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Rate of gestational weight gain and glucose-insulin metabolism among Hispanic pregnant women with overweight and obesity

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Abstract

Context

Hispanic women are at elevated risk of gestational glucose intolerance and postpartum type 2 diabetes compared to non-Hispanic White women. Identification of potentially modifiable factors contributing to this trajectory of beta-cell dysfunction is warranted.

Objective

To determine the association between rate of gestational weight gain (rGWG) and glucose-insulin metabolism in Hispanic pregnant women with overweight and obesity.

Design

Cross-sectional, observational study conducted between 2018-2020.

Setting

Clinical research center at University of California, Irvine.

Participants

Thirty-three non-diabetic Hispanic pregnant women at 28-30 weeks' gestation with pre-pregnancy body mass index (BMI) 25.0-34.9 kg/m^2.

Interventions

A standardized liquid mixed-meal was consumed after an overnight fast. Serial blood samples were collected at fasting and up to two hours postprandial.

Main outcome measures

The glucose and insulin area-under-the-curve (AUC), insulin sensitivity index (ISI) and insulin secretion sensitivity index (ISSI)-2 were computed.

Results

Average rGWG (0.36±0.22 kg/week) was classified as excessive in 60% of women. While rGWG was not associated with the glucose or insulin AUC or ISI, it did account for 13.4% of the variance in ISSI-2 after controlling for covariates (maternal age, parity and pre-pregnancy BMI); for each one unit increase in rGWG, ISSI-2 decreased 2.1 units (p=0.015).

Conclusions

Even in the absence of gestational diabetes, rGWG was inversely associated with beta-cell function in a high-risk population of Hispanic pregnant women with overweight and obesity. Beta-cell decline is an established risk factor for transition to type-2 diabetes, and these cross-sectional findings highlight rGWG as a potentially modifiable contributor to this process.

Keywords:

Beta-cell function; gestational weight gain; glucose-insulin metabolism; insulin sensitivity; maternal overweight/obesity; pregnancy.

Introduction

Pregnancy is a state of progressive insulin resistance which is compensated by increased insulin secretion (1). When pancreatic beta-cell compensation fails, hyperglycemia occurs and gestational diabetes mellitus (GDM) develops (2). Hyperglycemia in pregnancy exists along a continuum, and even in the absence of overt GDM, mildly impaired glycemic control is associated with adverse pregnancy and child health outcomes (3-5). There is evidence to suggest that glucose intolerance in the context of pregnancy reflects pre-existing, chronic beta-cell dysfunction that is unmasked due to the progressive demands of gestational insulin resistance (6, 7). Accordingly, decreased beta-cell function detected early in pregnancy has been found to predict postpartum diabetes risk (8), and any degree of impaired glucose tolerance in pregnancy is associated with continued beta-cell dysfunction postpartum (9), contributing to later development of type 2 diabetes (10). Measures of insulin sensitivity and secretion in pregnancy are therefore important indicators of future maternal cardiometabolic disease risk and may be detectable before hyperglycemia is evident. Investigation of potentially modifiable factors that influence the trajectory of beta-cell dysfunction among high risk prenatal groups is warranted.

Maternal overweight/obesity is an established risk factor for gestational hyperglycemia (11, 12). Compared to non-Hispanic White women, Hispanic women have significantly higher rates of obesity on entering pregnancy and are at higher risk of gestational hyperglycemia within each category of pre-pregnancy body mass index (BMI) (13). GDM prevalence is even more pronounced among immigrant Hispanic women, who have a lower percent attributable risk from pregravid obesity compared to their non-immigrant counterparts born in the U.S. (14, 15), suggesting that other risk factors related to life course trajectory, acculturation, or dietary patterns are at play (14). Furthermore, Hispanic women overall have a substantially higher risk of developing type 2 diabetes after GDM compared to non-Hispanic White

women (16). Thus, the Hispanic population, which is the largest ethnic minority group in the U.S., is at heightened risk for poor metabolic health before, during and after pregnancy, and this risk may be further moderated by factors pertaining to their nativity status (i.e. first or subsequent generation immigrants) in the U.S.

