were preterm. In this GDM population, 33% of women experienced delayed OL.

Results of a bivariate analysis between delayed OL and exposures of interest are also shown in Table 1. Higher education, higher prepregnancy BMI (as a continuous variable), longer labor duration, and lower LATCH scores were associated with delayed OL. In addition, delayed OL was more common in women who were primiparous, were prescribed insulin during pregnancy, and had a cesarean delivery. Subjects who were Hispanic (compared with non-Hispanic) or a Special Supplemental Nutrition Program for Women, Infants, and Children recipient had lower rates of delayed OL. No newborn variable was associated with delayed OL in the bivariate analysis (Table 1). Consistent with results for prepregnancy weight status, higher maternal postpartum BMI (as a continuous variable) and percentage body fat were associated with delayed OL.

Logistic regression models are presented in **Table 2**. Multivariate logistic regression results indicated that prepregnancy obesity was independently associated with increased odds of delayed OL in women with a history of GDM (OR: 1.56; 95% CI: 1.07, 2.29; *P* = 0.0421). Higher maternal age (OR: 1.05; 95% CI: 1.01, 1.08; *P* = 0.0048) and lower LATCH scores in the first 24 h (reflecting less successful in-hospital breastfeeding) were also associated with increased odds of experiencing delayed OL (OR: 1.65; 95% CI: 1.20, 2.26; *P* = 0.0020). The inclusion of GDM treatment in the model did not attenuate the strength of the association between prepregnancy weight status and delayed OL, but insulin prescribed as treatment (indicating a greater severity of GDM as compared with diet modification only) was also strongly independently associated with increased odds of delayed OL (OR: 3.11; 95% CI: 1.37, 7.05; *P* = 0.0076). A 1-wk increase in gestational age in newborns of multiparous women (but not of primiparous ones) was associated with decreased odds of delayed OL (OR: 0.79; 95% CI: 0.67, 0.94).

Finally, results from our sensitivity analysis in a smaller sample of participants with data of infant feeding intentions (*n* = 607) suggested that infant feeding intentions did not have a confounding effect in this analysis. OR estimations from both logistic regression models, one with the infant feeding intention variable and one without it, were very similar (data not shown). Furthermore, we observed similar risk factors for delayed OL in this smaller sample, although estimations were slightly weaker than those observed in the whole sample, which was possibly related to the reduced sample size. The only exception occurred with the interaction effect. In this reduced sample, each increase in newborn's gestational age (wk) was associated with an almost 50% increase in odds for delayed OL in primiparous women (OR: 1.49; 95% CI: 1.13, 1.97).

### DISCUSSION

Delayed OL was common in women with recent GDM, with one-third of subjects reporting a delayed arrival of milk, when using maternal perception of breast fullness as the lactogenesis cue. Our incidence rate came from an ethnically diverse population and was comparable with previous reports in the general

**TABLE 1**Maternal, labor and delivery, newborn, breastfeeding, and clinical characteristics in women with recent GDM, overall and by lactogenesis status ( $n = 883$ )<sup>1</sup>

