Contribution of Gestational Weight Gain on Maternal Glucose Metabolism in Women with GDM and Normal Glucose Tolerance

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Abbreviations: %BF, percentage body fat; BMI, body mass index; FFM, fat-free mass; FM, fat mass; GDM, gestational diabetes mellitus; GWG, gestational weight gain; IVGTT, intravenous glucose tolerance test; NGT, normal glucose tolerance; OGTT, oral glucose tolerance test.

Context: Efforts to decrease the risk of developing metabolic complications of pregnancy such as gestational diabetes (GDM) through lifestyle intervention (decreasing excessive gestational weight gain (GWG)) during pregnancy have met with limited success.

Objective: The purpose of this study was to determine the relationship between the longitudinal changes in weight/body composition and insulin sensitivity and response in women with normal glucose tolerance (NGT) and those who developed GDM.

Design: We conducted a secondary analysis of a prospective cohort developed before conception and again at 34 to 36 weeks gestation. A total of 29 NGT and 17 GDM women were evaluated for longitudinal changes in insulin sensitivity/response using the hyperinsulinemic-euglycemic clamp and an IV-glucose tolerance test. Body composition was estimated using hydrodensitometry. Both absolute change (Δ) and relative change (%Δ) between these 2 time points were calculated. We performed simple and multiple linear regression analysis to assess the relationship between GWG and measures of glucose metabolism, ie, insulin sensitivity and response.

Results: Based on the primary study design there was no significant difference in clinical characteristics between women with NGT and those developing GDM. Prior to pregnancy, women who developed GDM had lower insulin sensitivity levels (P = 0.01) compared with NGT women. Absolute change and %Δ in insulin sensitivity/insulin response and body weight/body composition were not significantly different between NGT and GDM women. Changes in body weight contributed to only 9% of the Δ in insulin sensitivity both in women developing GDM and NGT women.
Conclusions: These data suggest that other factors—such as maternal pre-pregnancy insulin sensitivity and placental derived factors affecting insulin sensitivity—rather than maternal GWG account for the changes in glucose metabolism during human pregnancy.

Key Words: gestational diabetes, gestational weight gain, changes in insulin sensitivity, body composition, lifestyle intervention, pregnancy

Gestational diabetes (GDM) is a common metabolic disorder of pregnancy affecting from 5% to 20% of pregnant women, depending on factors such as (but not limited to) the criteria used for diagnosis, ethnicity, family history of type 2 diabetes or past history of GDM, and prevalence of obesity in the population [1]. In addition to adverse maternal and neonatal pregnancy outcomes, GDM increases the risk of maternal impaired fasting glucose, impaired glucose tolerance, and type 2 diabetes 5 to 10 years postpartum [2]. Further, GDM is a risk factor for childhood metabolic dysfunction and obesity [3].

Gestational weight gain (GWG) is a physiologic and fundamental adaptation for maternal fetal well-being [4]. GWG outside of the Institute of Medicine guidelines are associated with adverse outcomes, not only for the mother but for her offspring [5, 6]. Studies indicate that 45% to 65% of women who begin pregnancy overweight or obese exceed Institute of Medicine GWG recommendations [5, 6], increasing the risk of postpartum weight retention and beginning subsequent pregnancies with higher weight and adiposity. Increased GWG early during pregnancy has been associated with the development of GDM [7, 8], but the role of excess GWG in the development of GDM is still unclear.

In nonpregnant individuals, significant weight gain has been associated with increased insulin resistance, and conversely, lifestyle interventions with goals of 5% to 7% weight loss have significantly improved metabolic function [9]. However, efforts to decrease the risk of GDM and other metabolic dysfunction through lifestyle interventions—primarily healthy eating and increased physical activity during pregnancy with the goal of avoiding excessive GWG—have met with limited success [10-13].

In late gestation, women developing GDM have both increased insulin resistance and inadequate pancreatic beta-cell insulin response to maintain normoglycemia compared with a control group [14]. The underlying rationale for many of these clinical trials has been that by decreasing excessive GWG, lifestyle interventions decrease the progression of insulin resistance. The relationship between GWG and changes in maternal insulin resistance are not well described, and few studies have baseline measures before pregnancy [15, 16].

