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Gestational weight gain as an independent risk factor for adverse pregnancy outcomes in women with gestational diabetes

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Abstract. – OBJECTIVE: Obesity and gestational diabetes mellitus (GDM) are rising worldwide. This study retrospectively evaluated the role of excessive gestational weight gain (eGWG) in women with GDM and different pre-pregnancy body mass indices (BMIs).

PATIENTS AND METHODS: Optimal glycaemic control was defined as achieving glucose target thresholds in more than 80% of measurements. 283 women with GDM were categorized as underweight, normal weight, overweight or obese based on WHO's classification scheme. eGWG was defined as >18.0 kilograms for women who were underweight, >15.8 kilograms for those who were normal weight, >11.3 kilograms for those who were overweight and >9.0 kilograms for those who were obese. For the analysis, women were divided into two groups: normal and excessive GWG. The main outcomes measured were incidences of large/small for gestational age (LGA/SGA), macrosomia, preterm delivery, hypertensive disorders and caesarean sections (CS).

RESULTS: Excessive GWG was associated with higher birth weight and percentile (p<0.001), and with a higher prevalence of LGA (p<0.001), macrosomia (p=0.002) and hypertensive disorders (p=0.036). No statistical differences were found for the week of delivery, or prevalence of CS and SGA. The multivariate analysis highlighted both pre-pregnant BMI and eGWG as independent risk factors for LGA and macrosomia. Women with a pre-pregnant BMI of at least 25 and eGWG have a 5.43-fold greater risk of developing LGA (p=0.005).

CONCLUSIONS: When combined with an inadequate pre-pregnant BMI, eGWG acts as a "synergic risk factor" for a poor outcome. When obesity or GDM occur, an optimal GWG can guarantee a better pregnancy outcome.

Key Words
Gestational diabetes mellitus, Gestational weight gain, Macrosomia, Large for gestational age, Obesity, Hypertension.

Introduction

Gestational diabetes mellitus (GDM) is the most common metabolic pregnancy complication, and it is associated with a higher risk of adverse obstetrical outcomes[1]. Good glycaemic control achieved through lifestyle changes, nutritional changes, and insulin treatments significantly reduces the risk of these complications.

Recent studies[2] have shown that pre-pregnancy body mass indices (BMIs), obesity and gestational weight gain (GWG) are additional independent risk factors for an adverse pregnancy outcome. There are strong associations among these conditions, as a rising maternal BMI is a significant risk factor for the development of GDM[3]. Both obesity and GDM are well known to be associated with large for gestational age (LGA) babies and foetal macrosomia. The increase in these complications worldwide is also related to a much higher risk that the offspring will develop metabolic complications[4]. Approximately 36% of pregnant women gain more weight than is recommended. This excessive weight gain is linked to LGA, caesarean deliveries and lower APGAR scores, even among women who do not develop GDM[5,6]. Some studies[1] have demonstrated that limiting GWG in overweight and obese women could be beneficial for pregnancy outcomes.

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Of note, excessive gestational weight gain (eGWG) could also be dangerous for normal and underweight women[7]. For this reason, the Institute of Medicine (IOM) revised the guidelines for optimal weight-gain ranges based on pre-pregnancy BMI in 2009[7].

In conclusion, the prevalence of obesity and GDM are rising worldwide. When both of these conditions occur, glycaemic control, GWG and lifestyle modifications are the only modifiable factors. The aim of this study is to investigate whether eGWG is a risk factor for adverse pregnancy outcome in women affected by GDM with optimal glycaemic control, regardless of pre-pregnancy BMI.