Prenatal healthy lifestyle interventions frequently target excess gestational weight gain (GWG) as a modifiable factor that may help reduce the risk of gestational hyperglycemia. However, several large clinical trials report limited success with this approach (17-19). Yet, the impact of GWG on beta-cell dysfunction, which may precede the development of overt GDM and predispose to long-term diabetes risk (8), is poorly understood. Evidence from non-pregnant and postpartum Hispanic cohorts suggests that weight or adiposity gain may play a critical role in the progression of beta-cell dysfunction (20, 21). Therefore, it is important to elucidate whether GWG may contribute to altered glucose-insulin metabolism, presenting as either hyperglycemia, impaired insulin sensitivity or beta-cell dysfunction, in the context of pregnancy in the Hispanic population. A recent study among Caucasian pregnant women with predominantly healthy pre-pregnancy weight detected a small but statistically significant contribution of GWG to glucose metabolism and beta-cell function measured in late pregnancy (22). We hypothesize that GWG will contribute a greater proportion of variance in beta-cell function in a higher risk, metabolically compromised, Hispanic population.

The aim of this study was to determine the association between rate of gestational weight gain (rGWG) and glucose-insulin metabolism, characterized from fasting and postprandial blood samples, in the early third trimester among non-diabetic Hispanic pregnant women with overweight and obesity. A secondary aim was to determine whether this association differed by U.S. nativity status. By examining markers of dysglycemia and beta-cell function

on a continuous spectrum in the absence of overt GDM, this study contributes valuable insight to the nuanced measures of glucose-insulin metabolism that may serve as early indicators for metabolic dysfunction even among those with clinically “normal” levels of gestational glucose tolerance.

Materials and Methods

Design and overview

This is a cross-sectional study of the postprandial metabolic response to a standard liquid meal in the early third trimester of pregnancy, which was performed as a secondary, exploratory analysis from a cross-over study. The parent study aimed to determine the effects of the superimposition of acute psychological stress on maternal glucose-insulin metabolism following a standardized meal. Baseline data (without stress exposure) were included in the present study for all available participants. The University of California, Irvine (UCI) institutional review board approved the study, and all participants provided informed consent.

Participants and Recruitment

Pregnant women were recruited to the study between February 2018 and March 2020. Women were eligible if they were of Hispanic ethnicity, aged 18-40 years, had a pre-pregnancy BMI 25.0-34.9 Kg/m^2, carrying a singleton pregnancy, between 28-30 week’s gestation, non-diabetic (with a normal result on the standard glucose challenge test at 24-28 weeks), non-smoker, and fluent in either English or Spanish. Women were excluded if they had diabetes (including GDM), hypertension, preeclampsia, or diagnosis or treatment of any other condition that may disrupt metabolic, endocrine or immune function. The eligible pre-pregnancy BMI range was chosen for the parent cross-over study in order to select a

homogenous cohort of women at heightened risk of impaired glucose-insulin metabolism that is also generalizable to the majority of Hispanic women of reproductive age in the U.S. (23, 24). Women with diabetes were excluded due to the potential confounding exposure of pharmaceutical treatment or lifestyle interventions that may affect the predictor or outcome variables of interest. Participants were primarily recruited from UCI Health-affiliated obstetric clinics in Orange County, California, after pre-screening of the medical record for potential eligibility. This was supplemented by passive recruitment through email registries and distribution of study brochures. Eligibility for the study was verified by confirming normal glucose tolerance on the standard GDM screening test (<135 mg/dl on 1-hr glucose challenge test or normal results on a 3-hr 100g glucose tolerance test according to Carpenter and Coustan criteria) (25).

Study procedures and data collection

Participants arrived at the clinical research facility in the morning (8-9 am) following an overnight fast. Weight and height were measured, and a nurse phlebotomist placed an indwelling catheter in the antecubital vein of the forearm for blood sample collections. The participant was then allowed to rest seated for 30 minutes while completing a sociodemographic questionnaire, which included questions about country of birth, total household income, and number of household dependents on this income. After the rest period, baseline fasting blood and saliva samples were collected. Participants then immediately consumed a liquid meal (Nestle Boost Plus, 237ml, 360 kcal, 15g protein, 45g carbohydrate, 22g sugar, 3g fiber, 14g fat; option of vanilla or strawberry flavor) and were asked to finish it within 10 minutes. Postprandial blood samples were collected at 6 time points: +15, +30, +45, +60, +90 and +120 minutes post-baseline (the start of meal consumption). Water was provided, but no other food or drink was consumed until the end of the study visit.