Hence, the purpose of this secondary analysis was to examine the relationship between the longitudinal changes in weight/body composition and insulin sensitivity/response and to estimate its impact in women with normal glucose tolerance (NGT) and those who developed GDM.

Methods

Study Design

This is a secondary analysis from a prospective observational cohorts of women recruited before a planned pregnancy and followed through delivery. All of the subjects in the primary analysis were included in the present work. The primary objectives of the original studies were to characterize the longitudinal changes in maternal carbohydrate metabolism, body composition, and energy expenditure [17-22] in women with NGT and those developing GDM.

The original study procedures were conducted at Medical Center Hospital of Vermont, and at MetroHealth Medical Center, Cleveland, Ohio. Study visits in the clinical research units were conducted before a planned pregnancy during the follicular phase of the menstrual cycle, in early (12 to 14 weeks), and in late (33 to 36 weeks) pregnancy. For the purpose of this analysis, we only used the pre-pregnancy and late pregnancy data. The research protocol was approved by the 2 institutional review boards and written informed consent was obtained from each participant.

The population consisted of healthy women who were planning a pregnancy, not breastfeeding, and not using any contraception. They were nonsmokers with no known preexisting cardiometabolic disorders (hypertension, diabetes, thyroid disorders). Before conception, all subjects were given a 75-g oral glucose tolerance test (OGTT) as defined by the National Diabetes Data Group to confirm absence of preexisting diabetes. In the preconception period, all women were screened for GDM risk factors. Twelve of the women had a history of GDM or an abnormal glucose screening test in a prior pregnancy; and 25 had a family history of type 2 diabetes [20]. Women who developed GDM were diagnosed at the time of routine third-trimester screening.
Study Procedures

Two weeks prior to the preconception visit, women were instructed to follow a dietary regimen designed to standardize nutritional intake for each subject, to maintain weight before conception, and to allow appropriate weight gain during pregnancy. This regimen was identical to the diet employed in the treatment of gestational diabetes at our institution; which consisted of approximately 50% complex carbohydrates, 30% fat with an emphasis to avoid saturated fats, and 20% protein [19].

The following tests were sequentially performed during a 3-day protocol: day 1, OGTT and islet cell antibodies; day 2, body composition and intravenous glucose tolerance test (IVGTT); and day 3, hyperinsulinemic-euglycemic clamp [23]. Detailed descriptions of the study procedures have been published [17, 18]. Brief descriptions of the study procedures follow. At the time of the pre-pregnancy visit, subjects were matched for pre-pregnancy body mass index (BMI). We elected to estimate body composition because BMI in nonpregnant individuals has a wide variation when correlated with fat mass or percent body fat, and the relationships are less robust with advancing gestation [24, 25].

BMI was calculated using the subject’s weight in kilograms divided by the square of her height in meters. Body composition was estimated by underwater weighing with adjustment for residual lung volume by helium dilution. The percent body fat was calculated according to Keys and Brozek to estimate fat-free mass [18, 19, 26]. Data are described as total kilograms of fat mass (FM), kilograms of fat-free mass (FFM), and percentage body fat (% BF) (kg of fat mass/kg of total body weight × 100).

Oral glucose tolerance test: pre-pregnancy subjects were given a 75-g OGTT using National Diabetes Data Group criteria for diabetes mellitus. During pregnancy women were given a 100-g OGTT. GDM was classified according to the Carpenter and Coustan criteria [27]. Venous plasma glucose concentrations were determined by the glucose oxidase method with a Yellow Springs glucose analyzer (Yellow Springs, OH).