Materials and Methods

We followed 3,508 women with a singleton pregnancy who used our tertiary referral centre between January 2009 to January 2014. Informed consent has been obtained from all patients. The institutional Ethics Committee has given approval. Each patient was screened for GDM using an oral glucose tolerance test (OGTT) between 24 and 28 weeks of gestation. Of these women, 393 were affected by GDM according to the IADSPG criteria. These women received advice on lifestyle modifications and were started on a therapeutic dietary regimen. All women were also provided with a reflectometer for capillary blood-glucose self-monitoring[8] and asked to monitor their glucose levels four times per day. Insulin treatment was prescribed if at least 20% of the glucose levels gathered in a week exceeded the following thresholds: fasting glucose of >95 mg/dl and/or one-hour postprandial of >140 mg/dl and/or two-hour post-prandial of >120 mg/dl.

Optimal glycaemic control was defined as achieving glucose target thresholds in more than 80% of the measurements from diagnosis until delivery. In this study, 283 women with GDM were classified as having optimal glycaemic control.

The following information was collected from patients' clinical histories, medical records and delivery-room reports: mother's age, pre-pregnancy BMI, timing, mode and indication to delivery, miscarriage, intrauterine death, week of delivery, birth weight, birth-weight percentile, presence of congenital anomalies and therapeutic strategy. Pre-pregnancy BMI was calculated at the first appointment before 14 gestational weeks based on the study by Fattah et al[9], which demonstrated that there were no changes in mean maternal weight and body composition during the first trimester in a cohort of non-diabetic women[9].

All women met with a gynaecologist monthly. Their glycaemic values and weights were monitored up to the point of delivery.

Definitions

Each woman was categorized according to WHO's definitions as underweight (BMI <18.5), normal weight (BMI ≥18.5 and <25.0), overweight (BMI ≥25.0 and <30.0) or obese (BMI ≥30.0) based on pre-pregnancy BMI (kg/m^2). Total gestational weight gain (GWG) was calculated as the difference between the maximum-recorded weight gain during pregnancy and the body weight recorded at the first visit prior to 14 weeks of gestation. According to the 2009 IMO guidelines[7], eGWG was defined as more weight gain exceeding 18.0 kilograms for underweight women, 15.8 kilograms for normal-weight woman, 11.3 kilograms for overweight women and 9.0 kilograms for obese women.

Gestational age was defined on the basis of the last maternal menstrual date and confirmed by early ultrasound examination. Preterm birth was defined as a delivery occurring prior to the 37th gestational week. Macrosomia was defined as a newborn infant with a birth weight of more than 4000 g. Large for gestational age (LGA) was defined as a birth weight above the 90th percentile (Pc), while small for gestational age (SGA) was defined as an estimated foetal weight below the 10th percentile (Pc), according to the national standard curve for singleton births[10]. According to ISSHP, hypertensive disorders of pregnancy included gestational hypertension, chronic hypertension, preeclampsia and preeclampsia on chronic hypertension[11].

Statistical Analysis

The statistical analysis was performed by using the Statistical Package for Social Science (SPSS), version 15.0 (SPSS Inc., Chicago, IL, USA). All data were first analysed for normality of distribution using the Kolmogorov-Smirnov test of normality. Continuous variables (maternal age, GWG, birth weight, gestational week at delivery, weight percentile, parity, OGTT-AUC) were expressed as the mean ± SD. Categorical variables (LGA, macrosomia, preterm delivery, Caesarean section, occurrence of hypertensive disorders) were displayed as frequencies, and the appropriate parametric or non-parametric test (Student's *t*-test, Mann-Whitney or χ^2-test) was used to assess the significance of differences between subgroups.

Appropriate parametric (one-way ANOVA, Student-Newman-Keuls post-hoc test) or non-parametric tests (χ^2-test) were used to assess the significance of the differences among subgroups.

Multiple linear or logistic regressions based on backward-stepwise methods (a reduced model) were also performed to study the dependence of the occurrence of macrosomia, LGA and hypertensive disorders on the maternal covariates of BMI, GWG, age, parity and basal glycaemia. The covariates introduced in the model were those variables found to be significantly correlated in the univariate analysis.

All tests for statistical significance were two-sided. A *p*-value of less than 0.05 indicated a significant difference.

