JDI Journal of Diabetes Investigation Open access
Official Journal of the Asian Association for the Study of Diabetes
ORIGINAL ARTICLE

The association between weight gain at different stages of pregnancy and risk of gestational diabetes mellitus

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Keywords
Gestational diabetes mellitus, Gestational weight gain, Body mass index

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J Diabetes Investig 2022; 13: 359–366

doi: 10.1111/jdi.13648

ABSTRACT

Aims/Introduction: Women with excessive gestational weight gain (GWG) are at a higher risk for complications during pregnancy, such as preeclampsia. However, the association between excessive GWG and gestational diabetes mellitus (GDM) remains unclear.

Materials and Methods: We retrospectively reviewed 8,352 women from our obstetric database with singleton pregnancies who gave birth after 28 completed weeks of gestation between January 1, 2012, and December 31, 2016, excluding pregnancies complicated by fetal anomalies, fetal death, and overt diabetes. Diagnosis of GDM was based on the criteria recommended by the International Association of Diabetes and Pregnancy Study Groups. We used two classification methods to define excessive GWG: a weight gain above the 90th percentile of the population, or exceeding the upper range recommended by the Institute of Medicine, stratified by pre-pregnancy body mass index. Statistical analysis was performed using multiple logistic regression to determine the association between excessive GWG and the risk of GDM.

Results: Overall, 1,129 women (13.5%) were diagnosed with GDM. There was no difference in GWG between women with and without GDM in the first trimester and before GDM screening. Women with GDM had significantly less GWG in the second trimester, after GDM screening, and throughout the whole gestation than women without GDM. No correlation was found between excessive GWG in the first and second trimesters, before GDM screening, and the later development of GDM.

Conclusions: Our results indicate that excessive GWG prior to GDM screening is not associated with an increased risk of GDM.

INTRODUCTION

Weight gain during pregnancy can affect fetal and maternal outcomes. Accumulating evidence indicates that in comparison with women with appropriate gestational weight gain (GWG) defined by the Institute of Medicine (IOM) in 2009, women with excessive weight gain during pregnancy have an elevated risk for operative deliveries and pregnancy complications including gestational hypertension, preeclampsia, and fetal macrosomia[1,2]. Furthermore, neonates of women with excessive GWG are more commonly large for gestational age, have higher rates of birth injury, and tend to have increased body weight, fat percentage, and hypertension in childhood[2,3]. Women with excessive GWG are more susceptible to developing type 2 diabetes mellitus (T2DM), cardiovascular disease, and metabolic syndrome later in life[4].

However, whether excessive GWG is directly correlated with gestational diabetes mellitus (GDM) remains controversial. While some studies concluded that women with excessive GWG are more likely to develop GDM[5–9], others have not found a similar association[10–16]. It has even been suggested that women with GDM have less GWG than women without GDM[17–20]. Explanations for the inconsistent results remain unclear. A possible explanation could be that prior studies

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Received 27 April 2021; revised 2 August 2021; accepted 17 August 2021

investigated the overall increase in weight during pregnancy instead of weight gain prior to GDM screening[5,10,15–20]. It is likely that overall weight gain, calculated by subtracting the maternal weight before pregnancy from weight at delivery, has been influenced by interventions for GDM, including lifestyle modification, increased exercise, and nutritional and pharmacological therapy. Another possibility is that previous studies did not adjust for the important confounders in maternal characteristics, such as pre-pregnancy body mass index (BMI), conception method, and a family history of type 2 diabetes mellitus, which are reportedly related to the development of GDM[7,13,14,21]. Our previous work has shown that GWG above the 2009 IOM guidelines has different rates of pregnancy complications among women who are underweight, normal weight, and overweight or obese before pregnancy[19].

Thus, we conducted this retrospective study to clarify the association between excessive GWG and the risk of GDM. The objectives of our study were (1) to compare the difference in weight gain at different stages of pregnancy, including the first and second trimesters, before and after GDM screening, throughout gestation, between women with and without GDM; and (2) to investigate the correlation between excessive GWG in the first and second trimester (before GDM screening) and the risk of GDM in later gestation, stratified by each subject's BMI prior to pregnancy and adjusted for confounding factors of important maternal characteristics.