Insulin sensitivity was assessed using the hyperinsulinemic-euglycemic clamp. Briefly, peripheral insulin sensitivity was assessed after an 11-hour fast [28]. Infusion of [6,6-2H2] glucose for 2 hours was used to estimate basal endogenous glucose production. At the end of the 2-hour period, the clamp procedure was initiated with a constant infusion of 40 mU m−2 min−1 of insulin, maintaining plasma insulin concentration of approximately 600 pmol m−2 mL−1. Plasma glucose was maintained at 90 mg/dL (5.0 mmol/L). The glucose and insulin concentrations were collected every 10 minutes during the last 40 minutes of the clamp; they were averaged and used to estimate the glucose disposal rate. Residual endogenous glucose production during the clamp was estimated by adding a calculated amount of [6,6-2H2]glucose to the 20% glucose infusion as described by Tserng and Kalhan [23]. The insulin (measured by radioimmunoassay) intra-assay coefficient of variation was 6% and the inter-assay coefficient of variation was 8% [17].

The estimated insulin sensitivity was defined as the glucose infusion rate required to maintain plasma glucose at 90 mg/dL (5.0 mmol/L) during the clamp. To account for the lack of complete suppression of endogenous glucose production during the clamp in women developing GDM and the variability of plasma insulin concentrations during the clamp across time and between groups, we defined insulin sensitivity as the glucose infusion rate plus any residual endogenous glucose produced per kg of FFM during the clamp divided by the mean insulin concentration achieved during the hyperinsulinemic-euglycemic clamp [23, 29].

The first-phase insulin response was measured using IVGTT. Briefly, insulin response was measured in participants with less than 120% ideal body weight (n = 35) by infusing 0.5 g/kg glucose over a 3-minute bolus. Samples of glucose and insulin were obtained at baseline and at 1, 3, 5, 10, 15, 30, 45, and 60 minutes. For participants whose weight was greater than 120% ideal body weight (n = 11), the glucose bolus was 19 g/m2 body surface area. Using the trapezoidal rule, we estimated the first-phase response as the area under the curve (AUC) from 0 to 5 minutes [23].

Disposition index was calculated to describe the degree of beta-cell compensation for decrements in insulin sensitivity. The disposition index is the product of the first-phase insulin secretory response (IVGTT insulin response) and the insulin sensitivity index (hyperinsulinemic-euglycemic clamp).

Statistical Analysis

Data describing maternal preconception demographics in GDM and NGT women are presented as mean ± SD. Difference between groups in absolute (Δ), from preconception to late pregnancy, and relative change (%Δ), which express the absolute change as a percentage based of the preconception period, were analyzed using paired Student t test. Frequency data were analyzed by Chi-square test. Maternal insulin sensitivity, insulin response, disposition index, and body composition (body weight, FM, %BF, FFM) were reported as the Δ and %Δ across those 2 time points.

All the absolute change (Δ) estimates were standardized and normalized using the Yeo-Johnson power
transformation. The Yeo-Johnson power transformation was applied because it handles both positive and negative values.

All variables had complete data (n = 46), with the exception of insulin response (n = 33) and disposition index (n = 33). In order to treat missing data, linear regression was estimated using full information maximum likelihood (FIML). FIML is a validated statistical treatment for missing data and it accounts for the “missing at random” and “missing completely at random” assumptions by using all the available information and the same patterns as if there were no missing data. These results are similar to the multiple imputation procedure [30, 31]. The R package lavaan was used to perform this analysis [32].

Using simple linear regression, we analyzed whether Δ insulin sensitivity, insulin response, and disposition index were associated with maternal Δ in body weight, FM, %BF, and FFM, in both NGT and GDM women.

A multilinear regression model was assessed to explore whether there were other potential mediators of pregnancy that could be associated with the Δ of maternal insulin sensitivity, insulin response, and disposition index. We included maternal age, estimated gestational age at delivery, parity, maternal pre-pregnancy weight, and study group (NGT and GDM) as covariates. Residuals from models were checked for conformance to assumptions of normality and homostasis. Models were assessed for multicollinearity by scoring the variance inflation factor.

For descriptive data, statistics were reported at the raw data level for ease of interpretation. Statistical analyses were performed with R studio, Boston, MA, version 3.6.2 [33]. P values ≤ 0.05 were considered statistically significant.

### Results

**Participant Characteristics**

A total of 46 women met inclusion criteria for this analysis. No subject had diabetes prior to a planned pregnancy, based on the 75-g OGTT. All subjects had normal preconception thyroid, renal, and liver function and negative islet cell antibodies during each period of the study. Seventeen (37%) women developed GDM.