Results

Data from 283 women were analysed. At the time of conception, 85 (30.0%) of these women were obese, 80 (28.3%) were overweight, 101 (35.7%) were of normal weight and 17 (6.0%) were underweight. Mean GWG was significantly different between those women with a BMI ≥25 (9.02±6.31) and those with a BMI <25 (12.35±5.96) ($p<0.0001$). Ninety-three women (32.9%) experienced eGWG.

Table I outlines the baseline and demographic characteristics of the women with eGWG and those with normal GWG (nGWG), as well as the mean glucose levels at the time of the OGTT. There were no significant differences between the two groups in term of maternal age, ethnicity, parity, gravidity, pre-pregnancy BMI and mean glucose values at 60 and 120 minutes of OGTT testing. Mean basal glucose levels were significantly higher in women with eGWG (92.70 ±19.31 versus 88.66±11.66, $p=0.03$). Obese women were more prevalent in the eGWG group than in the nGWG group ($p=0.03$).

Table II shows the pregnancy and neonatal outcomes according to excessive or non-excessive GWG. Women with eGWG had a significantly higher prevalence of LGA, macrosomia and hypertensive disorders of pregnancy. Furthermore, the mean birth weight and mean percentile were higher in this group than in the group of women with nGWG. We found no difference in terms of gestational week of delivery, prevalence of preterm deliveries, Caesarean sections and SGA.

The congenital malformation rate was about three times higher in women with eGWG than in women with nGWG (6.5% *vs.* 2.6% $p=0.12$). However, this difference was not statistically significant, probably due to the small sample size.

A multivariate logistic regression based on a backward-stepwise method (a reduced model) was used to evaluate the independent associations between exposure variables and the following outcomes: macrosomia, LGA and hypertensive disorders (Table III). Both pre-pregnancy BMI and eGWG were found to be independent risk

Table I. Maternal characteristics in relation to Gestational Weight Gain (GWG).

	Excessive GWG	Non-excessive GWG	*p*-value
No. (%)	93 (32.9%)	190 (67.1%)	
Age, y	34.2±5.5	34.8±5.5	0.19
Caucasian	77 (82.8%)	156 (82.1%)	0.87
Gravida	2.5±1.9	2.2±1.3	0.26
Parity	0.8±1.2	0.7±0.9	0.57
Pre-pregnancy BMI	27.9±6.0	26.5±7.1	0.08
Pre-pregnancy BMI category			
Obese	36 (38.7%)	49 (25.8%)	0.03
Overweight	29 (31.2%)	51 (26.8%)	0.44
Normal	26 (28.0%)	75 (39.5%)	0.06
Underweight	2 (2.1%)	15 (7.9%)	0.06
Mean GWG	16.0±5.5	7.7±4.8	<0.001
Glucose 0 min (mg/dl)	92.7±19.3	88.7±11.7	0.03
Glucose 120 min (mg/dl)	155.7±30.6	162.6±35.4	0.15

Table II. Pregnancy outcome in relation to Gestational Weight Gain (GWG).

	Excessive GWG	Non-excessive GWG	*p*-value
No. (%)	93 (32.9%)	190 (67.1%)	
Birth weight (g)	3339.8± 594.4	3072.4±524.1	<0.001
Birth percentile	60.1±25.9	48.6±26.5	<0.001
Week of delivery	38.9±1.7	38.6±1.9	0.25
Caesarean Section	48 (51.6%)	87 (45.0%)	0.59
LGA	14 (15.0%)	7 (3.7%)	<0.001
SGA	3 (3.2%)	18 (9.5%)	0.06
Macrosomia	11 (11.8%)	5 (2.6%)	0.002
Preterm delivery	13 (14.0%)	32 (16.8%)	0.53
Hypertensive disorders	25 (39.6%)	31 (16.3%)	0.036
Congenital malformations	6 (6.5%)	5 (2.6%)	0.12

factors for macrosomia and LGA after adjusting for other risk factors (i.e., parity, maternal age, insulin treatment, basal glycaemia). Pre-pregnancy BMI was associated with a risk of developing hypertension disorders of pregnancy ($p<$ 0.001), while eGWG was not an independent risk factor for this outcome. Furthermore, eGWG (p=0.002), pre-pregnancy BMI (p=0.012) and parity (p=0.48) were positively correlated with higher birth-weight percentiles.