Blood samples were collected in 3ml EDTA tubes. Each sample was immediately centrifuged upon collection at 1500g for 15 minutes, aliquoted and stored at -80°C until analyzed. Glucose was measured on a PolyChem clinical chemistry analyzer with reagents from Randox (Kearneysville, WV). Insulin was measured using a multiplex from Meso Scale Discovery (Rockville, MD).

Data processing

GWG up to the time of study visit was computed by subtracting pre-pregnancy weight from measured weight on assessment. Since women were assessed at 28-30 weeks, total GWG was not determined. However, average rate of weekly weight gain up to the time of assessment was estimated as follows: [weight at visit (kg) – pre-pregnancy weight (kg)] / (weeks' gestation at visit – 13). This assumed that no weight gain occurred in the first 13 weeks of pregnancy (i.e. first trimester), which has been previously reported across a range of BMI categories,(26) and weight gain of less than 2 kg is advocated by the National Academy of Medicine (NAM) (27). Computed rGWG per week was compared to NAM guidelines according to pre-pregnancy BMI category: 0.23-0.32 kg/week for overweight category and 0.18-0.27 kg/week for obese category (27). rGWG was then characterized as below, within, or above the NAM guidelines. Pre-pregnancy BMI was determined from the medical record where available (based on measured weight and height within 1 year preconception), or from maternal self-report of pre-pregnancy weight and measured height at the time of screening in their second trimester, using the formula: weight (kg)/height $(m)^2$. Self-reported pre-pregnancy weight has been shown to be a valid estimate of first trimester measured weight in U.S. and Hispanic populations (28, 29). BMI was also categorized as overweight (25.0-30.0 kg/m^2) or obese (≥30.0 kg/m^2). Nativity status was characterized as

born in (N=15) or outside (N=18) the U.S. Of those born outside the U.S., the percentage of life spent in the U.S. was estimated as: (years lived in U.S./age in years)*100.

The Homeostasis Model Assessment of Insulin Resistance (HOMA-IR) was computed according to the formula (30):

$$HOMA - IR = [\text{fasting glucose (mg/dl)} * \text{fasting insulin (mU/ml)}]/405$$

To characterize the degree of insulin resistance in the cohort, HOMA-IR values were compared to reference values previously defined for a Mexican pregnant population (31), that is, values ≥2.6 indicate insulin resistance. The area-under-the-curve (AUC) for glucose and insulin was computed using the trapezoidal method with respect to ground. Insulin Sensitivity Index (ISI) (32) was computed according to the formula:

$$ISI = 10{,}000 \div \sqrt{G_0 \; x \; I_0 \; x \; G_{mean} \; x \; I_{mean}}$$

where G_0 represents fasting glucose concentration (mg/dl), I_0 fasting insulin concentration (mU/ml), G_{mean} is the average glucose concentration from 0-120 minutes and I_{mean} is the average insulin concentration from 0-120 minutes. Higher values of ISI indicate greater insulin sensitivity. The Insulin Secretion Sensitivity Index-2 (ISSI-2), a validated proxy for beta-cell function that is analogous to the disposition index obtained from the intravenous glucose tolerance test (33), was computed according to the formula:

$$ISSI2 = \frac{AUC_{ins}}{AUC_{glu}} * ISI$$

Data analysis

All analyses were performed in SPSS version 26. Data were described by mean and standard deviation for continuous variables or as N (%) for categorical data. Metabolic variables were inspected for normality using histograms and log-transformed as applicable.

Pearson's correlations were used to assess associations between rGWG, pre-pregnancy BMI and metabolic variables. Independent samples t-tests were used to determine differences in mean levels of metabolic variables across categories of rGWG, pre-pregnancy BMI, and nativity status. To account for potential confounding by maternal age and parity, adjusted models were performed using linear regression for continuous and ANCOVA for categorical independent variables. Although this was a relatively homogenous sample with a pre-pregnancy BMI range of 25.0-34.9 Kg/m^2, a sensitivity analysis with additional adjustment for pre-pregnancy BMI was performed to determine the independent association of rGWG per week with metabolic outcomes. The potential moderating effects of nativity status on the association between rGWG and metabolic outcomes was assessed using the interaction term (rGWG*nativity) in the linear regression model. The variance inflation factor was used to test for multicollinearity. Data were considered statistically significant at $p<0.05$.