MATERIALS AND METHODS

Data collection

The study was a retrospective cross-sectional study. We enrolled all women who had GDM screening tests and delivered after 28 weeks of complete gestation at Taipei Chang Gung Memorial Hospital between January 1, 2012, and December 31, 2016. We excluded those with pregnancies that were complicated by multiple gestation, fetal death, and chromosomal or structural abnormalities. Women with overt DM diagnosed before pregnancy or at their first antenatal visit before 13 weeks of gestation were also excluded. The Institutional Review Board of Chang Gung Memorial Hospital approved this study (approval no. 201800894B0). Requirement for informed consent was waived by the approval body since the study was retrospective and anonymous.

Diagnosis of GDM

Gestational diabetes mellitus was screened for and the diagnosis confirmed using a one-step approach based on the recommendation of the International Association of Diabetes in Pregnancy Study Groups (IADPSG). All pregnant women between 24 and 28 weeks of gestation were given a 75 g, 2 h oral glucose tolerance, except for high-risk women, who were screened at the first prenatal visit. A diagnosis of GDM was made if at least one plasma glucose concentration equaled or exceeded the guideline thresholds: fasting, 92 mg/dL; 1 h, 180 mg/dL; or 2 h, 153 mg/dL. Once diagnosed with GDM, women were instructed to modify lifestyle and nutrition. They were instructed to regularly monitor blood sugar with glucose meters. Insulin treatment was prescribed when the aforementioned management did not manage a fasting glucose level <95 mg/dL and a 1 h postprandial level <140 mg/dL (or a 2 h level <120 mg/dL).

Determination of pre-pregnancy BMI and GWG

We measured every woman's height and recorded her self-reported pre-pregnancy body weight during her first prenatal examination. The values were used to calculate pre-gestational BMI with the formula (weight [kg]/height $[m]^2$).

Each woman was weighed at every antenatal examination. The GWG of different gestational periods were defined as follows: (1) first trimester GWG, defined by an increase in weight in kilograms from before pregnancy to 12–14 weeks of gestation. If a woman had more than two weight measurements during the period of 12–14 weeks, the latest measurement was selected for calculation; (2) second trimester GWG, defined as the weight change between 12–14 weeks and 26–28 weeks of gestation. If a woman had more than two weight measurements during the periods of 12–14 weeks and 26–28 weeks of gestation, the last measurement within each period was selected for calculation; (3) GWG before GDM screening, calculated by each woman's weight at the GDM screening test minus her pre-gestational weight; (4) GWG after GDM screening, calculated by each woman's weight at delivery minus her weight at the GDM screening; and (5) total GWG, calculated by each woman's weight at delivery minus her weight prior to gestation.

Definitions of excessive GWG

Two classification methods were used to define an excessive GWG, stratified by pre-pregnancy BMI (underweight [<18.5 kg/m^2], normal weight [18.5–24.9 kg/m^2], and overweight or obese [>24.9 kg/m^2]). The first was based on the percentile of the study population; an excessive GWG was defined as a weight gain above the 90th percentile of all women with the same pre-pregnancy BMI category and gestation. The second was based on the 2009 IOM guidelines; the highest recommended GWG in the first trimester is 2 kg for all pregnant women, while the highest recommended rate of GWG in the second trimester is 0.58 kg/week for underweight, 0.50 kg/week for normal weight, and 0.33 kg/week for overweight women. An excessive GWG was defined as a weight gain values exceeding the maximum recommended by the IOM, according to pre-pregnancy BMI and gestation.

Exposure variables

The following maternal characteristics were considered to be exposure variables: age at delivery (<20, 20–34, and >34 years), primiparity, a prior history of assisted or spontaneous abortion, preterm delivery, and stillbirth (>20 weeks of gestation), a

family history of type 2 diabetes mellitus (first- and second-degree relatives), conception by assisted reproductive technology (ART), cigarette smoking during pregnancy, uterine fibroids, and maternal diseases such as chronic hypertension, preeclampsia, hypothyroidism, and hyperthyroidism.