Figure 1 shows the percentage of LGA newborns among the different pre-pregnancy BMI categories in women with eGWG and nGWG. The proportion of LGA infants was significantly higher in women with an eGWG than in those with nGWG among both obese (p= 0.005) and overweight women (p=0.002). Excessive gestational weight gain was also associated with an increased risk for LGA, which was 5.4 times higher in women with a pre-pregnancy BMI ≥25 (OR=5.43 CI 1.6 to 17,7; p=0.005). A similar trend was observed in women with a BMI<25, although this difference was not significant (OR= 2.23 CI 0.35 to 14.07; p= 0.39).

Table III. Role of pre-pregnancy BMI and excessive Gestational weight gain (eGWG) in the development of Macrosomia (3a), Large for Gestational Age (3b) and Hypertensive disorders of pregnancy (3c) by multivariate analysis reduced model (data were adjusted for age, parity, and basal glycaemia).

IIIa. Outcome: Prevalence of Macrosomia			
Variable	**β ± SE**	**p-value**	**OR (95% CI)**
eGWG	1.60 ± 0.57	0.005	4.97 (1.63-15.17)
BMI	0.09 ± 0.04	0.007	1.10 (1.03-1.18)
IIIb. Outcome: Prevalence of Large for Gestational Age			
Variable	**β ± SE**	**p-value**	**OR (95% CI)**
eGWG	1.49 ± 0.5	0.003	4.43 (1.67-11.72)
BMI	0.09 ± 0.03	0.006	1.09 (1.03-1.16)
IIIc. Outcome: Prevalence of Hypertensive disorders of pregnancy			
Variable	**β ± SE**	**p-value**	**OR (95% CI)**
eGWG	0.60 ± 0.33	0.071	1.81 (0.95-3.46)
BMI	0.14± 0.02	<0.001	1.15 (1.10-1.21)

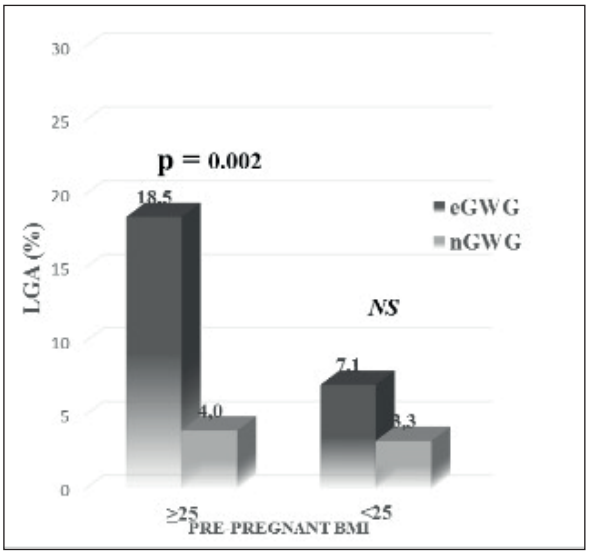

Figure 1. Percentage of LGA (large for gestational age) newborns among the different pre-pregnancy BMI (body mass index) categories in women with eGWG (excessive gestational weight gain) and nGWG (normal gestational weight gain

Discussion

Gestational diabetes and obesity represent high-risk conditions associated with adverse pregnancy and neonatal outcomes. Our findings suggest that pre-pregnancy BMI and eGWG are independent predictors of macrosomia and LGA when adjusted for other risk factors. This study is the first to exclusively consider the effects of GWG (as defined by the IOM guidelines) on a cohort of diabetic women with optimal glycaemic control.

