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The impact of gestational weight gain and pre-pregnancy body mass index on the prevalence of large-for-gestational age infants in two cohorts of women with Type I Insulin-Dependent Diabetes: A cross-sectional population study

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Objectives Despite improvements in treatment modalities, large-for-gestational age (LGA) prevalence has remained between 30-40% among infants of mothers with Type I Insulin-Dependent Diabetes (TIDM). Our objective was to estimate LGA prevalence and examine the association between gestational weight gain (GWG) and pre-pregnancy body mass index (BMI) with LGA among mothers with TIDM.

Design Cross-sectional study.

Setting Regional data in Cincinnati, OH, from the Diabetes in Pregnancy Program Project (PPG), a prospective cohort for the period 1978-1993; national data from Consortium on Safe Labor (CSL), a multi-center cross-sectional study for the period 2002-2008.

Participants The study included 333 pregnancies in the PPG, and 358 pregnancies in the CSL. Pregnancies < 23 weeks' gestation were excluded. Women with TIDM in the PPG were identified according to physician confirmation of ketoacidosis, and or c-peptide levels, and by International Classification of Diseases (ICD)-9 codes within the CSL. LGA was identified as birthweight > 90th percentile according to gestational age, race and sex.

Main outcome measure LGA at birth.

Results Mean ± standard deviation maternal age at delivery was 26.4 ±5.1 years for PPG women and 27.5 ±6.0 years for CSL women, p=0.008. LGA prevalence did not significantly change between cohorts (PPG: 40.2% vs CSL: 36.6%, p=0.32). More women began pregnancy as overweight in the later cohort (PPG (16.8%) vs CSL (27.1%), p<0.001). GWG exceeding Institute of Medicine (IOM) guidelines increased from PPG (42.3%) to CSL (56.2%), p<0.001. Normal weight women with GWG within IOM guidelines was associated with reduced LGA prevalence in CSL (PPG: 30.6% vs CSL: 13.7%), p=0.001.

Conclusions Normal weight women with GWG within IOM guidelines experienced a reduction in LGA prevalence, supporting the importance of adherence to IOM guidelines for GWG to reduce LGA. Increasing BMI and GWG may be hindering a reduction in LGA prevalence.

Key words

Type I Diabetes

Pre-pregnancy body mass index

Gestational weight gain

Large-for-gestational age

Strengths and limitations of this study

- We had access to two cohorts of women with TIDM across a 30-year time period covering an era of major advancements in insulin treatment and delivery, and emergence of obesity as a prevalent chronic disease, potentially representing opposing risks for delivery of a large-for-gestational age (LGA) baby.
- The Diabetes in Pregnancy Program Project (PPG) cohort includes frequent, repeated observations of women during pregnancy while the Consortium on Safe Labor (CSL) provides a national, contemporary large-scale database.
- Glucose control was not available in CSL precluding comparison between groups.
- The potential differences between local (PPG) and national (CSL) populations include regional differences in diet, methods of treatment, racial composition and geography, limiting the generalizability of our results.
- Despite the importance of nephropathy and retinopathy as indicators of diabetes severity potentially affecting glucose transport, differing definitions between the cohorts prevented variable harmonization and were, therefore, not included in our study.

BACKGROUND

Despite advancements in insulin treatment and delivery for those with Type I Insulin-Dependent Diabetes (TIDM)[1 2], the prevalence of neonatal large-for-gestational age (LGA) among women in this population remains high[1 3-5]. LGA prevalence has remained at 30-40% among infants of mothers with TIDM[5-7]. Independently associated maternal factors for LGA include maternal age, race, stature/height[8] , ethnicity and parity[5 9-12] , excessive fetal nutrition[13] mediated by maternal hyperglycemia[2], excessive gestational weight gain (GWG)[5 14-16] and pre-pregnancy body mass index (BMI)[10 14 17 18] . LGA infants of mothers with diabetes are at increased risk for fetal distress[6] leading to cesarean section[19], and also obesity[20-22], insulin resistance (IR)[20], type II diabetes mellitus (TIIDM) and cardiovascular compromise[23 24] in adolescence and adulthood.

The steady state of higher perinatal birthweight among offspring of mothers with TIDM, even in the presence of tight glucose control, has promoted studies that emphasize the independent role of both increased rates of pre-pregnancy BMI[19] and excessive GWG[15] on neonatal outcome. According to data from NHANES, between 2011 and 2014, nearly 34% of women aged 20-39 years were obese[25]. Most recently, among all women who delivered a live infant in 2014, nearly 50% had a pre-pregnancy BMI of either overweight (25.6%) or obese (24.8%)[25].

In addition to the trend in increasing pre-pregnancy BMI, more women are gaining weight in excess of the 2009 Institute of Medicine (IOM) guidelines for GWG[26-28]. According to the IOM and National Research Council in “Reexamining the Guidelines”, there has been an upward trend in GWG from 1990-2005[28]. Given these two trends and the link between the hyperglycemic intrauterine environment and fetal overnutrition[19 29 30] , women with TIDM belonging to higher BMI subgroups, who exceed IOM guidelines for GWG, may be at the greatest risk of LGA.

In an effort to understand the implications of excessive GWG and pre-pregnancy BMI within this population, we compared LGA infants observed in the Diabetes in Pregnancy

Program Project (PPG), a cohort of women with TIDM going through pregnancy, studied from 1978 to 1993, to those in the Consortium on Safe Labor (CSL), a more contemporary TIDM population delivering between 2002 and 2008. We aim to establish the potential change in prevalence of LGA among infants exposed to maternal TIDM between 1978-1993 and 2002-2008. We also aim to determine associations between adherence to IOM guidelines for GWG and LGA outcome among mothers with TIDM, across pre-pregnancy BMI categories, to identify subgroups who may be at highest risk for LGA. These findings will help interpret the literature on IOM guidelines for GWG in the TIDM population as well as inform future research focusing on reducing LGA births among infants exposed to maternal hyperglycemic environments.

RESEARCH DESIGN AND METHODS

Diabetes in Pregnancy Program Project (PPG): The PPG study enrolled 303 women with TIDM in a cohort in Cincinnati, Ohio from 1978-1993 for a total of 372 pregnancies going beyond 23 weeks' gestation. After exclusions (see below), the analytic population included 333 pregnancies. Participants in the PPG were recruited preconceptionally or during the first half of the pregnancy period as part of a program funded by the National Institute of Health (NIH) in order to examine the impact of strict glycemic control during pregnancy on the rate of adverse maternal and neonatal outcomes in mothers with TIDM. The interdisciplinary core of this study involved endocrinologists, perinatologists, and neonatologists. TIDM study subjects recruited and enrolled into the program belonged to White's classification B to RT[31] . Two levels of glycemic control were defined to manage diabetes care: subjects enrolling prior to 9 completed weeks of gestation were randomized to strict or customary glycemic control. A third group included women enrolling after 9 completed weeks' gestation; they were managed according to customary glycemic control. Fasting blood glucose and 90-minute post-prandial glucose targets for strict glycemic control were: <100 mg/dl and <120 mg/dl respectively; for customary glycemic control: <120 mg/dl and <140 mg/dl, respectively[31] . Extensive gestational and outcome data

were collected including weekly weight, blood pressure, insulin requirements, urinalysis and medication use, multiple daily glucose concentrations and detailed delivery and neonatal outcome information.

Consortium on Safe Labor (CSL): The CSL study enrolled 208,695 women in a national multi-center observational study from 2002-2008 for a total of 228,562 deliveries. A total of 594 singleton TIDM pregnancies with delivery at ≥23 weeks' gestation were identified. After exclusions, the analytic population included 358 pregnancies. There were 11 (out of 12) sites represented in the CSL sample of pregnancy complicated by TIDM.

The National Institute of Child Health and Human Development (NIHCD), of the NIH, initiated a retrospective, observational study in a contemporary U.S. obstetric population to reexamine labor progression trends that have long been guided by the Friedman curve. The CSL study included medical records from a population of women from a consortium of 12 U.S. hospitals located across 9 districts of the American College of Obstetricians and Gynecologists and has been described in detail elsewhere[32]. Briefly, patient electronic medical records were extracted, de-identified and entered into a Data Coordinating database which maintained over 225,000 deliveries ≥23 weeks' gestation from 2002 to 2008. Each delivery included ICD-9 codes as well as information related to maternal demographics, maternal weight (kg) and height (m) at admission, prenatal history, preeclampsia, blood pressure, reports of uterine and intra-amniotic infections, anesthesia, obstetric trauma, medication, delivery method, infant birthweight, length, Apgar scores at 1 and 5 minutes, gestational age at delivery and post-natal time spent in the neurointensive care unit (NICU). Data received by the Data Coordinating Center from each clinical site was mapped to pre-defined codes for each variable. Data underwent inquiries, cleaning, recoding and logic checking. In addition, validation studies were performed to ensure electronic medical records accurately represented medical record charts[32].

Inclusion and exclusion criteria for the current study were identical for each study cohort. Inclusion criteria included TIDM and gestation at 23 completed weeks or later. Exclusion criteria

were multiple gestation, fetal anomaly, stillbirth, and missing the outcome and primary exposure variables; birthweight of the neonate, maternal pre-pregnancy and delivery weight and maternal height. No exclusions were made regarding race/ethnicity or age. For women with more than one pregnancy during the study, all pregnancies were included. In addition, no exclusions were made in the CSL based on geographic site.

GWG and pre-pregnancy BMI were the primary exposures of interest, and LGA was the outcome of interest. Potential confounding maternal characteristics of interest included maternal age at delivery, race, parity and preeclampsia. Pre-pregnancy BMI was additionally treated as a potential modifier of the relationship between GWG and LGA. IRB approval was obtained from Cincinnati Children's Hospital Medical Center as well as the University of Cincinnati prior to the secondary analysis of PPG and CSL cohorts.