Data analysis

Statistical analysis was performed using SPSS version 26 (IBM Corp., Armonk, NY, USA). Continuous variables are presented as mean ± standard deviation, and categorical variables as number and frequency (%). Comparisons were first made to examine the differences in maternal characteristics between women with and without GDM using the Student's *t*-test, chi-square test, or Fisher exact test, when applicable. A value of $P < 0.05$ was considered statistically significant.

Using multiple logistic regression with the backward elimination method, four models were then generated to assess the correlation between excessive GWG at different periods of pregnancy and the risk of later GDM, stratified by pre-pregnancy BMI and adjusted for potential confounders that were statistically significant in the univariate analysis. Models 1 and 2 evaluated excessive GWG in the first two trimesters with the definition of above the 90th percentile of the population and exceeding the 2009 IOM recommended limits; Models 3 and 4 evaluated excessive GWG up to GDM screening with the definition of above the 90th percentile of the population and exceeding the upper limit of the 2009 IOM recommendations. The adjusted odds ratios and 95% confidence intervals were calculated to estimate the relative risk.

We also performed the trend analysis to investigate the association between increasing GWG and the later development of GDM. Women were classified into four quartiles according to their weight gain before GDM screening, stratified by pre-pregnancy BMI category. Women in the lowest quartile were set as the reference group and multivariate logistic regression was used to investigate whether there was a trend of increasing GWG quartile with risk of GDM.

RESULTS

Characteristics of the study population

Throughout the study period, 8,463 women gave birth to singleton neonates after completing at least 28 weeks of gestation at Taipei Chang Gung Memorial Hospital. After we excluded women with fetal death ($n = 17$), fetal chromosomal or structural anomalies ($n = 67$), and overt DM ($n = 27$), pregnancy outcomes of 8,352 women were included in this study. Among these women, 1,129 (13.5%) developed GDM.

The subjects' characteristics are shown in Table 1. When comparing women with and without GDM, those with GDM were more commonly with advanced maternal age and overweight (pre-pregnancy BMI >24.9 kg/m^2), had a history of assisted or spontaneous abortion, fetal death, preterm birth, conception by ART, and a family history of type 2 diabetes mellitus. They were also more likely to have coexisting chronic hypertension, preeclampsia, and hyperthyroidism.

Regarding GWG during different periods of pregnancy, women with GDM had a significantly lower mean GWG in the second trimester, after GDM screening, and throughout gestation than women without GDM. There was no difference in GWG in the first trimester and before GDM screening between the two groups.

Excessive GWG before GDM screening and risk of GDM

With the use of two different classification methods to define an excessive GWG, we found that there were no differences in the rates of excessive GWG during the first two trimesters, and up to GDM screening between women with and without GDM among those with a low or normal BMI before pregnancy (Tables 2 and 3). For women with a high pre-pregnancy BMI, a lower rate of excessive GWG in the second trimester was noted within women with GDM than in those without GDM. We did not find differences in the rates of excessive GWG from the first trimester and up to GDM screening between the two groups of women (Table 4).

Next, we used multiple logistic regression to evaluate the correlation between excessive GWG in the first two trimesters (Models 1 and 2), before GDM screening (Models 3 and 4), and the risk of later development of GDM, stratified by pre-pregnancy BMI and adjusted for the confounding effects from variables with statistical significance in the univariate analysis including maternal age >34 years, prior histories of assisted or spontaneous abortions, stillbirth, preterm delivery, conception by ART, family history of type 2 diabetes mellitus, chronic hypertension, preeclampsia, and hyperthyroidism.