Results

A total of 104 women were screened for this study and 67 were excluded for ineligibility. The primary reasons for ineligibility were BMI outside of the range or diagnosis of GDM. Of the eligible women invited to participate, 4 did not attend the scheduled visit. Thus, 33 women enrolled and completed study procedures.

Population descriptives

Descriptive statistics for maternal sociodemographic, glucose and insulin variables are presented in Table 1. The majority of women (88%) were in their second or subsequent pregnancy, 30% were below the federal poverty threshold, and 45% were born in the U.S. Mean pre-pregnancy BMI was 28.8 kg/m^{2,} and one-third of the participants were in the obese category. Mean GWG to the time of the study visit was 6.3kg, and over 60% of women had

excess rate of weight gain per week according to NAM guidelines for their BMI category. Women who were overweight had a higher rGWG compared to women with obesity (0.41±0.19 vs 0.25±0.23 kg/week, p=0.036). Fasting plasma glucose was in the normal healthy range and exhibited low variation. Fasting insulin levels were on average higher than has previously been reported for pregnant women in the third trimester (34) and the median HOMA-IR value indicates a high degree of insulin resistance in this cohort without GDM. Specifically, 62% of the population had a HOMA-IR value ≥2.6 which is the cut point for insulin resistance defined for Mexican pregnant women (31).

Correlations between anthropometric and metabolic variables

Figure 1 displays the median glucose and insulin response to the test meal. For both glucose and insulin, fasting values were highly correlated with their respective AUC values over the postprandial period (Table 2). Glucose and insulin were also moderately correlated with one another for both fasting and AUC values. As expected, HOMA-IR and fasting and AUC insulin values were strongly and inversely correlated with the ISI (as lower plasma insulin response to the meal indicates greater insulin sensitivity). Fasting and AUC glucose values had a strong inverse correlation with the ISSI-2, indicating higher glucose concentrations in the presence of lower insulin secretion. Pre-pregnancy BMI was inversely correlated with fasting glucose and positively correlated with ISSI-2 (i.e., better beta-cell function) (Table 2). Correlations between these factors and rGWG were in the opposite directions, i.e. positive correlation with fasting glucose and inverse correlation with ISSI-2 (Table 2, Fig. 2). Neither BMI nor rGWG were associated with fasting insulin, $AUC_{insulin}$ or ISI.

Independent association of rGWG with metabolic variables

The contrary results for the correlations of pre-pregnancy BMI and GWG with fasting glucose and ISSI-2 may be explained by the trend for women of higher BMI to gain less weight in pregnancy. Thus, the independent effect of rGWG on fasting glucose and ISSI-2 was tested in separate multilinear regression models that included maternal age, parity, pre-pregnancy BMI and rGWG as predictors, and either fasting glucose or ISSI-2 as the outcome variables. The association of rGWG on fasting glucose was attenuated and became non-significant after accounting for covariates (p=0.075; Table 3). The significant association between rGWG and ISSI-2 remained, although the positive association with BMI was still significant (Table 3). The adjusted R^2 for the full model with ISSI-2 indicated that the combination of maternal age, parity, BMI and rGWG explained 38% of the variance in beta-cell function. The change in R^2 with the addition of rGWG to the model indicated that this variable accounted for 13.4% of the variance in beta-cell function after accounting for maternal age, parity and BMI. For each 1 unit increase in rGWG per week, ISSI-2 decreased by 2.12 units (Table 3). The variance inflation factor ranged from 1.2 to 1.5 for each variable in the model, suggesting low-moderate multicollinearity. Mean values for metabolic variables did not differ across categroies of exceeding versus not exceeding the NAM guidelines for rGWG (data not shown).

Effect modification by nativity status

Women not born in the U.S. were significantly older (31.9±4.9 vs 28.1±4.8, p=0.032) and had a non-significantly lower rate of obesity (18% vs 47%; p=0.077) and higher average rGWG per week (0.41±0.22 vs 0.30±0.21, p=0.146) compared to those born in the U.S. The proportion of women exceeding the recommended rGWG was also non-significantly higher in non-U.S. versus U.S.-born women (70.6% vs 53.3%, p=0.314). Among women not born in the U.S., a greater percentage of life spent in the U.S. correlated with lower fasting glucose,

but not with indices of insulin sensitivity or secretion (Table 2). Independent sample t-tests revealed a significantly higher $AUC_{glucose}$ (10860±1084 vs 9968±1238, p=0.038) and a trend for lower ISI (3274.2±267.9 vs 3538.4±521.4, p=0.076) among non-U.S. versus U.S.-born women, however, adjusting for maternal age attenuated the significance of these differences between groups (p=0.176 and p=0.177, respectively). There were no other significant differences in average values of metabolic variables according to nativity status, nor were there any significant interaction effects for rGWG*nativity status on any metabolic outcomes (data not shown; p>0.05 for interaction terms).