Statistical Analysis

In two different cohorts, we conducted an analysis on mothers with TIDM who had singleton pregnancies. Women with TIDM in the PPG study were identified according to physician confirmation of ketoacidosis, and or c-peptide levels. Within the CSL cohort, International Classification of Diseases (ICD)-9 codes 250.01, 250.03, 250.21, 250.23, 250.31, 250.33, 250.41, 250.43, 250.51, 250.53, 250.61, 250.63, 250.71, 250.73, 250.81, 250.83, 250.91, 250.93 were utilized to identify women with TIDM. To determine LGA classification for each cohort, a McNemar's test of marginal homogeneity was performed comparing Lubchenco curves to both Cincinnati-based reference population growth curves for PPG and medical chart LGA classifications for CSL. LGA was finally defined as birthweight > 90th percentile and was classified by gestational age-, race- and sex-specific curves according to Lubchenco[33] for the PPG cohort and by the extracted variable from detailed medical chart review for CSL. Pre-pregnancy BMI was calculated by using self-reported weight prior to pregnancy and height, recorded at the initial visit for women in the PPG and at the labor and delivery admission for

women in the CSL. Underweight, normal weight, overweight and obese pre-pregnancy BMI classifications were defined as: BMI<18.5 kg/m^2; 18.5≤BMI<25 kg/m^2, 25≤BMI<30kg/m^2 and BMI≥30 kg/m^2, respectively. GWG was defined as weight at admission for delivery minus pre-pregnancy weight (kg). IOM adherence for GWG was categorized utilizing the pre-pregnancy BMI-specific 2009 guidelines as under, within (underweight: 12.5-18.0 kg; normal: 11.5-16.0 kg; overweight: 7.0-11.5 kg; obese (all classes): 5.0-9.0 kg) or over IOM guidelines. Calculations for recommended weight gain assume a 0.5-2.0 kg weight gain in the first trimester[28]. Variables within PPG and CSL were harmonized for comparative analysis. Race was based on self-identification, and was categorized as black, white or other. Due to the small number of obese women in the PPG cohort, overweight and obese BMI categories were combined for analysis. Continuous and categorical variables are represented with mean (±SD) and n (%), respectively. Maternal characteristics were compared between and within cohorts by LGA status and by adherence to IOM guidelines for GWG (under, within and over) using Chi-square or Fisher's exact test, and analysis of variance (ANOVA) or Wilcoxon rank sum, as appropriate. Normality testing for distribution of continuous variables was performed by examining histograms, stem-leaf plots, and Kolmogorov-Smirnov tests. A site frequency distribution was examined to investigate possible bias in site representation in the CSL sample. Bonferroni was used to adjust for multiple testing. Generalized Estimating Equations (GEE) were used to estimate the odds ratio (OR) of giving birth to an LGA infant for women exceeding IOM guidelines vs women who adhered to IOM guidelines to account for inherent correlation among women with multiple pregnancies in each study. General linear models were used to examine the relationships between GWG and birthweight. To determine whether IOM adherence varied across BMI categories (18.5≤BMI<25, 25≤BMI<30, BMI≥30 kg/m^2) interaction terms were used to evaluate effect modification. Normal weight women within IOM guidelines for GWG was used as the reference category. Models adjusted for potential confounders, selected a priori as risk factors for GWG and LGA and not on the causal pathway, included age, race, parity, pre-pregnancy

BMI and preeclampsia. All tests for significance were two-sided and a *p*-value of less than 0.05 was considered statistically significant, appropriately adjusted as necessary. Statistical analyses were completed using SAS® software version 9.4 (SAS Institute, Cary NC).

RESULTS

Table 1 shows maternal characteristics and neonatal outcomes in each cohort. Mean age at delivery was significantly higher for women in the CSL (27.5±6.0) than for women in the PPG (26.4±5.1), p=0.008. There was a higher proportion of black women in the CSL (19.3%) than in the PPG (14.1%). The CSL had a significantly greater proportion of overweight/obese women (51.4%) than the PPG (20.7%), p<0.001. More women exceeded IOM guidelines for GWG in the CSL (56.2%) than in the PPG (42.3%), p<0.001, with overweight/obese women accounting for 58.7% and 41.1% of all women who exceeded guidelines, respectively (table S1).

Table 1. Maternal characteristics and neonatal outcomes in PPG (1978-1993) and CSL (2002-2008) cohorts

	PPG	CSL	
Maternal Characteristics	n=333	n=358	*p* value
Maternal age at delivery (years)	26.4 ± 5.1	27.5 ± 6.0	0.008
Married, yes [b]	224 (67.3)	217 (60.6)	0.01
Race			<0.001
White	282 (84.7)	225 (62.8)	
Black	47 (14.1)	69 (19.3)	
Other	4 (1.20)	64 (17.9)	
Nulliparous, yes	166 (49.9)	183 (51.1)	0.74
Pre-pregnancy BMI (kg/m^2)	23.0 ± 3.4	26.9 ± 6.3	<0.001
Pre-pregnancy BMI category			<0.001
Underweight (BMI<18.5 kg/m^2)	11 (3.3)	6 (1.7)	
Normal (18.5 kg/m^2≤BMI<25.0 kg/m^2)	253 (76.0)	168 (46.9)	
Overweight (25.0 kg/m^2≤BMI<30.0 kg/m^2)	56 (16.8)	97 (27.1)	
Obese (BMI≥30.0 kg/m^2)	13 (3.90)	87 (24.3)	
Pre-pregnancy Overweight/Obese	69 (20.7)	184 (51.4)	<0.001
Gestational Weight Gain (kg)	14.4 ± 5.6	14.5 ± 7.4	0.77
IOM Guidelines			
Under	74 (22.2)	62 (17.3)	<0.001
Within	118 (35.5)	95 (26.5)	
Over	141 (42.3)	201 (56.2)	
Preeclampsia, yes	50 (15.0)	55 (15.4)	0.90
Previous cesarean section, yes [b]	105 (31.6)	86 (24.0)	0.08
Cesarean section, yes	233 (70.0)	239 (66.8)	0.36
Preterm delivery, yes			
Delivery prior to 34 weeks	33 (9.9)	48 (13.4)	0.15
Delivery prior to 37 weeks	114 (34.2)	152 (42.6)	0.03
Neonatal Outcomes [a]			
Male	186 (56.2)	193 (53.9)	0.60
Respiratory distress during labor	37 (11.1)	45 (12.8)	0.49
Gestational age (weeks)	37.0 ± 2.4	36.1 ± 2.7	<0.001
Apgar less than 7 (@5 min)	59 (17.7)	23 (6.4)	

Mean ± SD are shown for all continuous variables and n (%) are shown for categorical variables; PPG: Diabetes in Pregnancy Program Project; CSL: Consortium on Safe Labor.

[a] Neonatal outcomes exclude stillbirths and neonatal deaths

[b] PPG: Marital status missing for 11 women; CSL: Previous cesarean section missing for 20 women.

There was no significant difference in cesarean section rate between the CSL (66.8%) and PPG (70.0%), p=0.36. Women were more likely to deliver at less than 37 weeks' in the CSL (42.6%) than in the PPG (34.2%), p=0.03.

While we observed no difference in overall LGA prevalence between cohorts (CSL: 36.6% vs. PPG: 40.2%, p=0.32), Table 2 shows a lower prevalence of LGA among women in CSL compared with PPG (13.7% versus 30.6%) who were normal weight and gained within IOM guidelines.

Table 2. Large-for-Gestational Age prevalence within each BMI and IOM adherence subgroup for women in PPG (1978-1993) and CSL (2002-2008) cohorts

		PPG			CSL			
IOM adherence	Pre-pregnancy BMI	N	LGA	% LGA [a]	N	LGA	%LGA [a]	*p* value
under	underweight	4	1	0.7%	2	1	0.8%	-
under	normal	67	20	14.9%	33	8	6.1%	-
under	overweight/obese	3	1	0.7%	27	6	4.6%	-
within	underweight	7	3	2.2%	3	0	0.0%	0.09
within	normal	103	41	30.6%	53	18	13.7%	0.001
within	overweight/obese	8	0	0.0%	39	12	9.2%	0.0003
over	underweight	0	0	0.0%	1	0	0.0%	-
over	normal	83	38	28.4%	82	37	28.2%	0.94
over	overweight/obese	58	30	22.4%	118	49	37.4%	0.008
Total		333	134	40.2%	358	131	36.6%	0.32

IOM=Institute of Medicine; BMI=body mass index (kg/m^2); LGA=large-for-gestational age; PPG: Diabetes in Pregnancy Program Project; CSL: Consortium on Safe Labor.

[a] % LGA for each IOM guideline adherence and pre-pregnancy BMI category are presented as proportions of total LGA infants for each category.

BMI was defined as: underweight (BMI<18.5 kg/m^2); normal (18.5 kg/m^2≤BMI<25.0 kg/m^2); overweight (25.0 kg/m^2≤BMI<30.0 kg/m^2); obese (BMI≥30.0 kg/m^2).

The distribution of LGA by BMI categories has significantly changed over time (see table 3). While normal weight women still have the highest proportion of LGA infants in both the CSL and PPG (48.1% vs 73.9%), there was an increase in overweight women delivering LGA infants over time, from 17.2% (PPG) to 29.8% (CSL), *p*<.0001. Normal weight women in the CSL, on average, gained 2.4 kg more over gestation than normal weight women in the PPG. In contrast, overweight women in the CSL, on average, gained 2.6 kg less than overweight women in the PPG (table S2).

Table 3. Maternal characteristics of women in PPG (1978-1993) and CSL (2002-2008) cohorts by LGA classification

	PPG			CSL		
Characteristic	LGA Lubchenco	non-LGA	p value	LGA Chart	non-LGA	p value
n (%)	134 (40.2)	199 (59.8)		131 (36.6)	227 (63.4)	
Maternal age at delivery, years	26.5±4.9	26.4±5.2	0.83	27.5 ±6.1	27.6±6.0	0.92
Married, yes	94 (70.1)	130 (65.3)	0.08	87 (66.4)	130 (57.3)	0.09
Race			0.36			0.001
White	118 (88.1)	164 (82.4)		97 (74.1)	128 (56.4)	
Black	15 (11.2)	32 (16.1)		13 (9.9)	56 (24.7)	
Other	1 (0.78)	3 (1.5)		21 (16.0)	43 (18.9)	
Nulliparous, yes	59 (44.0)	107 (53.8)	0.08	60 (45.8)	123 (54.2)	0.13
Pre-pregnancy BMI (kg/m^2)	23.3±3.6	22.7±3.2	0.9	26.7±5.8	26.9±6.5	0.77
Pre-pregnancy BMI category			0.45			0.5
Underweight (BMI<18.5 kg/m^2)	4 (3.0)	7 (3.5)		1 (0.76)	5 (2.2)	
Normal (18.5 kg/m^2≤BMI<25.0 kg/m^2)	99 (73.9)	154 (77.4)		63 (48.1)	105 (46.3)	
Overweight (25.0 kg/m^2≤BMI<30.0 kg/m^2)	23 (17.2)	33 (16.6)		39 (29.8)	58 (25.6)	
Obese (BMI≥30.0 kg/m^2)	8 (6.0)	5 (2.5)		28 (21.4)	59 (26.0)	
Pre-pregnancy Overweight/Obese	31 (23.1)	38 (19.1)	0.38	67 (51.2)	117 (51.5)	0.94
Gestational Weight Gain (kg)	15.7±5.4	13.5±5.7	<.0001	16.3±7.2	13.5±7.3	0.0004
IOM Guidelines			0.02			0.01
Under	22 (16.4)	52 (26.1)		15 (11.5)	47 (20.7)	
Within	44 (32.8)	74 (37.2)		30 (22.9)	65 (28.6)	
Over	68 (50.8)	73 (36.7)		86 (65.7)	115 (50.7)	
Preeclampsia, yes	11 (8.2)	39 (19.6)	0.004	19 (14.5)	36 (15.9)	0.73
Previous cesarean section, yes	45 (33.8)	60 (30.2)	0.48	38 (29.9)	48 (22.8)	0.14
Cesarean section, yes	97 (72.4)	136 (68.3)	0.43	91 (69.5)	148 (65.2)	0.41
Preterm delivery						
Delivery prior to 34 weeks	6 (4.5)	27 (13.6)	0.007	11 (8.4)	37 (16.3)	0.03
Delivery prior to 37 weeks	38 (28.4)	76 (38.2)	0.06	55 (42.0)	97 (42.7)	0.89
Neonatal Outcomes						
Male	81 (61.4)	105 (52.8)	0.12	71 (54.2)	122 (54.2)	1.0
Respiratory distress during labor	11 (8.2)	26 (13.1)	0.17	16 (12.5)	29 (13.0)	0.89
Gestational Age, weeks	37.5±1.9	36.6±2.7	0.001	36.3±2.2	36.0±3.0	0.22
Apgar less than 7 (@5 min)	20 (14.9)	39 (19.6)	0.27	9 (6.87)	14 (6.2)	0.79

Mean ± SD are shown for all continuous variables and n(%) are shown for categorical variables

IOM=Institute of Medicine; BMI=body mass index (kg/m^2); LGA=large-for-gestational age; PPG=Diabetes in Pregnancy Program Project; CSL=Consortium on Safe Labor.