In Models 1 and 2, those women with a low BMI prior to pregnancy were at risk for GDM if the maternal age at delivery was greater than 34 years. A family history of type 2 diabetes mellitus was an additional risk factor for GDM in Models 3 and 4 (Table 2). For women with a normal pre-pregnancy BMI, a maternal age >34 years and a family history of type 2 diabetes mellitus were significant risk factors for GDM in all four models (Table 3). For women with a high pre-pregnancy BMI, a family history of type 2 diabetes mellitus was determined to be a risk factor for GDM in Models 1 and 2, while preeclampsia was an additional factor associated with GDM in Models 3 and 4 (Table 4). Regardless of the definitions of excessive GWG and pre-pregnancy BMI categories, no significant associations were found between excessive GWG and the development of GDM in all trimesters. When the comparison was restricted to those with excessive GWG and with adequate GWG, we were still unable to detect any significant correlation between excessive GWG throughout the period before GDM screening and the risk of GDM (data not presented). Furthermore, the trend analysis also failed to detect any significant association between increasing GWG and the later development of GDM, regardless of pre-pregnancy BMI category (Table S1).

Table 1 | Maternal characteristics of the study population

	No GDM (n = 7223)	GDM (n = 1129)	P
Age (year)			
<20	10 (0.2%)	1 (0.1%)	0.667
20–34	4631 (64.1%)	577 (51.1%)	<0.001
>34	2582 (35.7%)	551 (48.8%)	<0.001
Pre-pregnancy body mass index (kg/m^2)			
<18.5	1068 (14.80%)	109 (9.70%)	<0.001
18.5–24.9	5453 (75.50%)	764 (67.70%)	<0.001
>24.9	702 (9.70%)	256 (22.60%)	<0.001
Primiparity	4091 (56.6%)	601 (53.2%)	0.028
Prior induced or spontaneous abortions	2064 (28.6%)	371 (32.9%)	0.003
Prior fetal death	61 (0.8%)	26 (2.3%)	<0.001
Prior preterm birth	38 (0.5%)	12 (1.1%)	0.030
Conception by reproductive technology	142 (2.0%)	49 (4.3%)	<0.001
Cigarette smoking during pregnancy	6 (0.1%)	1 (0.1%)	0.953
Uterine fibroids	201 (2.8%)	41 (3.6%)	0.114
Family history of diabetes mellitus	2116 (29.3%)	489 (43.3%)	<0.001
Chronic hypertension	13 (0.2%)	10 (0.9%)	<0.001
Preeclampsia	83 (1.1%)	32 (2.8%)	<0.001
Hyperthyroidism	36 (0.5%)	11 (1.0%)	0.047
Hypothyroidism	19 (0.3%)	6 (0.5%)	0.125
Weight gain during pregnancy (kg)			
First trimester	1.6 ± 2.3	1.7 ± 2.5	0.194
Second trimester	6.3 ± 2.4	5.9 ± 2.6	<0.001
Before GDM screening	7.8 ± 3.4	7.6 ± 3.6	0.055
After GDM screening	5.2 ± 2.6	4.1 ± 2.9	<0.001
Total weight gain	13.0 ± 4.1	11.7 ± 4.5	<0.001

Data presented as number (%) or mean ± standard deviation. P value based on chi-square test, Fisher exact test, or Student's t-test. GDM, gestational diabetes mellitus.

DISCUSSION

The current study found that the amount of GWG in the first trimester and before GDM screening did not change the risk of developing GDM. Interestingly, women with GDM had significantly less GWG in the second trimester, after GDM screening, and throughout gestation than women without GDM. Furthermore, we did not find significant associations between excessive GWG, either defined as a weight gain above the 90th percentile of the whole population or exceeding the 2009 IOM recommendations, during the first and second trimester (before GDM screening), and the later development of GDM.