Variables	Overall ( $n = 883$ )	Timely lactogenesis ( $n = 588$ )	Delayed lactogenesis ( $n = 295$ )
<b>Sociodemographic characteristics</b>			
Age (y)	33.3 $\pm$ 4.8 <sup>2</sup>	33.1 $\pm$ 4.7	33.6 $\pm$ 4.9
Education (formal schooling) (y)	14.8 $\pm$ 2.9	14.7 $\pm$ 3.0	15.1 $\pm$ 2.7*
Race and ethnicity [ $n$ (%)]			
Non-Hispanic white	207 (23.4)	125 (21.3)	82 (27.8)
Non-Hispanic black	61 (6.9)	39 (6.6)	22 (7.5)
Hispanic other	272 (30.8)	196 (33.3)	76 (25.8)
Asian	324 (36.7)	216 (36.7)	108 (36.6)
Other race or ethnicity	19 (2.2)	12 (2.0)	7 (2.4)
WIC recipient (yes) [ $n$ (%)]	222 (25.1)	160 (27.2)	62 (21.0)*
<b>Prenatal characteristics</b>			
Prepregnancy BMI [ $n$ (%)]			
<25 kg/m <sup>2</sup>	279 (31.6)	195 (33.2)	84 (28.5)
$\geq$ 25 to <30 kg/m <sup>2</sup>	260 (29.5)	175 (29.8)	85 (28.8)
$\geq$ 30 kg/m <sup>2</sup>	344 (39.0)	218 (37.1)	126 (42.7)
Severe GDM (>2 abnormal OGTT values) [ $n$ (%)]	370 (41.9)	239 (40.7)	131 (44.4)
Treatment of GDM [ $n$ (%)]			
Diet modification only	607 (68.7)	415 (70.6)	192 (65.1)*
Oral hypoglycemic agents	247 (28.0)	162 (27.6)	85 (28.1)
Insulin	29 (3.3)	11 (1.9)	18 (6.1)
Gestational weight gain (kg)	10.3 $\pm$ 6.7	10.4 $\pm$ 6.5	10.3 $\pm$ 7.0
Excessive gestational weight gain (yes) [ $n$ (%)]	298 (33.8)	198 (33.7)	100 (33.9)
Recommended pregnancy weight gain (%)	87.8 $\pm$ 62.6	87.3 $\pm$ 60.4	88.7 $\pm$ 66.9
Infant feeding intentions score <sup>3</sup>	17.1 $\pm$ 3.8	17.1 $\pm$ 3.9	17.2 $\pm$ 3.8
Parity [ $n$ (%)]			
Primiparous	331 (37.5)	179 (30.4)	152 (51.5)***
Multiparous	552 (62.5)	409 (69.6)	143 (48.5)
<b>Labor and delivery [<math>n</math> (%)]</b>			
Cesarean delivery section	257 (29.1)	158 (26.9)	99 (33.6)*
Labor-duration categories <sup>4</sup>			
$\leq$ 9.0 h	397 (45.0)	292 (49.7)	105 (35.6)**
>9.0 h	364 (41.2)	220 (37.4)	144 (48.8)
No labor	122 (13.8)	76 (12.9)	46 (15.6)
<b>Newborn characteristics [<math>n</math> (%)]</b>			
Gestational age			
35–36 wk	38 (4.3)	23 (3.9)	15 (5.1)
37–39 wk	628 (71.1)	419 (71.3)	209 (70.9)
$\geq$ 40 wk	217 (24.6)	146 (24.8)	71 (24.1)
Birth weight			
1500–2499 g	21 (2.4)	12 (2.0)	9 (3.1)
2500–2999 g	164 (18.6)	107 (18.2)	57 (19.3)
3000–3999 g	605 (68.5)	405 (68.9)	200 (67.8)
$\geq$ 4000 g	93 (10.5)	64 (10.9)	29 (9.8)
Size			
Large-for-gestational-age	186 (21.1)	128 (21.8)	58 (19.7)
Small-for-gestational-age	18 (2.0)	10 (1.7)	8 (2.7)
Appropriate-for-gestational-age	679 (76.9)	450 (76.5)	229 (77.6)
Apgar score at 5 min			
$\leq$ 6	9 (1.0)	6 (1.0)	3 (1.0)
$\geq$ 7	840 (95.1)	555 (94.4)	285 (96.6)
Missing Apgar score	34 (3.9)	27 (4.6)	7 (2.4)
Sex			
M	461 (52.2)	312 (53.1)	149 (50.5)
F	422 (47.8)	276 (46.9)	146 (49.5)
<b>Early breastfeeding [<math>n</math> (%)]</b>			
LATCH-score categories on day 1 <sup>4</sup>			
$\leq$ 7.5	463 (52.4)	272 (46.3)	191 (64.8)***
>7.5	420 (47.6)	316 (53.7)	104 (35.3)

(Continued)

TABLE 1 (Continued)

Variables	Overall (n = 883)	Timely lactogenesis (n = 588)	Delayed lactogenesis (n = 295)
Postpartum status (6–9 wk)			
BMI categories [n (%)]			
<25 kg/m <sup>2</sup>	208 (23.6)	146 (24.8)	62 (21.0)
≥25 to <30 kg/m <sup>2</sup>	310 (35.1)	209 (35.5)	101 (34.2)
≥30 kg/m <sup>2</sup>	365 (41.3)	233 (39.6)	132 (44.8)
Percentage of body fat <sup>5</sup>	45.5 ± 7.3	45.1 ± 7.1	46.4 ± 7.6*
ISI <sub>0,120</sub> <sup>6</sup>	1.6 ± 0.4	1.6 ± 0.5	1.6 ± 0.4
HOMA-IR	5.5 ± 4.1	5.4 ± 4.2	5.6 ± 4.0

<sup>1</sup> Chi-square or Fisher's exact test was used for categorical variables; *t* test was used for continuous variables. \**P*<0.05; \*\**P*<0.001; \*\*\**P*<0.0001. GDM, gestational diabetes mellitus; ISI, insulin sensitivity index; OGTT, oral-glucose-tolerance test; WIC, Special Supplemental Nutrition Program for Women, Infants, and Children.

<sup>2</sup> Mean ± SD (all such values).

<sup>3</sup> *n* = 607 reported infant feeding intentions.

<sup>4</sup> Cutoff was the median value.

<sup>5</sup> *n* = 750 had bioelectrical impedance analysis measurements.