In the complete cohort, 98% of the subjects were Caucasian. Maternal characteristics of the NGT and GDM women pre-gravid are summarized in Table 1. Risk factors for GDM were significantly higher in the women who developed GDM. The second significant pre-pregnancy difference between the groups was decreased insulin sensitivity in women who developed GDM in late pregnancy (P = 0.01). There were no significant differences in insulin response and disposition index. Because of the original study design, there were no significant differences in maternal age, parity, weight, FM, %BF, and FFM.

### Relative and Absolute Change During Pregnancy

As shown in Table 2, absolute and relative changes, defined as changes between values taken at 34 to 36 weeks and the pre-pregnancy period—in body composition, insulin sensitivity, insulin response, and disposition index—were similar between GDM and NGT women. Absolute change in FM was slightly, but not significantly (P = 0.06), higher in the NGT women.

Relationships between Δ in maternal glucose metabolism and Δ in body composition are shown in Table 3. Absolute change in insulin sensitivity was negatively

| Table 1. Pre-Gravid Maternal Characteristics |
|---------------------------------------------|
|                                           |
| **NGT (n = 29)** | **GDM (n = 17)** | **P value** |
| Maternal age (years) | 31.6 ± 4 | 32 ± 4 | 0.69 |
| Parity | 0.9 ± 0.6 | 1.0 ± 0.4 | 0.32 |
| Weight (kg) | 63 ± 13 | 68 ± 15 | 0.22 |
| Fat mass (kg) | 19 ± 10 | 21 ± 12 | 0.44 |
| Body fat (%) | 28 ± 8 | 30 ± 9 | 0.54 |
| Fat-free mass (kg) | 44 ± 5 | 46 ± 4 | 0.09 |
| **Risk factors for GDM (n)** | | | |
| 1.Family history DM | 11 | 14 | 0.005 |
| 2.Previous GDM | 0 | 12 | <0.0001 |
| Insulin sensitivity (mg/kg*FFM/min)*100 | 13 ± 4 | 9 ± 6 | 0.01 |
| Insulin response (first-phase) | 235 ± 136 | 246 ± 132 | 0.80 |
| Disposition index (IS × IR) | 28 ± 12 | 20 ± 18 | 0.19 |

Values are mean ± SD. P value was calculated using Student t test. Frequency data were analyzed by Chi-square test.

Abbreviations: GDM, gestational diabetes mellitus; IS, insulin sensitivity; IR, insulin response; NGT, normal glucose tolerance.
correlated with $\Delta$ in body weight in the entire cohort ($R^2 = 0.20, P = 0.001$); however, when analyzed by GDM status, a significant correlation was observed only in the NGT women ($R^2 = 0.24, P = 0.002$).

To better examine the potential associations of adiposity and glucose metabolism, we performed the analysis using $\Delta$ FM and $\Delta$ %BF. The $\Delta$ in insulin sensitivity was negatively associated with $\Delta$ in FM in the combined cohort ($R^2 = 0.13, P = 0.008$) but was not significant in either of the NGT or GDM groups. There was no correlation between maternal $\Delta$ in insulin sensitivity and $\Delta$ %BF.

We found no association between $\Delta$ in insulin response and $\Delta$ in body composition: $\Delta$ FM, $\Delta$ %BF and $\Delta$ FFM. The $\Delta$ disposition index was negatively correlated with $\Delta$ body weight in GDM ($R^2 = 0.26, P = 0.01$), as shown in Table 3.

We performed a power analysis for the simple linear regression for both NGT and GDM subjects. For the NGT subjects, an $n = 29$ achieves 83% power to detect 32% difference on the $R^2$. However, for the GDM subjects, an $n = 17$ achieves 37% power to detect 18% difference on the $R^2$.