Several previous reports have indicated that the extent of GWG before GDM screening correlates with the risk of GDM, and women with excessive GWG before GDM screening have a higher risk for the development of GDM later on[6–9,12,13,22–24]. However, the definitions for excessive GWG varied, the association was not consistently demonstrated among women in various pre-pregnancy BMI categories, and only two prior studies were carried out on Asian women. Morisset *et al.* discovered that women with GDM had significantly more GWG in the first trimester in comparison with women without GDM[13]. Gibson *et al.* also demonstrated that while women who were underweight or had a normal weight prior to pregnancy did not seem to be at an elevated risk for GDM, those with a high GWG before 12 weeks and through 24 weeks of gestation were at an increased risk for GDM in overweight or obese women[7]. Similarly, Moore Simas *et al.* reported that women with first-trimester GWG exceeding 2009 IOM recommendations had a higher risk of GDM if they were overweight in comparison with women with appropriate weight gain, though the same findings were not observed in normal or obese groups[24]. Carreno *et al.* also found that GWG that exceeded the 2009 IOM guidelines in women up to 15–18 weeks of gestation had a higher risk for developing GDM, with the greatest effect in women with a normal BMI before pregnancy[6]. Qi *et al.* demonstrated that in women with underweight and normal weight prior to pregnancy, those with GWG greater than the 90th percentile of the whole population before GDM screening had an increased risk of developing GDM[9]. However, similar associations were not found in women who were overweight prior to pregnancy or when the excessive GWG was defined by surpassing the 2009 IOM recommendations, regardless of pre-pregnancy BMI. Furthermore, an upward weight gain trajectory in the first trimester was found to increase the development of GDM[22], and women with a high GWG in the first trimester and prior to GDM screening were at an elevated risk of

Table 2 | Results of multiple logistic regression in women with a low pre-pregnancy body mass index

	GDM (n = 109)	No GDM (n = 1068)	P	Model 1 AOR (95% CI)	Model 2 AOR (95% CI)	Model 3 AOR (95% CI)	Model 4 AOR (95% CI)
Maternal age > 34 years	45 (41.3%)	244 (22.8%)	<0.01	2.08 (1.16–3.73)	2.04 (1.14–3.65)	2.55 (1.52–4.27)	2.44 (1.47–4.06)
Primiparity	40 (36.7%)	376 (35.2%)	0.76	0.74 (0.42–1.31)	0.77 (0.44–1.35)	0.70 (0.43–1.16)	0.71 (0.43–1.17)
Prior induced or spontaneous abortions	30 (27.5%)	279 (26.1%)	0.75	0.68 (0.35–1.32)	0.64 (0.33–1.25)	0.92 (0.53–1.59)	0.90 (0.52–1.56)
Family history of diabetes	39 (36.8%)	266 (24.9%)	0.02	1.64 (0.92–2.92)	1.65 (0.93–3.00)	1.84 (1.12–3.03)	1.84 (1.12–3.03)
First-trimester GWG > 90th percentile	3 (4.1%)	77 (9.6%)	0.12	0.54 (0.15–1.93)	–	–	–
Second trimester GWG > 90th percentile	3 (4.3%)	66 (8.4%)	0.24	0.71 (0.20–2.53)	–	–	–
First-trimester GWG > IOM guidelines	31 (42.5%)	276 (34.4%)	0.17	–	1.48 (0.85–2.59)	–	–
Second trimester GWG > IOM guidelines	7 (10.1%)	91 (11.5%)	0.73	–	1.06 (0.43–2.61)	–	–
GWG before GDM test > 90th percentile	8 (8.7%)	106 (10.9%)	0.52	–	–	0.75 (0.33–1.72)	–
GWG before GDM test > IOM guidelines	14 (15.2%)	162 (16.6%)	0.73	–	–	–	1.01 (0.52–1.98)

Data presented as number (%); P value based on chi-square test or Fisher exact test. AOR, adjusted odds ratio; CI, confidence interval; GDM, gestational diabetes mellitus; GWG, gestational weight gain; IOM, Institute of Medicine. Variables including prior fetal death (n = 2), prior preterm birth (n = 3), conception by reproductive technology (n = 19), chronic hypertension (n = 0), preeclampsia (n = 6), and hyperthyroidism (n = 3) were not computed for adjusted odds ratio and associated 95% confidence intervals because of small case numbers.