Approaches aimed at preventing or minimizing GDM are mandatory. Categorizations as overweight or obese are strong predictors of GDM[12], while diet and exercise are known to be effective in preventing and controlling the disease. Therefore, most studies undertaken to date on this issue have investigated the role of these interventions in the prevention of GDM[13]. However, no significant effect of diet or of diet and exercise in combination has been found in trials enrolling women with no clear GDM risk factors[13]. In overweight and obese pregnant women, only one trial has found a reduction in GDM risk[14], while another trial revealed a reduction in macrosomia prevalence but no effects on GDM risk or gestational weight gain[15]. A recent multicentre, randomised, controlled European trial enrolling consecutive pregnant women with a BMI of at least 29 found that interventions focused on healthy eating combined with physical exercise resulted in less gestational weight gain, but had no impact on fasting plasma glucose[16]. In contrast, a recent meta-analysis found that physical activity before and in early pregnancy was effective in preventing GDM[17]. This finding was supported by a recent randomized controlled trial in a Chinese population[18]. Certainly, the heterogeneity of these studies can account for much of this disparity. Regardless, no definitive conclusions can be made and more trials with larger populations and longer follow-up periods are needed[13].

The ATLANTIC-DIP study[19] undertook an analysis similar to ours, although only women with full-term deliveries (>37 weeks' gestation) were enrolled and certain outcomes, such as neonatal birth weight, birth-weight percentile, congenital malformations and preterm deliveries, were not considered. In the present study, no statistically significant difference in the prevalence of preterm delivery was found. However, we suggest that preterm delivery is an important outcome that should be considered in analyses, especially as diabetes is known to delay foetal lung maturation and is associated with a higher prevalence of respiratory distress.

With regard to baseline characteristics, the mean basal glucose levels were higher in women with eGWG. This finding cannot be explained by the current analysis, but it highlights the possibility that eGWG could start during the first few gestational weeks and could be related to impaired glucose tolerance at the time of the basal test.

Our principal findings about eGWG relate to neonatal outcomes and, in particular, to indices of abnormal foetal growth (rate of LGA, macrosomia). LGA and macrosomia are associated with a two- to three-times greater risk of intrauterine death, shoulder dystocia and brachial plexus injuries[20,21].

In women affected by GDM, abnormal foetal growth could be related to other confounders (e.g., glucose control, obesity), as other observations indicate that about 75% of women who are obese develop GDM[22]. Mitanchez[23] suggests a linear relationship between maternal blood-glucose levels and an increased birth weight, and that treatment for GDM can reduce the prevalence of macrosomia. A recent study indicated that inflammation in pregnant women is closely associated with GDM[24], suggesting that an inflammatory environment can regulate maternal blood glucose. The concentration of exosomes in the plasma of pregnant women with GDM increased by about two times[25]. Exosomes can affect the function of endothelial cells and participate in the development of the inflammatory state of GDM. The decrease in serum C1q/tumor necrosis factor-related protein-3 – an

anti-inflammatory adipokine that is able to inhibit inflammatory responses caused by lipopolysaccharide – is believed to play a metabolic role in the pathogenesis of GDM[26]. It has been considered the role of insulin-like growth factor-1 (IGF-1) in pregnancy is gradually revealed, IGF-I detection can lead to the provision of more beneficial help with the aim of maternal, fetal and neonatal disease prevention, diagnosis and treatment. Another recent study[27] explored the relationship between the expression of IGF-1 in neonatal umbilical cord blood and abnormal glucose metabolism during pregnancy. The study found a significant positive correlation between the IGF-1 level of neonatal umbilical cord blood and neonatal weight. In addition, the level of HbA1c was positively correlated with the level of IGF-1 in neonatal umbilical cord blood at the end of pregnancy.