LGA was defined as infants with a birthweight >90th percentile, adjusted for age, sex and race.

Neonatal outcomes exclude stillbirths and neonatal deaths.

Table 4 shows separate associations between pre-pregnancy BMI and GWG with odds of LGA for all women in each cohort. Entering pregnancy with higher BMI did not appear to be an independent predictor of LGA in either group.

Table 4. Association between abnormal pre-pregnancy BMI and unrecommended gestational weight gain compared to normal weight participants within IOM adherence guidelines among PPG (1978-1993) and CSL (2002-2008) study cohorts

PPG	Model I	Model II	Model III
	OR (95% CI)	OR (95% CI)	OR (95% CI)
Pre-pregnancy BMI			-
Normal/Underweight	1.00 (ref)	1.00 (ref)	-
Overweight/Obese	1.28 (0.70, 2.32)	1.44 (0.79, 2.63)	-
Gestational Weight Gain			
Under	0.71 (0.39, 1.31)	0.76 (0.41, 1.41)	0.76 (0.41, 1.42)
Within	1.00 (ref)	1.00 (ref)	1.00 (ref)
Over	1.57 (0.92, 2.65)	1.55 (0.90, 2.67)	1.53 (0.86, 2.71)
CSL	Model I	Model II	Model III
	OR (95% CI)	OR (95% CI)	OR (95% CI)
Pre-pregnancy BMI			-
Underweight	0.33 (0.04, 2.92)	0.38 (0.03, 4.21)	-
Normal	1.00 (ref)	1.00 (ref)	-
Overweight	1.12 (0.67, 1.87)	1.32 (0.77, 2.26)	-
Obese	0.79 (0.46, 1.36)	1.04 (0.58, 1.86)	-
Gestational Weight Gain			
Under	0.69 (0.33, 1.43)	0.75 (0.35, 1.60)	0.73 (0.34, 1.58)
Within	1.00 (ref)	1.00 (ref)	1.00 (ref)
Over	1.62 (0.97, 2.72)	1.54 (0.91, 2.63)	1.46 (0.84, 2.52)

OR=odds ratio (95% confidence interval); IOM=Institute of Medicine; BMI=body mass index (kg/m^2); LGA=large-for-gestational age; PPG: Diabetes in Pregnancy Program Project; CSL: Consortium on Safe Labor.

Model I - Adjusted for age

Model II - Adjusted for Model I + maternal race, parity, preeclampsia

Model III - Adjusted for Model II + pre-pregnancy BMI

BMI was defined as: underweight (BMI<18.5 kg/m^2); normal (18.5 kg/m^2≤BMI<25.0 kg/m^2); overweight (25.0 kg/m^2≤BMI<30.0 kg/m^2); obese (BMI≥30.0 kg/m^2).

When considering all BMI groups collectively, exceeding IOM guidelines for GWG vs. remaining within IOM guidelines was not a significant predictor of increased risk for LGA in either cohort. The OR adjusted for age for mothers who exceeded IOM guidelines compared to those who remained within guidelines was similar for women in the CSL [OR 1.60, 95%CI (0.95, 2.68), p=0.08] compared to mothers in the PPG [OR 1.57, 95%CI (0.92, 2.65), p=0.10]. There was

also no significant difference in average total GWG between the groups, 14.5±7.4 for CSL and 14.4±5.6 for PPG (p=0.77). There remained no significant increase in risk of LGA after further adjustments for covariates and pre-pregnancy BMI for either group.

In the CSL, normal weight women who exceeded IOM guidelines [OR 2.14 95%CI (1.17, 3.91), p=0.01] and overweight women who exceeded IOM guidelines [OR 2.35 95%CI (1.26, 4.40), p=0.01] had an increased odds of LGA after adjusting for age when compared to the normal weight women who did not exceed IOM guidelines, as shown in Table 5.

Table 5. Adjusted odds ratios (95% CI) for LGA by abnormal pre-pregnancy BMI and unrecommended gestational weight gain compared to normal weight participants within IOM adherence guidelines among PPG (1978-1993) and CSL (2002-2008) cohorts

			Model I		Model II	
PPG			OR (95% CI)		OR (95% CI)	
IOM adherence	Pre-pregnancy BMI	n		*p* value		*p* value
within	normal/underweight	110	1.00 (ref)		1.00 (ref)	
within	overweight/obese	8	-		-	
over	normal/underweight	83	1.61 (0.93, 2.80)	0.09	1.48 (0.83, 2.64)	0.18
over	overweight/obese	58	2.04 (1.05, 3.97)	**0.03**	2.12 (1.11, 4.04)	**0.02**
			Model I		Model II	
CSL			OR (95% CI)		OR (95% CI)	
IOM adherence	Pre-pregnancy BMI	n				
within	Normal	56	1.00 (ref)		1.00 (ref)	
within	Overweight	15	0.38 (0.08, 1.81)	0.23	0.53 (0.10, 2.73)	0.45
within	Obese	23	1.86 (0.75, 4.60)	0.18	1.99 (0.79, 5.01)	0.15
over	Normal	82	2.14 (1.17, 3.91)	**0.01**	1.83 (0.99, 3.40)	0.06
over	Overweight	70	2.35 (1.26, 4.40)	**0.01**	2.25 (1.18, 4.28)	**0.01**
over	Obese	49	1.26 (0.61, 2.59)	0.53	1.49 (0.70, 3.19)	0.30

OR=odds ratio; 95% confidence interval (CI); IOM=Institute of Medicine; BMI=body mass index (kg/m^2); LGA=large-for-gestational age; PPG: Diabetes in Pregnancy Program Project; CSL: Consortium on Safe Labor.

Model I - Adjusted for age

Model II - Adjusted for Model I + maternal race, parity, preeclampsia

BMI was defined as: underweight (BMI<18.5 kg/m^2); normal (18.5 kg/m^2≤BMI<25.0 kg/m^2); overweight (25.0 kg/m^2≤BMI<30.0 kg/m^2); obese (BMI≥30.0 kg/m^2).

Insufficient LGA infants of overweight/obese women who remained within IOM guidelines to make LGA OR determination

After adjusting for other risk factors, the combined effect of overweight and exceeding IOM guidelines remained, with an increase in odds of LGA [OR 2.25, 95%CI (1.18, 4.28), p=0.01] compared to the reference group. The increased odds for LGA in normal weight women who exceed IOM guidelines was slightly attenuated [OR 1.83 95%CI (0.99, 3.40), p=0.06]. Similar results were shown for overweight/obese women in the PPG who exceeded IOM guidelines. There was an increase in odds of LGA for these women in both models adjusted for age only [OR 2.04 95%CI (1.05, 3.97), p=0.03] and fully adjusted models [OR 2.12 95%CI (1.11, 4.04), p=0.02] compared with normal weight women who remain within IOM guidelines.

DISCUSSION

Although delivery of LGA infants in the TIDM population has been examined in several epidemiological studies, few studies have examined LGA prevalence over time. In this analysis of GWG, pre-pregnancy BMI and LGA infant births among mothers with TIDM, we identified several important overall and GWG- and BMI-specific patterns. Our results suggest no change in overall LGA prevalence over a 30-year period. However, the proportion of infants born LGA to women of normal weight who adhered to GWG guidelines was reduced by 17%. This reduction appeared to be offset by a 15.0% increase in LGA prevalence among overweight/obese women who exceeded IOM guidelines.

Persson et al, 2009 showed that in a contemporary population of women with TIDM, obstetric and perinatal complications, particularly higher birthweight, remain markedly higher than the general population[6]. Similarly, the results of our study demonstrate that high weight for gestational age remains a frequent outcome in pregnancies complicated by TIDM, despite advancements throughout the years in glucose management and insulin treatment and delivery. Overall, our study showed LGA prevalence, for both groups, was markedly higher than the general population, despite observing reductions within select BMI subgroups.

Historically, obesity has been associated with TIIDM. However, the TIDM population has shown a significant increase in women entering pregnancy as overweight and obese. There was a marked increase in the proportion of overweight/obese women in the CSL compared to the PPG (51.4% vs 20.7%). Women in the CSL belonging to the overweight/obese subgroup accounted for a greater proportion of those who exceeded IOM guidelines (58.7%) compared with women in the PPG (41.1%). Overweight/obese women who exceeded IOM guidelines showed a 15.0% (p=0.01) increase in LGA over time. Our results confirm previous studies that have linked maternal overweight[19 29], GWG[34] and adverse birth outcomes in the TIDM population. Despite the improvement, this subgroup remains at the highest risk of delivering an LGA infant compared to normal weight women who adhered to IOM guidelines. Interestingly, despite a lower average GWG for women with higher BMI in the CSL compared to women in the PPG, women with overweight and obesity remained in excess of IOM guidelines for GWG. On average, overweight and obese CSL women gained 2.6 kg less and 0.30 kg more, respectively, over total gestation than overweight and obese women in the PPG. These results suggest that women in the PPG with higher BMI far exceeded IOM guidelines. The reduction in average GWG for overweight and obese women could help explain the lowered LGA prevalence over time in this subgroup, 41.2% in the CSL compared to 51.7% in the PPG. Previous studies in the literature have shown the effect of excessive GWG on risk of LGA, independent of BMI[14-16 35]. However, the results of our study did not show BMI and adherence to IOM guidelines as independent predictors of LGA. Women who were not only overweight (or obese for PPG) but who also exceeded GWG guidelines were at a greater than 2-fold increase risk of delivering an LGA infant (CSL: OR 2.25 (1.18, 4.28), PPG: OR 2.12 (1.11, 4.04)), compared with women who were normal weight and with GWG within IOM guidelines.

This study has several limitations. Our analysis was unable to include a comparison of glucose control between groups as this data was not available for CSL participants. Although Secher et. al. showed higher GWG was associated with LGA outcomes, independent of glucose

control[15], these measurements could potentially account for the reduction in LGA prevalence among normal weight women who adhered to IOM guidelines in our study. Second, our study compared women with TIDM from a local population to women in a nationally representative population. The differences between the populations, which include regional differences in diet, methods of treatment, racial composition and geography limit the generalizability of our results. However, this study serves as an important start for assessing impact of policy changes on perinatal outcomes like LGA over time. Our sample size for overweight and obese women who remain within IOM guidelines for PPG limited our power to robustly test effect modification, and thus no comparisons across time could be made between groups. However, we were able to examine the role of pre-pregnancy BMI as an effect modifier in the contemporary CSL cohort. Lastly, despite the importance of nephropathy and retinopathy as indicators of diabetes severity, potentially affecting glucose transport, differing definitions between cohorts prevented variable harmonization and, therefore, inclusion in our study. Prevalence of nephropathy according to each group's definition was 18.9% for PPG and 7.8% for CSL.

Despite these limitations, important strengths exist and this study extends beyond prior studies in several important areas. Our study compared two cohorts of women across a time period wherein major advancements have been made in the treatment of TIDM while simultaneously obesity has become a prevalent chronic disease– representing opposing risks for LGA. Each data set is comprehensive and has unique strengths. For instance, the PPG cohort includes frequent, repeated observations of women during pregnancy, while the CSL is large and contemporary.