### Table 2. Study Variables; Absolute and Relative Change Difference Between NGT and GDM Women

| Variables             | Absolute ($\Delta$) | Relative (%$\Delta$) |
|-----------------------|---------------------|----------------------|
|                       | NGT (n = 29)        | GDM (n = 17)         | $P$ value |
| Weight (kg)           | 13 ± 5              | 12 ± 4               | 0.27      |
| Fat mass (kg)         | 5 ± 3               | 3 ± 4                | 0.06      |
| Body fat (%)          | 2 ± 4               | -0.4 ± 4             | 0.07      |
| Fat-free mass (kg)    | 8 ± 3               | 9 ± 3                | 0.55      |
| Insulin sensitivity   | -5 ± 2              | -4 ± 4               | 0.35      |
| Insulin response      | 209 ± 122           | 168 ± 232            | 0.54      |
| Disposition index     | 5 ± 7               | 3 ± 10               | 0.44      |

Values are mean ± SD. Absolute and relative change between values at 34-36 weeks and the pre-pregnancy period. $P$ value was calculated by Student $t$ test and it shows the difference between NGT and GDM women.

Abbreviations: GDM, gestational diabetes mellitus; NGT, normal glucose tolerance.

### Table 3. Relationship Between Absolute Changes of Glucose Metabolism Parameters and Absolute Change in Body Composition

| $\Delta$ Absolute$^a$ | Insulin sensitivity | Insulin response | Disposition index |
|-----------------------|---------------------|------------------|------------------|
|                       | $\beta$  | SE   | $P$ value | $R^2$       | $\beta$ | SE   | $P$ value | $R^2$       | $\beta$ | SE   | $P$ value | $R^2$       |
| Body weight           |          |      |          |            |          |      |          |            |          |      |          |            |
| ALL$^b$               | -0.44   | 0.13 | 0.001    | 0.20       | -0.01   | 0.18 | 0.94    | 0.00       | -0.32   | 0.17 | 0.06     | 0.10       |
| NGT                   | -0.38   | 0.12 | 0.002    | 0.24       | 0.23    | 0.21 | 0.27    | 0.07       | -0.07   | 0.20 | 0.70     | 0.01       |
| GDM                   | -0.49   | 0.28 | 0.08     | 0.15       | -0.30   | 0.27 | 0.26    | 0.07       | -0.61   | 0.25 | 0.01     | 0.26       |
| Fat mass              |          |      |          |            |          |      |          |            |          |      |          |            |
| ALL$^b$               | -0.36   | 0.13 | 0.008    | 0.13       | 0.03    | 0.18 | 0.66    | 0.00       | -0.28   | 0.18 | 0.12     | 0.07       |
| NGT                   | -0.25   | 0.14 | 0.07     | 0.10       | 0.18    | 0.26 | 0.48    | 0.04       | -0.16   | 0.23 | 0.47     | 0.04       |
| GDM                   | -0.44   | 0.28 | 0.11     | 0.13       | -0.13   | 0.26 | 0.61    | 0.02       | -0.43   | 0.26 | 0.09     | 0.14       |
| Body fat (%)          |          |      |          |            |          |      |          |            |          |      |          |            |
| ALL$^b$               | -0.24   | 0.14 | 0.08     | 0.06       | 0.03    | 0.17 | 0.83    | 0.00       | -0.12   | 0.17 | 0.48     | 0.01       |
| NGT                   | -0.17   | 0.13 | 0.20     | 0.05       | 0.13    | 0.19 | 0.49    | 0.02       | -0.10   | 0.17 | 0.55     | 0.02       |
| GDM                   | -0.27   | 0.33 | 0.41     | 0.04       | 0.13    | 0.29 | 0.53    | 0.02       | -0.24   | 0.31 | 0.44     | 0.02       |
| Fat-free mass         |          |      |          |            |          |      |          |            |          |      |          |            |
| ALL$^b$               | -0.24   | 0.14 | 0.09     | 0.05       | -0.05   | 0.18 | 0.76    | 0.00       | -0.17   | 0.17 | 0.31     | 0.03       |
| NGT                   | -0.26   | 0.12 | 0.02     | 0.14       | 0.13    | 0.18 | 0.47    | 0.02       | 0.01    | 0.16 | 0.93     | 0.00       |
| GDM                   | -0.24   | 0.36 | 0.50     | 0.03       | -0.41   | 0.33 | 0.22    | 0.09       | -0.55   | 0.34 | 0.11     | 0.14       |

Abbreviations: $\beta$, beta coefficient; GDM, gestational diabetes mellitus; NGT, normal glucose tolerance.