Discussion

In this cohort of high-risk Hispanic pregnant women with overweight and obesity, rGWG was found to be independently and inversely associated with reduced beta-cell function even at normal levels of fasting and postprandial glucose. A large proportion of participants were gaining weight at a higher than recommended rate through their second trimester, which associated with reduced insulin secretion sensitivity after accounting for the effect of pre-pregnancy BMI, age and parity. Since GWG was retrospectively assessed in this study, and beta-cell function measured at a single timepoint, we cannot infer any direction of causality between these two variables. However, the findings highlight rGWG as a relevant factor worthy of further investigation in the context of gestational and postpartum beta-cell function. Although rGWG also appeared to contribute towards higher fasting glucose, the unexpected inverse association between pre-pregnancy BMI and glycemia attenuated this effect. This may be partly explained by the study's eligibility criteria that excluded women with severe obesity and GDM/type 2 diabetes, perhaps resulting in a population with somehwat healthier beta-cell function despite having an elevated pre-pregnancy BMI.

The findings of the present study somewhat differ from the results recently reported by Alvarado et al. (22), who examined the association between change in maternal body weight and change in insulin sensitivity from pre-conception to late gestation in pregnant women with either normal glucose tolerance (N=29) or GDM (N=17). Their analysis demonstrated that change in maternal body weight accounted for only 9% of the variance in change of insulin sensitivity (measured by the hyperinsulinemic-euglycemic clamp) across pregnancy in the entire cohort, after accounting for multiple covariates. Change in body weight accounted for only 6% of the change in the variance of the disposition index, an index of beta-cell function, in a subset of women (N=33), substantially lower than the 12% change in ISSI-2 variation observed in the present study with a similar size cohort. The authors concluded that although their observed associations between weight gain and glucose/insulin metabolism were statistically significant, they were not clinically meaningful, and therefore, GWG is not a good target for intervention studies to mitigate risk of GDM. However, we note several distinctions in study population and methodology in our present study which may contribute to the differences in findings. Firstly, and most notably, the cohort in the study by Alvarado et al. (22) was almost exclusively Caucasian (98%). Secondly, although pre-pregnancy BMI or maternal height was not described, the average pre-pregnancy weight suggests that many women were likely in the normal weight range. Similarly, compliance to NAM guidelines was not reported, but the average total GWG was within the recommended range assuming majority of women were of a normal BMI. This is in contrast to our study participants who are exclusively Hispanic, with elevated pre-pregnancy BMI, a high rate of excess GWG, and high rate of underlying insulin resistance, suggesting that they are metabolically compromised despite screening negative for GDM. Methodological differences are also apparent between the present study and that of Alvarado et al. (22) with respect to assessment of insulin secretion through use of an oral mixed-meal containing a set glucose load versus intravenous glucose infusion to stimulate a beta-cell response. Although both studies may lack generalizability to other cohorts with greater ethnic diversity, our findings indicate that within this higher risk group of pregnant

women, the tendency for excess rGWG contributes more meaningfully to risk of maternal beta-cell dysfunction compared to lower risk women.