In conclusion, while overall LGA prevalence has remained relatively unchanged over time, normal weight women with TIDM who adhere to IOM guidelines have experienced a reduction in LGA prevalence. Women in a more recent TIDM population are starting the pregnancy period with significantly higher proportions of overweight and obesity than in previous years. Entering pregnancy as overweight while exceeding IOM guidelines for GWG places

women in this population at the highest risk of LGA. This study demonstrates the importance of strict adherence to IOM guidelines for GWG, particularly for women who enter pregnancy as overweight, in order to address reduction of LGA rates in the TIDM population.

Contributors

Study concept and design: KLM, JCK; acquisition of data: KLM, JCK; statistical analysis: KLM; interpretation of data: KLM, JCK, KB, CLJ, RD, LMD; drafting of the manuscript: KLM; critical revision of the manuscript for important intellectual content: KLM, JCK, KB, CLJ; administrative, technical, and material support: KLM, JCK. All authors approved of the version of the manuscript to be published.

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Competing interests None declared.

Patient consent Yes.

Ethics approval IRB approval was obtained from Cincinnati Children's Hospital Medical center as well as the University of Cincinnati prior to the secondary analysis of the Diabetes in Pregnancy Program Project (PPG) and the Consortium on Safe Labor (CLS) data.

Data sharing statement No additional data are available.

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Table S1. Maternal characteristics of women in PPG (1978-1993) and CSL (2002-2008) by adherence to IOM recommendations for gestational weight gain

	PPG n=333				CSL n=358			
	n=74	n=118	n=141		n=62	n=95	n=201	
Characteristic	IOM under[1]	IOM within	IOM over	*p*-value	IOM under	IOM within	IOM over	*p*-value
Maternal age (at delivery), years	25.6 ± 5.2	26.7 ± 4.8	26.5 ± 5.1	0.33	28.2 ± 6.0	27.7 ± 5.9	27.3±6.1	0.53
Married, yes [a]	41 (22.1)	89 (77.4)	94 (69.1)	**0.02**	39 (62.9)	56 (59.0)	122 (60.7)	0.88
Race				0.15				**0.02**
White	56 (75.7)	103 (87.3)	123 (87.2)		30 (48.4)	57 (60.0)	138 (68.7)	
Black	17 (23.0)	13 (11.0)	17 (12.1)		20 (32.3)	18 (19.0)	31 (15.4)	
Other	1 (1.3)	2 (1.7)	1 (0.7)		12 (19.3)	20 (21.1)	32 (15.9)	
Nulliparous, yes	43 (58.1)	59 (50.0)	64 (45.4)	0.21	26 (41.9)	50 (52.6)	107 (53.2)	0.28
Pre-pregnancy BMI (kg/m^2)	21.9 ± 2.9	22.0 ± 2.7	24.4 ± 3.6	**<.0001**	27.2 ± 7.2	26.3 ± 6.6	27.0 ± 5.7	0.62
Pre-pregnancy BMI category				**<.0001**				**0.007**
Underweight (BMI<18.5 kg/m^2)	4 (5.4)	7 (5.9)	0 (0.0)		2 (3.2)	3 (3.2)	1 (0.5)	
Normal (18.5 kg/m^2≤BMI<25.0 kg/m^2)	67 (90.5)	103 (87.3)	83 (58.9)		33 (53.2)	53 (55.8)	82 (48.8)	
Overweight (25.0 kg/m^2≤BMI<30.0 kg/m^2)	1 (1.4)	7 (5.9)	48 (34.0)		12 (19.4)	15 (15.8)	70 (34.8)	
Obese (BMI≥30.0 kg/m^2)	2 (2.7)	1 (0.9)	10 (7.1)		15 (24.2)	24 (25.3)	48 (23.9)	
Pre-pregnancy Overweight/Obese (BMI≥25.0 kg/m^2)	3 (4.1)	8 (6.8)	58 (41.1)	**<.0001**	27 (43.6)	39 (41.1)	118 (58.7)	**0.007**
Gestational Weight Gain (kg)	7.2 ± 3.9	13.4 ± 1.8	18.9 ± 4.0	**<.0001**	4.9 ±5.3	11.6 ± 3.0	18.8 ± 5.7	**<.0001**
Preeclampsia, yes	13 (17.6)	17 (14.4)	20 (14.2)	0.78	10 (16.1)	9 (9.5)	36 (17.9)	0.17
Previous cesarean section, yes [a]	16 (21.9)	40 (33.9)	49 (34.8)	0.13	15 (25.9)	22 (25.3)	49 (25.4)	1.00
Cesarean section, yes	50 (67.6)	84 (71.2)	99 (70.2)	0.86	37 (59.7)	59 (62.1)	143 (71.1)	0.13
Large-for-gestational age	22 (29.7)	44 (37.3)	68 (48.2)	**0.02**	15 (24.2)	30 (31.6)	86 (42.8)	**0.01**

Mean ± SD are shown for all continuous variables and n(%) are shown for categorical variables

LGA was defined as infants with a birthweight >90th percentile, adjusted for age, sex and race.

[a] PPG: Marital status missing for 11 women; CSL: Previous cesarean section missing for 20 women.

Table S2. Mean ± SD of reproductive characteristics for PPG (1978-1993) and CSL (2002-2008) stratified by BMI

	PPG				CSL			
	n=333				n=358			
n	11	253	56	13	6	168	97	87
	Underweight	Normal	Overweight	Obese	Underweight	Normal	Overweight	Obese
Maternal age at delivery (years)	24.4 ± 5.2	26.5 ± 4.8	25.9 ± 5.9	29.3 ±4.9	28.8 ± 4.1	27.4 ± 5.9	26.6 ± 6.3	28.8 ± 5.8
Birthweight (g)	2994 ± 945	3269 ± 796	3390 ± 767	3293 ± 903	2942 ± 666	3264 ± 796	3277 ± 823	3149 ± 910
Gestational age (weeks)	35.7 ± 3.7	36.9 ± 2.47	37.4 ± 2.17	37.4 ±1.5	35.7 ± 5.4	36.3 ± 2.6	36.0 ± 2.3	36.0 ± 3.1
Gestational Weight Gain (kg)	11.5 ± 5.0	14.0 ± 5.5	17.1 ± 5.4	10.7 ±5.4	11.3 ± 8.6	16.4 ± 6.4	14.5 ± 6.7	11.0 ± 8.5
Prepregnancy BMI	17.3 ± 0.7	21.9 ± 1.6	26.6 ± 1.35	33.6 ±3.7	17.5 ± 1.0	23.4 ± 1.7	27.2 ± 1.5	35.8 ± 5.3

Mean ± SD are shown for all continuous variables

BMI=body mass index (kg/m^2); PPG=Diabetes in Pregnancy Program Project; CSL=Consortium on Safe Labor.

BMI was defined as: underweight (BMI<18.5 kg/m^2); normal (18.5 kg/m^2≤BMI<25.0 kg/m^2); overweight (25.0 kg/m^2≤BMI<30.0 kg/m^2); obese (BMI≥30.0 kg/m^2).

STROBE Statement—checklist of items that should be included in reports of observational studies

	Item No	Recommendation
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract **[Within the title page 1 and design section of the abstract page 2]**
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found **[Results section of abstract page 2]**
Introduction		
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported **[page 5]**
Objectives	3	State specific objectives, including any prespecified hypotheses **[page 6]**
Methods		
Study design	4	Present key elements of study design early in the paper **[Methods pages 6-7]**
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection **[Methods pages 6-7]**
Participants	6	(*a*) *Cohort study*—Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up **[ ]** *Case-control study*—Give the eligibility criteria, and the sources and methods of case ascertainment and control selection. Give the rationale for the choice of cases and controls **[ ]** *Cross-sectional study*—Give the eligibility criteria, and the sources and methods of selection of participants **[pages 6-7]**
		(*b*) *Cohort study*—For matched studies, give matching criteria and number of exposed and unexposed **[ ]** *Case-control study*—For matched studies, give matching criteria and the number of controls per case **[ ]**
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable **[pages 8-9]**
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group **[pages 8-9]**
Bias	9	Describe any efforts to address potential sources of bias **[page 8]**
Study size	10	Explain how the study size was arrived at **[pages 6-7]**
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why **[pages 8-9]**
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding **[pages 8-10]**
		(*b*) Describe any methods used to examine subgroups and interactions **[page 9]**
		(*c*) Explain how missing data were addressed **[N/A]**
		(*d*) *Cohort study*—If applicable, explain how loss to follow-up was addressed **[ ]** *Case-control study*—If applicable, explain how matching of cases and controls was addressed **[ ]**

		Cross-sectional study—If applicable, describe analytical methods taking account of sampling strategy **[N/A]**
		(*e*) Describe any sensitivity analyses **[N/A]**
Results		
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed **[page 11 table 1]**
		(b) Give reasons for non-participation at each stage **[N/A]**
		(c) Consider use of a flow diagram **[N/A]**
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders **[pages 10-11 and table 1]**
		(b) Indicate number of participants with missing data for each variable of interest **[table 1]**
		(c) *Cohort study*—Summarise follow-up time (eg, average and total amount) **[ ]**
Outcome data	15*	*Cohort study*—Report numbers of outcome events or summary measures over time **[ ]**
		Case-control study—Report numbers in each exposure category, or summary measures of exposure **[ ]**
		Cross-sectional study—Report numbers of outcome events or summary measures **[tables 2 and 3]**
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included **[table 4]**
		(*b*) Report category boundaries when continuous variables were categorized **[N/A]**
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period **[N/A]**
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses **[table 5]**
Discussion		
Key results	18	Summarise key results with reference to study objectives **[page 16]**
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias [**pages 17-18]**
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence **[pages 18-19]**
Generalisability	21	Discuss the generalisability (external validity) of the study results **[page 18]**
Other information		
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based **[page 20]**

*Give information separately for cases and controls in case-control studies and, if applicable, for exposed and unexposed groups in cohort and cross-sectional studies.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at www.strobe-statement.org.

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The impact of gestational weight gain and pre-pregnancy body mass index on the prevalence of large-for-gestational age infants in two cohorts of women with Type I Insulin-Dependent Diabetes: A cross-sectional population study

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The impact of gestational weight gain and pre-pregnancy body mass index on the prevalence of large-for-gestational age infants in two cohorts of women with Type I Insulin-Dependent Diabetes: A cross-sectional population study

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Objectives Despite improvements in treatment modalities, large-for-gestational age (LGA) prevalence has remained between 30-40% among infants of mothers with Type I Insulin-Dependent Diabetes (TIDM). Our objective was to estimate LGA prevalence and examine the association between gestational weight gain (GWG) and pre-pregnancy body mass index (BMI) with LGA among mothers with TIDM.

Design Cross-sectional study.

Setting Regional data in Cincinnati, OH, from the Diabetes in Pregnancy Program Project (PPG), a prospective cohort for the period 1978-1993; national data from Consortium on Safe Labor (CSL), a multi-center cross-sectional study for the period 2002-2008.

Participants The study included 333 pregnancies in the PPG, and 358 pregnancies in the CSL. Pregnancies delivered prior to 23 weeks' gestation were excluded. Women with TIDM in the PPG were identified according to physician confirmation of ketoacidosis, and or c-peptide levels, and by International Classification of Diseases (ICD)-9 codes within the CSL. LGA was identified as birthweight > 90th percentile according to gestational age, race and sex.