<sup>6</sup> Calculated by using the fasting (0-min) and 120-min concentrations of glucose and insulin in the OGTT.

population (4). Consistent with previous scientific evidence from the general population, primiparity (5–9), maternal obesity (4, 5, 10, 11), maternal age (11), and less successful early breastfeeding (11) were independently associated with delayed OL in women with recent GDM. To our knowledge, before our study, associations of older maternal age and less optimal early breastfeeding with delayed OL had been reported only in primiparous women (11). A GDM diagnosis is associated with higher prepregnancy weight (16), which was reflected in the high prepregnancy BMI observed in our population. However, even in this population characterized by overweight and obesity, being in the heaviest category (ie, obese) increased the risk of delayed OL. Evidence from animal studies indicated that maternal obesity, particularly before conception and during pregnancy, interferes with the normal mammary gland development, which, in turn, affects lactogenesis (32). In humans, a decreased prolactin response to infant sucking was observed at 48 h in overweight and obese women in the general population (33), and it could also play a role in GDM women. A threshold of prolactin is necessary for a fall in progesterone to act as the lactogenesis trigger, but more importantly, it is needed for milk production (2), particularly during the time when lactogenesis II occurs (34). Insulin resistance, which is also associated with obesity, may be another possible mechanism that links obesity and delayed OL. Because of the potential for breastfeeding to ameliorate the higher risk that GDM women face for the development of type 2 diabetes (20, 35), skilled lactation support is particularly important for obese GDM women. Such support would prevent or promptly resolve delayed OL, and, consequently, reduce mother-infant dyad's higher risk of shorter breastfeeding duration (19, 36).

To our knowledge, we are the first authors to report an association between lower LATCH scores and delayed OL, although another indicator of ineffective breastfeeding behavior has been previously related to delayed OL (11). The LATCH scoring system is based on the assessment of 5 key breastfeeding components, with lower scores indicating suboptimal or less successful breastfeeding. Previously, LATCH scores have shown to predict breastfeeding duration (30, 31). The LATCH scoring system is relatively easy to implement and widely used in clinical

settings and, thus, could be a useful tool to identify GDM women who may need extra in-hospital, or postdischarge skilled lactation support until breastfeeding has been established.

Older maternal age, which is a known risk factor for GDM (37), was associated with an increased odds of delayed OL, with a 5-y increase in maternal age being associated with a 26% increase in risk of experiencing delayed milk arrival (data not shown). In our sample, women who were prescribed insulin treatment during pregnancy were older than women whose treatment included diet only or oral hypoglycemic agents (data not shown), as expected on the basis of a likelihood of greater glucose intolerance in pregnant women who are older. Nonetheless, older maternal age, prepregnancy obesity, and insulin treatment were independent risk factors for delayed OL. The relation with insulin treatment suggested that the severity of GDM is also an important predictor of delayed OL in this population. In a previous small study of healthy primiparas (*n* = 16), Nommsen-Rivers et al (38) showed that a lower serum insulin secretion relative to that of serum glucose after a glucose challenge during pregnancy was associated with subsequent delayed OL. Studies of women with overt diabetes have reported an increased occurrence of delayed lactogenesis associated with poorer metabolic control during pregnancy (39). Thus, marked gestational disturbances in insulin and glucose metabolism may interfere with the hormonal pathways for initiation of lactogenesis. Although the mechanisms are not yet well understood, results from a recent 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 (40). Another potential explanation for the association between insulin treatment and delayed OL in our study may have been relate to the specific clinical management of babies born to women with GDM (eg, macrosomia). These newborns may be separated from their mothers longer or may be more likely to receive non-breast-milk liquids in the neonatal period to treat hypoglycemia, which, in turn, could interfere with the normal lactogenesis process. In our sample, birth weight and gestational age were significantly associated with GDM treatment, but the Apgar score was not (data not

**TABLE 2**Unadjusted and adjusted logistic regression models for delayed onset of lactogenesis II in women with recent GDM ( $n = 883$ )<sup>1</sup>