Among pregnancies that are metabolically compromised from the outset, for example, through elevated adiposity and insulin resistance, it is possible that a high rGWG places additional stress on beta-cells with a pre-existing underlying dysfunction, thereby potentially contributing to reduced insulin secretory function across pregnancy. The underlying mechanisms by which rGWG potentially influences beta-cell function is not yet clear, although some evidence points towards the insulin-sensitizing adipokine adiponectin, as well as advancing insulin resistance with adiposity gain (35). Maternal adiponectin concentrations have been shown to differ by race/ethnicity, such that Black and Hispanic pregnant women have consistently lower levels across pregnancy than White women (36, 37), potentially predisposing to higher risk of decreased insulin sensitivity in these minority groups. In a longitudinal study of non-pregnant Hispanic individuals, serum adiponectin was positively associated with change in disposition index, suggesting a possible role of this adipokine on preserving beta-cell function (20). However, in the same study, rate of change in BMI had a stronger independent inverse association with disposition index, which was largely driven by advancing insulin resistance with weight gain (20). Similarly, in a cohort of Hispanic women with a recent GDM-affected pregnancy, postpartum adiposity gain was the strongest predictor of declining beta-cell function, which was explained 31% by changes in adiponectin and C-reactive protein, and 40% by changes in insulin resistance (38). Thus, factors contributing to the association between a high rGWG and beta-cell dysfunction may lie at the intersection of decreased adiponectin concentrations, increased inflammation, and cellular insulin resistance, but further research is required to elucidate these pathways. Alterations in levels of the placentally-derived hormones prolactin and human placental lactogen (2, 39), as well as the furan fatty acid metabolite 3-carboxy-4-methyl-5-propyl-2-furanpropanoic acid (CMPF) (40), have also been implicated in the pathogenesis of beta-cell dysfunction in

pregnancy. However, findings are inconsistent, and it is yet unknown whether GWG may influence these pathways for declining insulin secretory capacity.

Although the rGWG and postprandial glucose output trended higher among immigrant women to the U.S., nativity status, *per se*, was not associated with markers of glucose and insulin metabolism after accounting for maternal age, nor did it moderate the effect of rGWG on beta-cell function. Migration status has been highlighted as a key social determinant of health (41), and significantly higher rates of GDM have been identified among non-U.S. born Hispanic women compared to their U.S.-born counterparts in previous studies (14, 15). Although no statistically significant disparities in markers of insulin sensitivity or secretion were evident in our study cohort among Hispanic women without GDM, the sample size may be underpowered to detect such differences.

This study provides important insight into the determinants of metabolic dysfunction among Hispanic pregnant women, who represent a higher risk maternal population in need of carefully designed, culturally-appropriate intervention strategies to support maternal and child health outcomes. The homogenous cohort with respect to ethnicity, BMI range, and gestational age at assessment provides analytical strength by minimizing potential confounding factors and increasing internal validity. However, these aspects also limit generalizability of the study findings to women of other ethnic groups and those with a higher or lower BMI. By assessing the postprandial state, we are able to conduct a more informative assessment of maternal glucose-insulin metabolism than relying on fasting values alone. Although insulin sensitivity and secretion were estimated by indirect formulas rather than direct measurement, the ISSI-2 has been shown to highly correlate with the disposition index measured by intravenous glucose tolerance test, and therefore, represents a reliable proxy of beta-cell function (42). Our choice of a standardized and widely-available

liquid meal facilitates repeatability in future studies, is more palatable compared to the standard oral glucose load used in clinical settings, and is more comparable to the mixed nutrient compositions of meals consumed in the real-world setting (33). We also acknowledge limitations of our study, particularly regarding the small sample size and assessment at only a single time point in pregnancy, which precludes the ability to determine if any GWG occurred in the first trimester or to assess beta-cell decline, and no follow-up to determine longer term effects of rate of excess GWG on postpartum beta-cell function and type 2 diabetes. We also have no data on other risk factors for GDM (e.g., family history of diabetes, GDM in previous pregnancy), or on habitual dietary intake, which might influence beta-cell function either directly or indirectly via GWG or changes in adiposity. Lastly, we did not correct for multiple comparisons or measure concentrations of adiponectin or placenta-derived hormones which may influence beta-cell function either in interaction with or independently of rGWG.

In conclusion, the high prevalence of excess rGWG that was evident in Hispanic pregnant women with overweight and obesity was associated with lower beta-cell function even in the absence of GDM, potentially contributing to the risk for future type 2 diabetes. These results suggest that in certain higher risk populations, GWG may remain relevant as a modifiable factor with potential to improve maternal metabolic health in addition to other pregnancy and child health outcomes already linked to excess GWG (e.g. gestational hypertension, large for gestational age). Therefore early attention to the rGWG before the third trimester may be warranted. Future research should consider whether genetic, early life programming, or life course factors influence susceptibility to declining beta-cell function during pregnancy and postpartum in this vulnerable group, and whether appropriately tailored, targeted lifestyle interventions beginning early in gestation may mitigate this risk.