Main outcome measure LGA at birth.

Results Mean ± standard deviation maternal age at delivery was 26.4 ±5.1 years for PPG women and 27.5 ±6.0 years for CSL women, p=0.008. LGA prevalence did not significantly change between cohorts (PPG: 40.2% vs CSL: 36.6%, p=0.32). More women began pregnancy as overweight in the later cohort (PPG (16.8%) vs CSL (27.1%), p<0.001). GWG exceeding Institute of Medicine (IOM) guidelines increased from PPG (42.3%) to CSL (56.2%), p<0.001. Normal weight women with GWG within IOM guidelines was associated with reduced LGA prevalence in CSL (PPG: 30.6% vs CSL: 13.7%), p=0.001.

Conclusions Normal weight women with GWG within IOM guidelines experienced a reduction in LGA prevalence, supporting the importance of adherence to IOM guidelines for GWG to reduce LGA. Increasing BMI and GWG may be hindering a reduction in LGA prevalence.

Key words

Type I Diabetes

Pre-pregnancy body mass index

Gestational weight gain

Large-for-gestational age

Strengths and limitations of this study

- We had access to two cohorts of women with TIDM across a 30-year time period covering an era of major advancements in insulin treatment and delivery, and emergence of obesity as a prevalent chronic disease, potentially representing opposing risks for delivery of a large-for-gestational age (LGA) baby.
- The Diabetes in Pregnancy Program Project (PPG) cohort includes frequent, repeated observations of women during pregnancy while the Consortium on Safe Labor (CSL) provides a national, contemporary large-scale database.
- Glucose control was not available in CSL precluding comparison between groups.
- The potential differences between local (PPG) and national (CSL) populations include regional differences in diet, methods of treatment, racial composition and geography, limiting the generalizability of our results.
- Despite the importance of nephropathy and retinopathy as indicators of diabetes severity potentially affecting glucose transport, differing definitions between the cohorts prevented variable harmonization, and therefore prohibited the adjustment of these factors in our study.

BACKGROUND

Despite advancements in insulin treatment and delivery for those with Type I Insulin-Dependent Diabetes (TIDM)[1 2], the prevalence of neonatal large-for-gestational age (LGA) among women in this population remains high[1 3-5]. LGA prevalence has remained at 30-40% among infants of mothers with TIDM[5-7]. Independently associated maternal factors for LGA include maternal age, race, stature/height[8] , ethnicity and parity[5 9-12] , excessive fetal nutrition[13] mediated by maternal hyperglycemia[2], excessive gestational weight gain (GWG)[5 14-16] and pre-pregnancy body mass index (BMI)[10 14 17 18] . LGA infants of mothers with diabetes are at increased risk for fetal distress[6] leading to cesarean section[19], and also obesity[20-22], insulin resistance (IR)[20], type II diabetes mellitus (T2DM) and cardiovascular compromise[23 24] in adolescence and adulthood.

The steady state of higher perinatal birthweight among offspring of mothers with TIDM, even in the presence of tight glucose control, has promoted studies that emphasize the independent role of both increased rates of pre-pregnancy BMI[19] and excessive GWG[15] on neonatal outcome. According to data from NHANES, between 2011 and 2014, nearly 34% of women aged 20-39 years were obese[25]. Most recently, among all women who delivered a live infant in 2014, nearly 50% had a pre-pregnancy BMI of either overweight (25.6%) or obese (24.8%)[25].

In addition to the trend in increasing pre-pregnancy BMI, more women are gaining weight in excess of the 2009 Institute of Medicine (IOM) guidelines for GWG[26-28]. According to the IOM and National Research Council in “Reexamining the Guidelines”, there has been an upward trend in GWG from 1990-2005[28]. Women with TIDM who gain excessive gestational weight have been found to be at even greater risk of LGA, perhaps due to excessive fetal nutrition resulting from increased maternal carbohydrate intake following hypoglycemic events[15] . Other studies have suggested insulin resistance developing as early as in utero[29] as a result of overproduction of fetal insulin in response to circulating maternal glucose crossing the placenta[30]. The fetus then stores this surplus energy as fat and can result in perinatal

complications such as LGA[18]. Given these two trends and the link between the hyperglycemic intrauterine environment and fetal overnutrition[19 31 32] , women with TIDM belonging to higher BMI subgroups, who exceed IOM guidelines for GWG, may be at the greatest risk of LGA.

In an effort to understand the implications of excessive GWG and pre-pregnancy BMI within this population, we compared LGA infants observed in the Diabetes in Pregnancy Program Project (PPG), a cohort of women with TIDM going through pregnancy, studied from 1978 to 1993, to those in the Consortium on Safe Labor (CSL), a more contemporary TIDM population delivering between 2002 and 2008. We aim to establish the potential change in prevalence of LGA among infants exposed to maternal TIDM between 1978-1993 and 2002-2008. We also aim to determine associations between adherence to IOM guidelines for GWG and LGA outcome among mothers with TIDM, across pre-pregnancy BMI categories, to identify subgroups who may be at highest risk for LGA. These findings will help interpret the literature on IOM guidelines for GWG in the TIDM population as well as inform future research focusing on reducing LGA births among infants exposed to maternal hyperglycemic environments.

RESEARCH DESIGN AND METHODS

Diabetes in Pregnancy Program Project (PPG): The PPG study enrolled 303 women with TIDM in a cohort in Cincinnati, Ohio from 1978-1993 for a total of 372 pregnancies going beyond 23 weeks' gestation. After exclusions (see below), the analytic population included 333 pregnancies. Participants in the PPG were recruited preconceptionally or during the first half of the pregnancy period as part of a program funded by the National Institute of Health (NIH) in order to examine the impact of strict glycemic control during pregnancy on the rate of adverse maternal and neonatal outcomes in mothers with TIDM. The interdisciplinary core of this study involved endocrinologists, perinatologists, and neonatologists. TIDM study subjects recruited and enrolled into the program belonged to White's classification B to RT[33] . Two levels of glycemic control were defined to manage diabetes care: subjects enrolling prior to 9 completed

weeks of gestation were randomized to strict or customary glycemic control. A third group included women enrolling after 9 completed weeks' gestation; they were managed according to customary glycemic control. Fasting blood glucose and 90-minute post-prandial glucose targets for strict glycemic control were: <100 mg/dl and <120 mg/dl respectively; for customary glycemic control: <120 mg/dl and <140 mg/dl, respectively[33] . Extensive gestational and outcome data were collected including weekly weight, blood pressure, insulin requirements, urinalysis and medication use, multiple daily glucose concentrations and detailed delivery and neonatal outcome information.

Consortium on Safe Labor (CSL): The CSL study enrolled 208,695 women in a national multi-center observational study from 2002-2008 for a total of 228,562 deliveries. A total of 594 singleton TIDM pregnancies with delivery at ≥23 weeks' gestation were identified. After exclusions, the analytic population included 358 pregnancies. There were 11 (out of 12) sites represented in the CSL sample of pregnancy complicated by TIDM.

The National Institute of Child Health and Human Development (NIHCD), of the NIH, initiated a retrospective, observational study in a contemporary U.S. obstetric population to reexamine labor progression trends that have long been guided by the Friedman curve. The CSL study included medical records from a population of women from a consortium of 12 U.S. hospitals located across 9 districts of the American College of Obstetricians and Gynecologists and has been described in detail elsewhere[34]. Briefly, patient electronic medical records were extracted, de-identified and entered into a Data Coordinating database which maintained over 225,000 deliveries ≥23 weeks' gestation from 2002 to 2008. Each delivery included ICD-9 codes as well as information related to maternal demographics, maternal weight (kg) and height (m) at admission, prenatal history, preeclampsia, blood pressure, reports of uterine and intra-amniotic infections, anesthesia, obstetric trauma, medication, delivery method, infant birthweight, length, Apgar scores at 1 and 5 minutes, gestational age at delivery and post-natal time spent in the neurointensive care unit (NICU). Data received by the Data Coordinating

Center from each clinical site was mapped to pre-defined codes for each variable. Data underwent inquiries, cleaning, recoding and logic checking. In addition, validation studies were performed to ensure electronic medical records accurately represented medical record charts[34].

Inclusion and exclusion criteria for the current study were identical for each study cohort. Inclusion criteria included TIDM and gestation at 23 completed weeks or later. Exclusion criteria were multiple gestation, fetal anomaly, stillbirth, and missing the outcome and primary exposure variables; birthweight of the neonate, maternal pre-pregnancy and delivery weight and maternal height. No exclusions were made regarding race/ethnicity or age. For women with more than one pregnancy during the study, all pregnancies were included. In addition, no exclusions were made in the CSL based on geographic site.

GWG and pre-pregnancy BMI were the primary exposures of interest, and LGA was the outcome of interest. Potential confounding maternal characteristics of interest included maternal age at delivery, race, parity and preeclampsia. Pre-pregnancy BMI was additionally treated as a potential modifier of the relationship between GWG and LGA. IRB approval was obtained from Cincinnati Children's Hospital Medical Center as well as the University of Cincinnati prior to the secondary analysis of PPG and CSL cohorts.

Statistical Analysis

In two different cohorts, we conducted an analysis on mothers with TIDM who had singleton pregnancies. Women with TIDM in the PPG study were identified according to physician confirmation of ketoacidosis, and or c-peptide levels. Within the CSL cohort, International Classification of Diseases (ICD)-9 codes 250.01, 250.03, 250.21, 250.23, 250.31, 250.33, 250.41, 250.43, 250.51, 250.53, 250.61, 250.63, 250.71, 250.73, 250.81, 250.83, 250.91, 250.93 were utilized to identify women with TIDM. To determine LGA classification for each cohort, a McNemar's test of marginal homogeneity was performed comparing Lubchenco curves to both Cincinnati-based reference population growth curves for PPG and medical chart

LGA classifications for CSL. LGA was finally defined as birthweight > 90th percentile and was classified by gestational age-, race- and sex-specific curves according to Lubchenco[35] for the PPG cohort and by the extracted variable from detailed medical chart review for CSL. Pre-pregnancy BMI was calculated by using self-reported weight prior to pregnancy and height, recorded at the initial visit for women in the PPG and at the labor and delivery admission for women in the CSL. Underweight, normal weight, overweight and obese pre-pregnancy BMI classifications were defined as: BMI<18.5 kg/m^2; 18.5≤BMI<25 kg/m^2, 25≤BMI<30kg/m^2 and BMI≥30 kg/m^2, respectively. GWG was defined as weight at admission for delivery minus pre-pregnancy weight (kg). IOM adherence for GWG was categorized utilizing the pre-pregnancy BMI-specific 2009 guidelines as under, within (underweight: 12.5-18.0 kg; normal: 11.5-16.0 kg; overweight: 7.0-11.5 kg; obese (all classes): 5.0-9.0 kg) or over IOM guidelines. Calculations for recommended weight gain assume a 0.5-2.0 kg weight gain in the first trimester[28]. Variables within PPG and CSL were harmonized for comparative analysis. Race was based on self-identification, and was categorized as black, white or other. Due to the small number of obese women in the PPG cohort, overweight and obese BMI categories were combined for analysis. Continuous and categorical variables are represented with mean (±SD) and n (%), respectively. Maternal characteristics were compared between and within cohorts by LGA status and by adherence to IOM guidelines for GWG (under, within and over) using Chi-square or Fisher's exact test, and analysis of variance (ANOVA) or Wilcoxon rank sum, as appropriate. Normality testing for distribution of continuous variables was performed by examining histograms, stem-leaf plots, and Kolmogorov-Smirnov tests. A site frequency distribution was examined to investigate possible bias in site representation in the CSL sample. Bonferroni was used to adjust for multiple testing. Generalized Estimating Equations (GEE) were used to estimate the odds ratio (OR) of giving birth to an LGA infant for women exceeding IOM guidelines vs women who adhered to IOM guidelines to account for inherent correlation among women with multiple pregnancies in each study. General linear models were used to examine the relationships

between GWG and birthweight. To determine whether IOM adherence varied across BMI categories (18.5≤BMI<25, 25≤BMI<30, BMI≥30 kg/m^2) interaction terms were used to evaluate effect modification. Normal weight women within IOM guidelines for GWG was used as the reference category. Models adjusted for potential confounders, selected a priori as risk factors for GWG and LGA and not on the causal pathway, included age, race, parity, pre-pregnancy BMI and preeclampsia. All tests for significance were two-sided and a *p*-value of less than 0.05 was considered statistically significant, appropriately adjusted as necessary. Statistical analyses were completed using SAS® software version 9.4 (SAS Institute, Cary NC).