A study by Alberico et al[28] clearly indicated that maternal obesity, eGWG and gestational diabetes should be considered as independent risk factors for macrosomia, and that all of these variables need to be carefully assessed and monitored. In fact, the authors demonstrated that diabetes was associated with a 2.1-fold increase in the risk of macrosomia relative to women without diabetes, and that obesity was associated with a 1.7-fold increase in the risk of macrosomia relative to normal-weight women[17].

In the DEPOSIT study[29], investigators evaluated the influence of maternal weight gain or perinatal complications in women with pre-gestational and gestational diabetes. For every five-kilogram increase in GWG, the risk of LGA increased by 30% and the risk of hypertensive disorders rose by 40%. Furthermore, eGWG is the strongest risk factor for postpartum weight retention. In the Norwegian Mother and Child cohort study[30,31], weight gain beyond the level set in the IOM guidelines resulted in a weight retention of at least two kilograms at 18 months postpartum across all pregnancy BMI categories.

Our study is novel, as it tests the importance of GWG in pregnancies complicated by the presence of GDM. Through a multivariate analysis adjusted for other potential confounders, we demonstrated that eGWG is positively related to foetal growth (expressed in terms of birth percentile) (p=0.002), and to the risk of macrosomia (OR=4.97) and LGA (OR=4.43), regardless of pre-pregnancy BMI. Moreover, we observed an increasing proportion of LGA in certain BMI categories. More specifically, in obese and overweight women, eGWG was an independent risk factor for LGA.

Figure 1 clearly shows that eGWG is not the only independent risk factor for an increased rate of LGA. In women with BMIs of less than 25, eGWG increases the risk of having an LGA infant with an effect that appears to be additive. In women with a BMI of at least 25 (overweight and obese women), eGWG produces a "synergic effect" on the prevalence of LGA. However, when pregnant women with a BMI of at least 25 have adequate GWG, the prevalence of LGA is similar to that observed in women with a BMI of less than 25. Consistent with these results, Di Benedetto et al[32] report a similar prevalence of macrosomia (around 4.8%) between overweight and normal weight women with nGWG, and a higher occurrence of macrosomia (13.0%) in overweight women with eGWG. These findings confirm that eGWG (based on the IOM cut-off) plays a crucial role in determining foetal weight regardless of the mother's nutritional and diabetic status.

The prevalence of hypertensive disorders of pregnancy was higher in women with eGWG. However, our multivariate analysis shows that only pre-pregnancy BMI is an independent risk factor for this outcome. These findings could suggest that "maternal over-nutrition" may play a role in the development of an adverse "metabolic milieu". Weight gain, obesity and pregnancy hypertension are harbingers of metabolic syndrome and type 2 diabetes. Therefore, metabolic status during pregnancy and in the postpartum period is a likely contributor to long-term maternal health.

Moreover, a meta-analysis by Stothard et al[33] shows that infants carried by obese women have an increased risk of congenital malformations. In their conclusions, the authors recognized that some of these adverse outcomes could be due to undiagnosed hyperglycaemia. As expected, our study did not show any statistical difference between the two groups because it was designed to uncover the role of eGWG in women with optimal glucose control.

The main limits of our study are the relatively small sample size and the observational design. However, after adjusting our multivariate regression analysis, we found strong associations between eGWG and adverse pregnancy outcomes.

Conclusions

GWG is a crucial but modifiable risk factor for GDM. Our data suggest that improved obstetrical outcomes can be achieved by introducing

effective controls over GWG for all women with diabetes, irrespective of their antenatal BMIs. Care providers should pay the same attention to diet, lifestyle and weight-gain control in obese, normal-weight and underweight women. In this regard, they can use IOM recommendations for the different BMI classes as a target.

Women with an impaired basal glucose level should be carefully managed. As pre-pregnancy BMI is an independent risk factor for an adverse pregnancy outcome and for GDM, pre-conception counselling should be offered to all women planning a pregnancy.

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The last two authors should be considered co-seniors.

Conflict of Interests
The authors declare that they have no conflicts of interest.

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