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Data Availability

Some or all datasets generated during and/or analyzed during the current study are not publicly available but are available from the corresponding author on reasonable request.

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Table 1: Maternal characteristics, anthropometry and metabolic markers

Maternal age (years)	30.21 ± 5.12
Below poverty threshold [N(%)]	11 (29.7)
Born in US [N(%)]	15 (45.5)
Gestational age at visit (days)	207.45 ± 8.68
Multiparous [N(%)]	29 (87.9)
Pre-pregnancy BMI (Kg/m^2)	28.77 ± 2.72
Pre-pregnancy obesity (BMI 30-35 Kg/m2)	11 (33.3)
GWG from pre-pregnancy to visit (Kg)	6.30 ± 3.86
rGWG (Kg per week)	0.36 ± 0.22
Below NAM weight gain per week [N(%)]	7 (21.2)
Within NAM weight gain per week [N(%)]	6 (18.2)
Above NAM weight gain per week [N(%)]	20 (60.6)
Fasting glucose (mg/dl)	80.30 ± 6.29
Fasting insulin (uU/ml)	14.82 (12.84 - 20.62)
AUC glucose	10452.08 ± 1208.70
AUC insulin	12996.18 (9412.46 - 19436.90)
Homeostasis Model Assessment of Insulin Resistance	3.03 (1.23 - 7.07)
Insulin Sensitivity Index	2.59 (2.01 - 3.47)
Insulin Secretion Sensitivity Index-2	3.12 (2.58 - 3.99)

Data presented as mean ± standard deviation for normally distributed continuous variables, median (interquartile range) for non-normally distributed continuous variables, or as N(%) for categorical variables. AUC, area-under-the-curve; BMI, body mass index; NAM, National Academy of Medicine; rGWG, rate of gestational weight gain.

Table 2: Correlations between demographic, anthropometric and metabolic factors

	Fasting glucose	AUC glucose	Fasting insulin	AUC insulin	HOMA-IR	ISI	ISSI-2
Fasting glucose	1	0.645**	0.348*	0.124	0.386*	-0.463**	-0.747**
AUC glucose	0.645**	1	0.382*	0.380*	0.292	-0.560**	-0.663**
Fasting insulin	0.348*	0.382*	1	0.714**	0.645*	-0.907**	-0.413*
AUC insulin	0.124	0.380*	0.714**	1	0.411*	-0.872**	0.090
HOMA-IR	0.386*	0.292	0.645*	0.411*	1	-0.643**	0.203
ISI	-0.463**	-0.560**	-0.907**	-0.872**	-0.643**	1	0.350*
ISSI-2	-0.747**	-0.663**	-0.413*	0.090	0.203	0.350*	1
Gestational age (days)	-0.071	-0.070	0.049	0.102	0.112	-0.036	0.026
Maternal age	0.190	0.422*	-0.042	0.098	0.001	-0.065	-0.213
Percentage of life in US	-0.565*	-0.479	0.194	-0.226	0.073	0.209	0.140
Pre-pregnancy BMI	-0.387*	-0.126	0.146	0.242	0.054	-0.091	0.356*
rGWG per week	0.421*	0.387*	0.169	-0.080	0.240	-0.105	-0.546**

Data presented as Pearson correlation coefficients. *p<0.05; **p<0.01.

AUC, area-under-the-curve; HOMA-IR, homeostasis model assessment of insulin resistance; ISI, insulin sensitivity index; ISSI-2, insulin secretion sensitivity index; BMI, body mass index; rGWG, rate of gestational weight gain.

Table 3: Multilinear regression of rGWG predicting fasting glucose and beta-cell function

	Beta	SE	p-value	Adj. R^2	Change in R^2
Dependent variable: Fasting glucose					
Maternal age	0.001	0.001	0.448	0.074	-
Parity	0.004	0.005	0.477	0.045	0.003
Pre-pregnancy BMI	-0.006	0.002	0.015	0.284	0.247
rGWG per week	0.046	0.025	0.075	0.341	0.073
Dependent variable: Insulin secretion sensitivity index (ISSI-2)					
Maternal age	-0.007	0.037	0.847	0.083	-
Parity	-0.242	0.165	0.154	0.032	0.011
Pre-pregnancy BMI	0.170	0.164	0.028	0.325	0.230
rGWG per week	-2.124	0.821	0.015	0.379	0.134

BMI, body mass index; rGWG, rate of gestational weight gain; SE, standard error; VIF, variance inflation factor.