RESULTS

Table 1 shows maternal characteristics and neonatal outcomes in each cohort. Mean age at delivery was significantly higher for women in the CSL (27.5±6.0) than for women in the PPG (26.4±5.1), p=0.008. There was a higher proportion of black women in the CSL (19.3%) than in the PPG (14.1%). The CSL had a significantly greater proportion of overweight/obese women (51.4%) than the PPG (20.7%), p<0.001. More women exceeded IOM guidelines for GWG in the CSL (56.2%) than in the PPG (42.3%), p<0.001, with overweight/obese women accounting for 58.7% and 41.1% of all women who exceeded guidelines, respectively (table S1).

There was no significant difference in cesarean section rate between the CSL (66.8%) and PPG (70.0%), p=0.36. Women were more likely to deliver at less than 37 weeks' in the CSL (42.6%) than in the PPG (34.2%), p=0.03.

Table 1. Maternal characteristics and neonatal outcomes in PPG (1978-1993) and CSL (2002-2008) cohorts

	PPG	CSL	
Maternal Characteristics	n=333	n=358	*p* value
Maternal age at delivery (years)	26.4 ± 5.1	27.5 ± 6.0	0.008
Married, yes [b]	224 (67.3)	217 (60.6)	0.01
Race			<0.001
White	282 (84.7)	225 (62.8)	
Black	47 (14.1)	69 (19.3)	
Other	4 (1.20)	64 (17.9)	
Nulliparous, yes	166 (49.9)	183 (51.1)	0.74
Pre-pregnancy BMI (kg/m^2)	23.0 ± 3.4	26.9 ± 6.3	<0.001
Pre-pregnancy BMI category			<0.001
Underweight (BMI<18.5 kg/m^2)	11 (3.3)	6 (1.7)	
Normal (18.5 kg/m^2≤BMI<25.0 kg/m^2)	253 (76.0)	168 (46.9)	
Overweight (25.0 kg/m^2≤BMI<30.0 kg/m^2)	56 (16.8)	97 (27.1)	
Obese (BMI≥30.0 kg/m^2)	13 (3.90)	87 (24.3)	
Pre-pregnancy Overweight/Obese	69 (20.7)	184 (51.4)	<0.001
Gestational Weight Gain (kg)	14.4 ± 5.6	14.5 ± 7.4	0.77
IOM Guidelines			
Under	74 (22.2)	62 (17.3)	<0.001
Within	118 (35.5)	95 (26.5)	
Over	141 (42.3)	201 (56.2)	
Preeclampsia, yes	50 (15.0)	55 (15.4)	0.90
Previous cesarean section, yes [b]	105 (31.6)	86 (24.0)	0.08
Cesarean section, yes	233 (70.0)	239 (66.8)	0.36
Preterm delivery, yes			
Delivery prior to 34 weeks	33 (9.9)	48 (13.4)	0.15
Delivery prior to 37 weeks	114 (34.2)	152 (42.6)	0.03
Neonatal Outcomes [a]			
Male	186 (56.2)	193 (53.9)	0.60
Respiratory distress during labor	37 (11.1)	45 (12.8)	0.49
Gestational age (weeks)	37.0 ± 2.4	36.1 ± 2.7	<0.001
Apgar less than 7 (@5 min)	59 (17.7)	23 (6.4)	

Mean ± SD are shown for all continuous variables and n (%) are shown for categorical variables; PPG: Diabetes in Pregnancy Program Project; CSL: Consortium on Safe Labor.

[a] Neonatal outcomes exclude stillbirths and neonatal deaths

[b] PPG: Marital status missing for 11 women; CSL: Previous cesarean section missing for 20 women.

While we observed no difference in overall LGA prevalence between cohorts (CSL: 36.6% vs. PPG: 40.2%, p=0.32), Table 2 shows a lower prevalence of LGA among women in

CSL compared with PPG (13.7% versus 30.6%) who were normal weight and gained within IOM guidelines.

Table 2. Large-for-Gestational Age prevalence within each BMI and IOM adherence subgroup for women in PPG (1978-1993) and CSL (2002-2008) cohorts

		PPG			CSL			
IOM adherence	Pre-pregnancy BMI	N	LGA	% LGA [a]	N	LGA	%LGA [a]	*p* value
Under								
	underweight	4	1	0.7%	2	1	0.8%	0.99
	normal	67	20	14.9%	33	8	6.1%	0.02
	overweight/obese	3	1	0.7%	27	6	4.6%	0.06
Within								
	underweight	7	3	2.2%	3	0	0.0%	0.25
	normal	103	41	30.6%	53	18	13.7%	0.001
	overweight/obese	8	0	0.0%	39	12	9.2%	0.0003
Over								
	underweight	0	0	0.0%	1	0	0.0%	-
	normal	83	38	28.4%	82	37	28.2%	0.98
	overweight/obese	58	30	22.4%	118	49	37.4%	0.008
Total		333	134	40.2%	358	131	36.6%	0.32

IOM=Institute of Medicine; BMI=body mass index (kg/m^2); LGA=large-for-gestational age; PPG: Diabetes in Pregnancy Program Project; CSL: Consortium on Safe Labor.

[a] % LGA for each IOM guideline adherence and pre-pregnancy BMI category are presented as proportions of total LGA infants for each category.

BMI was defined as: underweight (BMI<18.5 kg/m^2); normal (18.5 kg/m^2≤BMI<25.0 kg/m^2); overweight (25.0 kg/m^2≤BMI<30.0 kg/m^2); obese (BMI≥30.0 kg/m^2).

The distribution of LGA by BMI categories has significantly changed over time (see table 3). While normal weight women still have the highest proportion of LGA infants in both the CSL and PPG (48.1% vs 73.9%), there was an increase in overweight women delivering LGA infants over time, from 17.2% (PPG) to 29.8% (CSL), p<.0001. Normal weight women in the CSL, on average, gained 2.4 kg more over gestation than normal weight women in the PPG. In contrast, overweight women in the CSL, on average, gained 2.6 kg less than overweight women in the PPG (table S2).

Table 3. Maternal characteristics of women in PPG (1978-1993) and CSL (2002-2008) cohorts by LGA classification

	PPG			CSL		
Characteristic	LGA Lubchenco	non-LGA	p value	LGA Chart	non-LGA	p value
n (%)	134 (40.2)	199 (59.8)		131 (36.6)	227 (63.4)	
Maternal age at delivery, years	26.5±4.9	26.4±5.2	0.83	27.5 ±6.1	27.6±6.0	0.92
Married, yes	94 (70.1)	130 (65.3)	0.08	87 (66.4)	130 (57.3)	0.09
Race			0.36			0.001
White	118 (88.1)	164 (82.4)		97 (74.1)	128 (56.4)	
Black	15 (11.2)	32 (16.1)		13 (9.9)	56 (24.7)	
Other	1 (0.78)	3 (1.5)		21 (16.0)	43 (18.9)	
Nulliparous, yes	59 (44.0)	107 (53.8)	0.08	60 (45.8)	123 (54.2)	0.13
Pre-pregnancy BMI (kg/m^2)	23.3±3.6	22.7±3.2	0.9	26.7±5.8	26.9±6.5	0.77
Pre-pregnancy BMI category			0.45			0.5
Underweight (BMI<18.5 kg/m^2)	4 (3.0)	7 (3.5)		1 (0.76)	5 (2.2)	
Normal (18.5 kg/m^2≤BMI<25.0 kg/m^2)	99 (73.9)	154 (77.4)		63 (48.1)	105 (46.3)	
Overweight (25.0 kg/m^2≤BMI<30.0 kg/m^2)	23 (17.2)	33 (16.6)		39 (29.8)	58 (25.6)	
Obese (BMI≥30.0 kg/m^2)	8 (6.0)	5 (2.5)		28 (21.4)	59 (26.0)	
Pre-pregnancy Overweight/Obese	31 (23.1)	38 (19.1)	0.38	67 (51.2)	117 (51.5)	0.94
Gestational Weight Gain (kg)	15.7±5.4	13.5±5.7	<.0001	16.3±7.2	13.5±7.3	0.0004
IOM Guidelines			0.02			0.01
Under	22 (16.4)	52 (26.1)		15 (11.5)	47 (20.7)	
Within	44 (32.8)	74 (37.2)		30 (22.9)	65 (28.6)	
Over	68 (50.8)	73 (36.7)		86 (65.7)	115 (50.7)	
Preeclampsia, yes	11 (8.2)	39 (19.6)	0.004	19 (14.5)	36 (15.9)	0.73
Previous cesarean section, yes	45 (33.8)	60 (30.2)	0.48	38 (29.9)	48 (22.8)	0.14
Cesarean section, yes	97 (72.4)	136 (68.3)	0.43	91 (69.5)	148 (65.2)	0.41
Preterm delivery						
Delivery prior to 34 weeks	6 (4.5)	27 (13.6)	0.007	11 (8.4)	37 (16.3)	0.03
Delivery prior to 37 weeks	38 (28.4)	76 (38.2)	0.06	55 (42.0)	97 (42.7)	0.89
Neonatal Outcomes						
Male	81 (61.4)	105 (52.8)	0.12	71 (54.2)	122 (54.2)	1.0
Respiratory distress during labor	11 (8.2)	26 (13.1)	0.17	16 (12.5)	29 (13.0)	0.89
Gestational Age, weeks	37.5±1.9	36.6±2.7	0.001	36.3±2.2	36.0±3.0	0.22
Apgar less than 7 (@5 min)	20 (14.9)	39 (19.6)	0.27	9 (6.87)	14 (6.2)	0.79

Mean ± SD are shown for all continuous variables and n(%) are shown for categorical variables

IOM=Institute of Medicine; BMI=body mass index (kg/m^2); LGA=large-for-gestational age; PPG=Diabetes in Pregnancy Program Project; CSL=Consortium on Safe Labor.

LGA was defined as infants with a birthweight >90th percentile, adjusted for age, sex and race.

Neonatal outcomes exclude stillbirths and neonatal deaths.

Table 4 shows separate associations between pre-pregnancy BMI and GWG with odds of LGA for all women in each cohort. Entering pregnancy with higher BMI did not appear to be an independent predictor of LGA in either group.