Variables	Model 1 OR (95% CI)	Model 2 AOR (95% CI)	Model 3 AOR (95% CI)	Model 4 AOR (95% CI)	Model 5 AOR (95% CI)
Prepregnancy weight status (compared with normal)					
Overweight	1.13 (0.78, 1.62)	1.17 (0.81, 1.69)	1.21 (0.82, 1.77)	1.23 (0.83, 1.80)	1.26 (0.85, 1.85)
Obese	1.34 (0.96, 1.88)	1.45 (1.02, 2.07)	1.59 (1.10, 2.30)	1.54 (1.06, 2.26)	1.56 (1.07, 2.29)
Age (y)	—	1.02 (0.99, 1.05)	1.05 (1.01, 1.08)	1.04 (1.01, 1.08)	1.05 (1.01, 1.08)
Race and ethnicity (compared with white)	—				
Hispanic	—	0.57 (0.39, 0.85)	0.76 (0.50, 1.14)	0.77 (0.51, 1.17)	0.78 (0.52, 1.18)
Non-Hispanic/nonwhite (Asian, black, other)	—	0.83 (0.58, 1.18)	0.92 (0.64, 1.32)	0.94 (0.65, 1.36)	0.97 (0.67, 1.40)
Primiparous (compared with multiparous)	—	—	2.41 (1.73, 3.34)	2.38 (1.71, 3.32)	—
Cesarean delivery (compared with vaginal delivery)	—	—	1.18 (0.85, 1.63)	1.13 (0.82, 1.57)	1.12 (0.81, 1.55)
Gestational age (wk)	—	—	0.90 (0.80, 1.03)	0.90 (0.79, 1.03)	—
LATCH score (compared with >7.5)	—	—			
≤7.5	—	—	1.64 (1.20, 2.24)	1.66 (1.21, 2.28)	1.65 (1.20, 2.26)
GDM treatment (compared with diet only)	—	—	—	—	—
Oral hypoglycemic agents	—	—	—	1.05 (0.75, 1.46)	1.05 (0.75, 1.47)
Insulin	—	—	—	3.03 (1.34, 6.83)	3.11 (1.37, 7.05)
Gestational age × parity <sup>4</sup>	—	—	—	—	—
1-wk increase in gestational age in primiparas	—	—	—	—	1.08 (0.89, 1.32)
1-wk increase in gestational age in multiparas	—	—	—	—	0.79 (0.67, 0.94)

<sup>1</sup> Model 1 was adjusted for the main effect. Model 2 was adjusted as for model 1 and for maternal sociodemographics. Model 3 was adjusted as for model 2 and for parity and delivery and newborn and early breastfeeding factors. Model 4 was adjusted as for model 3 and for GDM treatment during pregnancy. Model 5 was adjusted as for model 4 and for the interaction term gestational age × parity. Wald's chi-square test was used to assess the contribution of individual predictors to the models.  $P$ -interaction = 0.0186. AOR, adjusted OR; GDM, gestational diabetes mellitus.

shown). However, additional analyses including birth weight in the final logistic regression model yielded similar results (data not shown). Future studies to disentangle the physiologic compared with clinical factors involved in the association between insulin GDM treatment and delayed OL in this population are needed. Nevertheless, insulin treatment during pregnancy should be considered a targeting indicator for providing extra skilled breastfeeding support to GDM women who decide to breastfeed.

We showed an interaction effect between parity and gestational age in the risk of delayed OL; a 1-wk increase in the newborn's gestational age was associated with a 30% reduction in odds of experiencing delayed OL but only if the mother was multiparous. Primiparous mothers are at higher risk of experiencing early breastfeeding problems (5), including delayed OL. Newborn health status (ie, a lower Apgar score) has been associated with delayed OL in primiparous mothers in another population (27). We speculate that greater gestational age is another newborn characteristic that is related to developmental or physiologic readiness for breastfeeding and, thereby, modifies the risk of delayed OL. This effect may be more evident in mothers at lower risk, such as multiparous mothers.

As in any observational study, this study had limitations. One limitation was that delayed OL, which is an early postpartum outcome, was measured retrospectively at 6–9 wk postpartum, which could have introduced recall bias. However, a previous comparison of actual and recalled timing of OL have shown that women can recall the onset of lactation with high sensitivity (93.8%) and reasonable specificity (63.0%) when asked at 6.7 ± 1.5 mo postpartum (26). Because we asked about lactogenesis at 6–9 wk postpartum, we expect that our assessment had at least a similar degree of sensitivity and specificity as reported for the assessment at a later time postpartum. This study also had

several strengths, including the use of an integrated health care system with universal screening for glucose tolerance during pregnancy and uniform treatment protocols for GDM, the racial-ethnic and socioeconomic diversity of the sample, and the availability of detailed clinical information on mother and newborn health outcomes from electronic medical records.

In conclusion, to our knowledge, our results provide new information regarding the risk factor profiles for delayed OL in women with recent GDM. Because the infants of these mothers are at greater risk of neonatal morbidities, it is important that GDM women who choose to breastfeed receive preventive support to resolve infant feeding problems early. These risk profiles could be used to develop a screening tool for health care providers to assist GDM mothers and their infants who may benefit from enhanced skilled breastfeeding support.

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The authors' responsibilities were as follows—SLM: conceived the research question that was the topic of the current analysis, developed and implemented the data-analysis plan, and wrote the original draft of the manuscript; EPG: conceived and is the principal investigator of the SWIFT study; KGD and CPQ: made substantial contributions to the study design for the SWIFT study; and all authors: participated in the interpretation of data analyses and revision of the original manuscript and read and approved the final manuscript. None of the authors had a conflict of interest.

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