$^a$Absolute change, individual difference between values at 34-36 weeks and the pre-pregnancy period. $P$ value was calculated using simple linear regression.

$^b$Data were analyzed with both NGT and GDM women together. A positive coefficient implies an increase in absolute change. $P$ value was calculated using simple linear regression.
Last, as shown in Table 4, we performed a multilinear regression analysis to assess the effects of each maternal characteristic and their relationship to the Δ in insulin sensitivity during pregnancy. In the analysis, we adjusted for maternal age, gestational age at delivery, maternal prepregnancy weight, parity, Δ body weight, and group (NGT and GDM). The dependent variable was Δ insulin sensitivity. This model explains 33% of the variation of Δ in insulin sensitivity. The 2 variables that were significantly associated with Δ insulin sensitivity were gestational age at delivery (ΔR² = 0.16, P = 0.03), and Δ body weight (ΔR² = 0.09, P = 0.02). We ran a model including baseline insulin sensitivity; however, adjusting for this variable in the model increased collinearity, and decreased the contribution of Δ body weight (ΔR² = 0.03, P = 0.68).

We performed a power analysis for the multiple linear regression and determined that an n = 46 achieves 86% power to detect 38% difference on the R² between Δ in insulin sensitivity and Δ in body weight with an alpha level of 0.05.

Discussion

We report that women who developed GDM, despite having a similar pre-pregnancy percentage body fat, had decreased insulin sensitivity before pregnancy compared with NGT women. Furthermore, the absolute and relative changes in body composition and insulin sensitivity were similar between NGT and GDM women. Adjusting for relevant maternal characteristics, Δ body weight contributed to just 9% of the Δ insulin sensitivity. These results may help explain why many of the clinical trials of dietary and lifestyle intervention during pregnancy for mitigation or prevention of GDM have not achieved the desired results [1, 12].

In nonpregnant individuals, increase in weight is associated with the development of obesity, insulin resistance, and type 2 diabetes. Therefore, similar increases in GWG have been assumed to underlie the changes in glucose metabolism during pregnancy. However, in a longitudinal study of nondiabetic Pima Indians, Swinburn et al showed that baseline insulin resistance was inversely correlated with weight gain over a 3.5-year follow-up period [34]. Our results suggest that the pre-pregnancy measure of insulin sensitivity is a stronger determinant of the changes in glucose metabolism during the 40 weeks of a full-term gestation. An approximately 30% decrease in insulin sensitivity by late gestation was seen in both GDM and NGT subjects.

During a normal pregnancy there is an increase in insulin response [29], however; excessive GWG, preexisting obesity, and certain genetic predisposition may trigger failure of beta-cell adaptation [35]. In our data, the higher the Δ body weight, the lower the Δ in insulin response in GDM women, although this was not statistically significant. This likely points out the development of a beta-cell defect in women with GDM vs NGT, which when combined with insulin sensitivity as the disposition index, becomes significant for women with GDM.

The use of body weight or BMI as a marker of body fat during pregnancy may result in misclassification of obesity in pregnancy because of the varying contribution of total body water to FFM on body weight [6, 36]. Berggren et al demonstrated that during pregnancy, fat mass constitutes

| Table 4. Multilinear Regression Analysis for Factors That Affect Absolute Change in Insulin Sensitivity, Insulin Response, and Disposition Index |
|---------------------------------------------------------------|
| **Insulin sensitivity (Δ)**                                    |
| Maternal Age (years)                                          | 0.2 | 0.11 |
| Gestational age (weeks)                                       | 0.18| 0.03 |
| Maternal PP weight                                            | 0.22| 0.20 |
| Parity                                                        | 0.23| 0.13 |
| Body weight (Δ)                                               | 0.32| 0.02 |
| Group (NGT)                                                  | 0.33| 0.27 |
| **Insulin response (Δ)**                                      |
| Maternal age (years)                                          | 0.8 | 0.05 |
| Maternal PP weight                                            | 0.12| 0.21 |
| Group (NGT)                                                  | 0.13| 0.26 |
| **Disposition index (Δ)**                                    |
| Maternal age (years)                                          | 0.03| 0.15 |
| Body weight (Δ)                                               | 0.09| 0.05 |
| Group (NGT)                                                  | 0.13| 0.12 |