Table 4. Association between abnormal pre-pregnancy BMI and unrecommended gestational weight gain compared to normal weight participants within IOM adherence guidelines among PPG (1978-1993) and CSL (2002-2008) study cohorts

PPG	Model I	Model II	Model III
	OR (95% CI)	OR (95% CI)	OR (95% CI)
Pre-pregnancy BMI			-
Normal/Underweight	1.00 (ref)	1.00 (ref)	-
Overweight/Obese	1.28 (0.70, 2.32)	1.44 (0.79, 2.63)	-
Gestational Weight Gain			
Under	0.71 (0.39, 1.31)	0.76 (0.41, 1.41)	0.76 (0.41, 1.42)
Within	1.00 (ref)	1.00 (ref)	1.00 (ref)
Over	1.57 (0.92, 2.65)	1.55 (0.90, 2.67)	1.53 (0.86, 2.71)
CSL	Model I	Model II	Model III
	OR (95% CI)	OR (95% CI)	OR (95% CI)
Pre-pregnancy BMI			-
Underweight	0.33 (0.04, 2.92)	0.38 (0.03, 4.21)	-
Normal	1.00 (ref)	1.00 (ref)	-
Overweight	1.12 (0.67, 1.87)	1.32 (0.77, 2.26)	-
Obese	0.79 (0.46, 1.36)	1.04 (0.58, 1.86)	-
Gestational Weight Gain			
Under	0.69 (0.33, 1.43)	0.75 (0.35, 1.60)	0.73 (0.34, 1.58)
Within	1.00 (ref)	1.00 (ref)	1.00 (ref)
Over	1.62 (0.97, 2.72)	1.54 (0.91, 2.63)	1.46 (0.84, 2.52)

OR=odds ratio (95% confidence interval); IOM=Institute of Medicine; BMI=body mass index (kg/m^2); LGA=large-for-gestational age; PPG: Diabetes in Pregnancy Program Project; CSL: Consortium on Safe Labor.

Model I - Adjusted for age

Model II - Adjusted for Model I + maternal race, parity, preeclampsia

Model III - Adjusted for Model II + pre-pregnancy BMI

BMI was defined as: underweight (BMI<18.5 kg/m^2); normal (18.5 kg/m^2≤BMI<25.0 kg/m^2); overweight (25.0 kg/m^2≤BMI<30.0 kg/m^2); obese (BMI≥30.0 kg/m^2).

When considering all BMI groups collectively, exceeding IOM guidelines for GWG vs. remaining within IOM guidelines was not a significant predictor of increased risk for LGA in either cohort. The OR adjusted for age for mothers who exceeded IOM guidelines compared to those who remained within guidelines was similar for women in the CSL [OR 1.60, 95%CI (0.95, 2.68), p=0.08] compared to mothers in the PPG [OR 1.57, 95%CI (0.92, 2.65), p=0.10]. There was

also no significant difference in average total GWG between the groups, 14.5±7.4 for CSL and 14.4±5.6 for PPG (p=0.77). There remained no significant increase in risk of LGA after further adjustments for covariates and pre-pregnancy BMI for either group.

In the CSL, normal weight women who exceeded IOM guidelines [OR 2.14 95%CI (1.17, 3.91), p=0.01] and overweight women who exceeded IOM guidelines [OR 2.35 95%CI (1.26, 4.40), p=0.01] had increased odds of LGA after adjusting for age when compared to the normal weight women who did not exceed IOM guidelines, as shown in Table 5.

Table 5. Adjusted odds ratios (95% CI) for LGA by abnormal pre-pregnancy BMI and unrecommended gestational weight gain compared to normal weight participants within IOM adherence guidelines among PPG (1978-1993) and CSL (2002-2008) cohorts

			Model I		Model II	
PPG			OR (95% CI)		OR (95% CI)	
IOM adherence	Pre-pregnancy BMI	n		*p* value		*p* value
Within	normal/underweight	110	1.00 (ref)		1.00 (ref)	
	overweight/obese	8	-		-	
Over	normal/underweight	83	1.61 (0.93, 2.80)	0.09	1.48 (0.83, 2.64)	0.18
	overweight/obese	58	2.04 (1.05, 3.97)	0.03	2.12 (1.11, 4.04)	0.02
			Model I		Model II	
CSL			OR (95% CI)		OR (95% CI)	
IOM adherence	Pre-pregnancy BMI	n				
Within	Normal	56	1.00 (ref)		1.00 (ref)	
	Overweight	15	0.38 (0.08, 1.81)	0.23	0.53 (0.10, 2.73)	0.45
	Obese	23	1.86 (0.75, 4.60)	0.18	1.99 (0.79, 5.01)	0.15
Over	Normal	82	2.14 (1.17, 3.91)	0.01	1.83 (0.99, 3.40)	0.06
	Overweight	70	2.35 (1.26, 4.40)	0.01	2.25 (1.18, 4.28)	0.01
	Obese	49	1.26 (0.61, 2.59)	0.53	1.49 (0.70, 3.19)	0.30

OR=odds ratio; 95% confidence interval (CI); IOM=Institute of Medicine; BMI=body mass index (kg/m^2); LGA=large-for-gestational age; PPG: Diabetes in Pregnancy Program Project; CSL: Consortium on Safe Labor.
Model I - Adjusted for age
Model II - Adjusted for Model I + maternal race, parity, preeclampsia
BMI was defined as: underweight (BMI<18.5 kg/m^2); normal (18.5 kg/m^2≤BMI<25.0 kg/m^2); overweight (25.0 kg/m^2≤BMI<30.0 kg/m^2); obese (BMI≥30.0 kg/m^2).
Insufficient LGA infants of overweight/obese women who remained within IOM guidelines to make LGA OR determination

After adjusting for other risk factors, the combined effect of overweight and exceeding IOM guidelines remained, with an increase in odds of LGA [OR 2.25, 95%CI (1.18, 4.28), p=0.01] compared to the reference group. The increased odds for LGA in normal weight women who exceed IOM guidelines was slightly attenuated [OR 1.83 95%CI (0.99, 3.40), p=0.06]. Similar results were shown for overweight/obese women in the PPG who exceeded IOM guidelines. There was an increase in odds of LGA for these women in both models adjusted for age only [OR 2.04 95%CI (1.05, 3.97), p=0.03] and fully adjusted models [OR 2.12 95%CI (1.11, 4.04), p=0.02] compared with normal weight women who remain within IOM guidelines.

DISCUSSION

Although delivery of LGA infants in the TIDM population has been examined in several epidemiological studies, few studies have examined LGA prevalence over time. In this analysis of GWG, pre-pregnancy BMI and LGA infant births among mothers with TIDM, we identified several important overall and GWG- and BMI-specific patterns. Our results suggest no change in overall LGA prevalence over a 30-year period. However, the proportion of infants born LGA to women of normal weight who adhered to GWG guidelines was reduced by 17%. This reduction appeared to be offset by a 15.0% increase in LGA prevalence among overweight/obese women who exceeded IOM guidelines.

Persson et al, 2009 showed that in a contemporary population of women with TIDM, obstetric and perinatal complications, particularly higher birthweight, remain markedly higher than the general population[6]. Similarly, the results of our study demonstrate that high weight for gestational age remains a frequent outcome in pregnancies complicated by TIDM, despite advancements throughout the years in glucose management and insulin treatment and delivery. Overall, our study showed LGA prevalence, for both groups, was markedly higher than the general population, despite observing reductions within select BMI subgroups.

Historically, obesity has been associated with T2DM. However, the TIDM population has shown a significant increase in women entering pregnancy as overweight and obese. There was a marked increase in the proportion of overweight/obese women in the CSL compared to the PPG (51.4% vs 20.7%). Women in the CSL belonging to the overweight/obese subgroup accounted for a greater proportion of those who exceeded IOM guidelines (58.7%) compared with women in the PPG (41.1%). Overweight/obese women who exceeded IOM guidelines showed a 15.0% (p=0.01) increase in LGA over time. Our results confirm previous studies that have linked maternal overweight[19 31], GWG[36] and adverse birth outcomes in the TIDM population. Despite the improvement, this subgroup remains at the highest risk of delivering an LGA infant compared to normal weight women who adhered to IOM guidelines. Interestingly, despite a lower average GWG for women with higher BMI in the CSL compared to women in the PPG, women with overweight and obesity remained in excess of IOM guidelines for GWG. On average, overweight and obese CSL women gained 2.6 kg less and 0.30 kg more, respectively, over total gestation than overweight and obese women in the PPG. These results suggest that women in the PPG with higher BMI far exceeded IOM guidelines. The reduction in average GWG for overweight and obese women could help explain the lowered LGA prevalence over time in this subgroup, 41.2% in the CSL compared to 51.7% in the PPG. Previous studies in the literature have shown the effect of excessive GWG on risk of LGA, independent of BMI[14-16 37]. However, the results of our study did not show BMI and adherence to IOM guidelines as independent predictors of LGA. Women who were not only overweight (or obese for PPG) but who also exceeded GWG guidelines were at a greater than 2-fold increase risk of delivering an LGA infant (CSL [OR 2.25, (1.18, 4.28)], PPG [OR 2.12, (1.11, 4.04)]), compared with women who were normal weight and with GWG within IOM guidelines.

The results of our study point to need of future research that includes additional parameters to consider when establishing appropriate GWG guidelines specific to this population, such as age at onset of diabetes (or duration), pre-pregnancy glucose control and diabetes severity upon

entering pregnancy. Although in a gestational diabetes (GDM) population, Bowers et al. were also able to show racial variation in the joint effects of pre-pregnancy obesity, GWG and GDM on birthweight[38]. Women with TIDM who are planning pregnancies are urged to achieve optimal weight and clinically acceptable glucose control prior to pregnancy. For women in this population with unplanned pregnancies, future research is needed that examines more longitudinal studies that include regular monitoring of glucose and insulin dosage throughout pregnancy, as well as caloric intake. Not only is GWG of key concern, but gestational timing of weight gain may also play a role in increased risk of LGA infants. Studies have demonstrated that first trimester GWG showed the strongest effect on adverse maternal, fetal and childhood outcomes, including increased neonatal adiposity[39]. All of these factors should be considered when designing studies that seek to establish new GWG guidelines specific to this population.

This study has several limitations. Our analysis was unable to include a comparison of glucose control between groups, indicated by measures of $HbA1_c$, as this data was not available for CSL participants. Although Secher et. al. showed higher GWG was associated with LGA outcomes, independent of glucose control[15], these measurements could potentially account for the reduction in LGA prevalence among normal weight women who adhered to IOM guidelines in our study. Secondly, women with TIDM, when compared to women with T2DM, often have higher $HbA1_c$ throughout pregnancy due to higher diabetes duration accompanied with greater variations in glycaemic control[40]. We did not have access to diabetes duration for women in the CSL. However, it is plausible that diabetes duration was similar for both groups as there was no significant difference in mean maternal age at delivery between the groups for women with LGA infants across all levels of IOM adherence, *data not shown*. Further, our study compared women with TIDM from a local population to women in a nationally representative population. The differences between the populations, which include regional differences in diet, methods of treatment, access to quality health care, racial composition and geography limit the

generalizability of our results. However, this study serves as an important start for assessing impact of policy changes on perinatal outcomes like LGA over time. Our sample size for overweight and obese women who remain within IOM guidelines for PPG limited our power to robustly test effect modification, and thus no comparisons across time could be made between groups. However, we were able to examine the role of pre-pregnancy BMI as an effect modifier in the contemporary CSL cohort. In addition, pre-pregnancy BMI was determined, in part, by self-reported pre-pregnancy weight in both cohorts, yielding our calculation of pre-pregnancy BMI subject to recall bias. The ICD-9 codes that were used to identify women in the CSL with TIDM have not been validated in this study. However, according to Zhang et al., validation studies were conducted for four key outcomes, including method of delivery, gestational age ≥34 and ≥37 weeks and clinical diagnosis of shoulder dystocia[34], common in LGA deliveries. Most variables that were reviewed were highly accurate, indicating information provided in the validation studies was reliable and likely generalizable to the entire database. Lastly, despite the importance of nephropathy and retinopathy as indicators of diabetes severity, potentially affecting glucose transport, differing definitions between cohorts prevented variable harmonization and, therefore, prohibited the adjustment of these factors in our study. Prevalence of nephropathy according to each group's definition was 18.9% for PPG and 7.8% for CSL.