Figure Legend

Figure 1: Median plasma glucose (A) and insulin (B) response to the standardized meal across the study population.

Figure 2: Inverse association between rate of gestational weight gain per week and beta-cell function, measured by the insulin secretion sensitivity index (ISSI)-2.

Figure 1

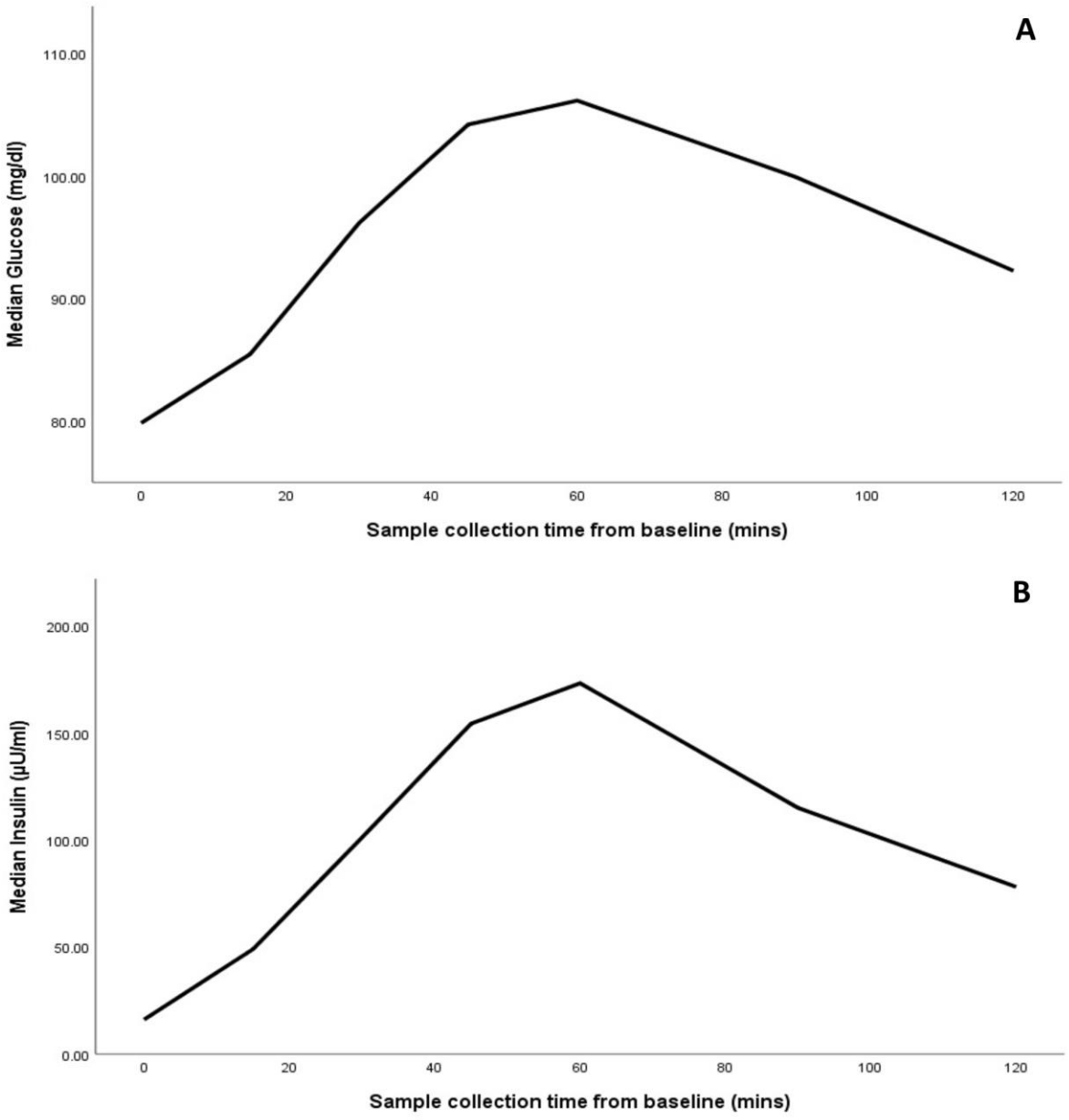

Figure 2