Absolute (Δ) changes between values at 34-36 weeks and the pre-pregnancy period. P value was calculated using multiple linear regression model. Abbreviations: NGT, normal glucose tolerance; PP, pre-pregnancy.
the greatest variance in GWG [37]. Hence in our analysis, in addition to the change in weight, we assessed the changes in body composition to examine if accumulation of adipose tissue was related to alterations in maternal glucose metabolism. We did not find a correlation of measures of adiposity with either Δ in insulin sensitivity, insulin response, or disposition index.

Our group has reported a 120% increase in insulin sensitivity in the immediate postpartum period in women with GDM compared with late gestation measures [38]. These data support our findings. The placenta, and not maternal GWG, underlies the metabolic changes in pregnancy. The placenta serves as the main interface between the mother and the fetus, and it is a rich source of hormones, cytokines, and adipokines, which are released into the maternal circulation and modulate maternal glucose metabolism during pregnancy [39, 40].

Placental hormones such as progesterone, estradiol, human placental lactogen, prolactin, and cortisol have all been described as possible mediators for pregnancy-induced insulin resistance; however, there is yet no consensus as to the exact mechanism [41]. Cytokines and adipokines such as tumor necrosis factor-α and leptin have been negatively correlated with insulin sensitivity, although the authors of these studies concluded that further studies were needed in order to confirm their findings [41, 42]. Recent data suggests that placental exosomes and miRNAs may be involved in changes in maternal metabolic status [43, 44]. Despite the obvious association between whole-body insulin resistance in pregnancy and the placenta, the precise mechanism remains poorly understood, and further studies need to be developed.

A major strength of this study is its longitudinal data with measurements from preconception through late pregnancy. The estimates of insulin sensitivity were measured with the gold-standard hyperinsulinemic-euglycemic clamp. Maternal body composition measurements in pregnancy are specific to gestational age. Our study is limited by a small number of subjects and a lack of ethnic diversity. This is particularly true for the GDM group, as 24 samples were needed to achieve 80% power; however, as this was a secondary analysis, we are constrained by the original trial’s criteria.

In conclusion, we did not find a clinically significant correlation between changes in components of glucose metabolism and weight or body composition from preconception to late pregnancy. Given that insulin sensitivity improves 120% in the immediate postpartum period [38], further studies are needed to more easily estimate insulin sensitivity prior to conception or in early pregnancy as well as to understand the potential mediators released by the placenta. Since weight gain explains a relatively small component of the variation in insulin sensitivity, we continue to recommend avoidance of excessive GWG to prevent postpartum weight retention which increases the risk of long-term maternal metabolic dysfunction and increased pre-pregnancy adiposity in subsequent pregnancies [45]. If the effects of these risk factors are chronic rather than acute, then prevention of GDM would ideally require initiating lifestyle interventions before a planned pregnancy [1].

In summary, we showed that gestational weight gain contributes only 9% of the absolute changes in insulin sensitivity during pregnancy. We hypothesize that this low contribution is the main reason why lifestyle interventions during pregnancy targeting maternal weight have not impacted the progression of insulin resistance during pregnancy.

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Additional Information

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Data Availability: The datasets generated during and/or analyzed during the current study are not publicly available but are available from the corresponding author on reasonable request.

Prior Presentations

These data were presented in abstract form at the 49th Annual Meeting of the Diabetes Pregnancy Study Group of the European Association for the Study of Diabetes, Nyborg, Denmark, September 7-10, 2017, and the SMFM’s 38th Annual Pregnancy Meeting, Dallas, Texas, January 29 to February 3, 2018.

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