Despite these limitations, important strengths exist and this study extends beyond prior studies in several important areas. Our study compared two cohorts of women across a time period wherein major advancements have been made in the treatment of TIDM while simultaneously obesity has become a prevalent chronic disease– representing opposing risks for LGA. Each data set is comprehensive and has unique strengths. For instance, the PPG cohort includes frequent, repeated observations of women during pregnancy, while the CSL is large and contemporary.

In conclusion, while overall LGA prevalence has remained relatively unchanged over time, normal weight women with TIDM who adhere to IOM guidelines have experienced a reduction in LGA prevalence. Women in a more recent TIDM population are starting the pregnancy period with significantly higher proportions of overweight and obesity than in previous years. Entering pregnancy as overweight while exceeding IOM guidelines for GWG places women in this population at the highest risk of LGA. This study demonstrates the importance of strict adherence to IOM guidelines for GWG, particularly for women who enter pregnancy as overweight, in order to address reduction of LGA rates in the TIDM population.

Contributors

Study concept and design: KLM, JCK; acquisition of data: JCK; statistical analysis: KLM; interpretation of data: KLM, JCK, KB, CLJ, RD, LMD; drafting of the manuscript: KLM; critical revision of the manuscript for important intellectual content: KLM, JCK, KB, CLJ; administrative, technical, and material support: CLJ, JCK. All authors approved of the version of the manuscript to be published.

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Competing interests None declared.

Patient consent Yes.

Ethics approval IRB approval was obtained from Cincinnati Children's Hospital Medical center as well as the University of Cincinnati prior to the secondary analysis of the Diabetes in Pregnancy Program Project (PPG) and the Consortium on Safe Labor (CLS) data.

Data sharing statement No additional data are available.

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Table S1. Maternal characteristics of women in PPG (1978-1993) and CSL (2002-2008) by adherence to IOM recommendations for gestational weight gain

	PPG n=333				CSL n=358			
	n=74	n=118	n=141		n=62	n=95	n=201	
Characteristic	IOM under[1]	IOM within	IOM over	*p*-value	IOM under	IOM within	IOM over	*p*-value
Maternal age (at delivery), years	25.6 ± 5.2	26.7 ± 4.8	26.5 ± 5.1	0.33	28.2 ± 6.0	27.7 ± 5.9	27.3±6.1	0.53
Married, yes [a]	41 (22.1)	89 (77.4)	94 (69.1)	0.02	39 (62.9)	56 (59.0)	122 (60.7)	0.88
Race				0.15				0.02
White	56 (75.7)	103 (87.3)	123 (87.2)		30 (48.4)	57 (60.0)	138 (68.7)	
Black	17 (23.0)	13 (11.0)	17 (12.1)		20 (32.3)	18 (19.0)	31 (15.4)	
Other	1 (1.3)	2 (1.7)	1 (0.7)		12 (19.3)	20 (21.1)	32 (15.9)	
Nulliparous, yes	43 (58.1)	59 (50.0)	64 (45.4)	0.21	26 (41.9)	50 (52.6)	107 (53.2)	0.28
Pre-pregnancy BMI (kg/m^2)	21.9 ± 2.9	22.0 ± 2.7	24.4 ± 3.6	<.0001	27.2 ± 7.2	26.3 ± 6.6	27.0 ± 5.7	0.62
Pre-pregnancy BMI category				<.0001				0.007
Underweight (BMI<18.5 kg/m^2)	4 (5.4)	7 (5.9)	0 (0.0)		2 (3.2)	3 (3.2)	1 (0.5)	
Normal (18.5 kg/m^2≤BMI<25.0 kg/m^2)	67 (90.5)	103 (87.3)	83 (58.9)		33 (53.2)	53 (55.8)	82 (48.8)	
Overweight (25.0 kg/m^2≤BMI<30.0 kg/m^2)	1 (1.4)	7 (5.9)	48 (34.0)		12 (19.4)	15 (15.8)	70 (34.8)	
Obese (BMI≥30.0 kg/m^2)	2 (2.7)	1 (0.9)	10 (7.1)		15 (24.2)	24 (25.3)	48 (23.9)	
Pre-pregnancy Overweight/Obese (BMI≥25.0 kg/m^2)	3 (4.1)	8 (6.8)	58 (41.1)	<.0001	27 (43.6)	39 (41.1)	118 (58.7)	0.007
Gestational Weight Gain (kg)	7.2 ± 3.9	13.4 ± 1.8	18.9 ± 4.0	<.0001	4.9 ±5.3	11.6 ± 3.0	18.8 ± 5.7	<.0001
Preeclampsia, yes	13 (17.6)	17 (14.4)	20 (14.2)	0.78	10 (16.1)	9 (9.5)	36 (17.9)	0.17
Previous cesarean section, yes [a]	16 (21.9)	40 (33.9)	49 (34.8)	0.13	15 (25.9)	22 (25.3)	49 (25.4)	1.00
Cesarean section, yes	50 (67.6)	84 (71.2)	99 (70.2)	0.86	37 (59.7)	59 (62.1)	143 (71.1)	0.13
Large-for-gestational age	22 (29.7)	44 (37.3)	68 (48.2)	0.02	15 (24.2)	30 (31.6)	86 (42.8)	0.01

Mean ± SD are shown for all continuous variables and n(%) are shown for categorical variables

LGA was defined as infants with a birthweight >90th percentile, adjusted for age, sex and race.

[a] PPG: Marital status missing for 11 women; CSL: Previous cesarean section missing for 20 women.

Table S2. Mean ± SD of reproductive characteristics for PPG (1978-1993) and CSL (2002-2008) stratified by BMI

	PPG				CSL			
	n=333				n=358			
n	11	253	56	13	6	168	97	87
	Underweight	Normal	Overweight	Obese	Underweight	Normal	Overweight	Obese
Maternal age at delivery (years)	24.4 ± 5.2	26.5 ± 4.8	25.9 ± 5.9	29.3 ±4.9	28.8 ± 4.1	27.4 ± 5.5	26.6 ± 6.3	28.8 ± 5.8
Birthweight (g)	2994 ± 945	3269 ± 796	3390 ± 767	3293 ± 903	2942 ± 666	3264 ± 792	3277 ± 823	3149 ± 910
Gestational age (weeks)	35.7 ± 3.7	36.9 ± 2.47	37.4 ± 2.17	37.4 ±1.5	35.7 ± 5.4	36.3 ± 2.6	36.0 ± 2.3	36.0 ± 3.1
Gestational Weight Gain (kg)	11.5 ± 5.0	14.0 ± 5.5	17.1 ± 5.4	10.7 ±5.4	11.3 ± 8.6	16.4 ± 6.4	14.5 ± 6.7	11.0 ± 8.5
Prepregnancy BMI	17.3 ± 0.7	21.9 ± 1.6	26.6 ± 1.35	33.6 ±3.7	17.5 ± 1.0	23.4 ± 1.7	27.2 ± 1.5	35.8 ± 5.3

Mean ± SD are shown for all continuous variables

BMI=body mass index (kg/m^2); PPG=Diabetes in Pregnancy Program Project; CSL=Consortium on Safe Labor.

BMI was defined as: underweight (BMI<18.5 kg/m^2); normal (18.5 kg/m^2≤BMI<25.0 kg/m^2); overweight (25.0 kg/m^2≤BMI<30.0 kg/m^2); obese (BMI≥30.0 kg/m^2).

STROBE Statement—checklist of items that should be included in reports of observational studies

	Item No	Recommendation
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract **[Within the title page 1 and design section of the abstract page 2]**
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found **[Results section of abstract page 2]**
Introduction		
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported **[page 5]**
Objectives	3	State specific objectives, including any prespecified hypotheses **[page 6]**
Methods		
Study design	4	Present key elements of study design early in the paper **[Methods pages 6-7]**
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection **[Methods pages 6-7]**
Participants	6	(*a*) *Cohort study*—Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up **[ ]** *Case-control study*—Give the eligibility criteria, and the sources and methods of case ascertainment and control selection. Give the rationale for the choice of cases and controls **[ ]** *Cross-sectional study*—Give the eligibility criteria, and the sources and methods of selection of participants **[pages 6-7]**
		(*b*) *Cohort study*—For matched studies, give matching criteria and number of exposed and unexposed **[ ]** *Case-control study*—For matched studies, give matching criteria and the number of controls per case **[ ]**
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable **[pages 8-9]**
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group **[pages 8-9]**
Bias	9	Describe any efforts to address potential sources of bias **[page 8]**
Study size	10	Explain how the study size was arrived at **[pages 6-7]**
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why **[pages 8-9]**
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding **[pages 8-10]**
		(*b*) Describe any methods used to examine subgroups and interactions **[page 9]**
		(*c*) Explain how missing data were addressed **[N/A]**
		(*d*) *Cohort study*—If applicable, explain how loss to follow-up was addressed **[ ]** *Case-control study*—If applicable, explain how matching of cases and controls was addressed **[ ]**

		Cross-sectional study—If applicable, describe analytical methods taking account of sampling strategy **[N/A]**
		(*e*) Describe any sensitivity analyses **[N/A]**
Results		
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed **[page 11 table 1]**
		(b) Give reasons for non-participation at each stage **[N/A]**
		(c) Consider use of a flow diagram **[N/A]**
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders **[pages 10-11 and table 1]**
		(b) Indicate number of participants with missing data for each variable of interest **[table 1]**
		(c) *Cohort study*—Summarise follow-up time (eg, average and total amount) **[ ]**
Outcome data	15*	*Cohort study*—Report numbers of outcome events or summary measures over time **[ ]**
		Case-control study—Report numbers in each exposure category, or summary measures of exposure **[ ]**
		Cross-sectional study—Report numbers of outcome events or summary measures **[tables 2 and 3]**
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included **[table 4]**
		(*b*) Report category boundaries when continuous variables were categorized **[N/A]**
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period **[N/A]**
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses **[table 5]**
Discussion		
Key results	18	Summarise key results with reference to study objectives **[page 16]**
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias [**pages 17-18]**
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence **[pages 18-19]**
Generalisability	21	Discuss the generalisability (external validity) of the study results **[page 18-19]**
Other information		
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based **[page 21]**

*Give information separately for cases and controls in case-control studies and, if applicable, for exposed and unexposed groups in cohort and cross-sectional studies.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at www.strobe-statement.org.