Table 3 | Results of multiple logistic regression in women with a normal pre-pregnancy body mass index

	GDM (n = 764)	No GDM (n = 5453)	P	Model 1 AOR (95% CI)	Model 2 AOR (95% CI)	Model 3 AOR (95% CI)	Model 4 AOR (95% CI)
Maternal age >34 years	378 (49.5%)	2048 (37.6%)	<0.01	1.76 (1.40–2.11)	1.70 (1.38–2.08)	1.68 (1.40–2.01)	1.68 (1.39–2.01)
Primiparity	343 (44.9%)	2371 (43.5%)	0.46	0.87 (0.70–1.06)	0.87 (0.71–1.07)	0.90 (0.75–1.09)	0.90 (0.75–1.09)
Prior induced or spontaneous abortions	254 (33.2%)	1558 (28.6%)	<0.01	1.18 (0.95–1.45)	1.18 (0.95–1.45)	1.19 (0.98–1.43)	1.18 (0.98–1.43)
Prior fetal death	13 (1.7%)	49 (0.9%)	0.04	1.52 (0.65–3.56)	1.49 (0.63–3.50)	1.56 (0.75–3.25)	1.56 (0.75–3.25)
Prior preterm birth	7 (0.9%)	34 (0.6%)	0.35	0.86 (0.22–3.40)	0.84 (0.21–3.32)	1.46 (0.53–4.01)	1.46 (0.53–4.01)
Conception by reproductive technology	31 (4.1%)	112 (2.1%)	<0.01	1.30 (0.71–2.38)	1.31 (0.72–2.39)	1.46 (0.89–2.42)	1.47 (0.89–2.43)
Family history of diabetes	316 (42.1%)	1581 (29.0%)	<0.01	1.62 (1.33–1.98)	1.63 (1.33–1.99)	1.68 (1.40–2.01)	1.68 (1.40–2.02)
Chronic hypertension	2 (0.3%)	4 (0.1%)	0.12	4.71 (0.40–55.77)	4.51 (0.39–52.77)	2.68 (0.35–20.41)	2.63 (0.35–19.91)
Preeclampsia	9 (1.2%)	54 (1.0%)	0.63	1.98 (0.82–4.79)	1.98 (0.82–4.79)	1.85 (0.78–4.41)	1.86 (0.78–4.43)
Hyperthyroidism	7 (0.9%)	31 (0.6%)	0.25	1.16 (0.46–2.93)	1.18 (0.47–2.97)	1.13 (0.45–2.84)	1.16 (0.46–2.91)
First-trimester GWG > 90th percentile	61 (10.4%)	417 (10.0%)	0.74	0.96 (0.70–1.32)	–	–	–
Second trimester GWG > 90th percentile	68 (11.7%)	446 (10.8%)	0.51	1.21 (0.89–1.64)	–	–	–
First-trimester GWG > IOM guidelines	229 (39.1%)	1527 (36.5%)	0.23	–	1.06 (0.87–1.30)	–	–
Second trimester GWG > IOM guidelines	157 (27.1%)	1139 (27.7%)	0.79	–	1.02 (0.82–1.27)	–	–
GWG before GDM test > 90th percentile	79 (11.0%)	506 (10.1%)	0.44	–	–	1.24 (0.94–1.66)	–
GWG before GDM test > IOM guidelines	215 (30.1%)	1402 (28.0%)	0.26	–	–	–	1.11 (0.92–1.35)

Data presented as number (%); P value based on chi-square test or Fisher exact test. AOR, adjusted odds ratio; CI, confidence interval; GDM, gestational diabetes mellitus; GWG, gestational weight gain; IOM, Institute of Medicine.

Table 4 | Results of multiple logistic regression in women with a high pre-pregnancy body mass index

	GDM (n = 256)	No GDM (n = 702)	P	Model 1 AOR (95% CI)	Model 2 AOR (95% CI)	Model 3 AOR (95% CI)	Model 4 AOR (95% CI)
Maternal age > 34 years	128 (50.0%)	290 (41.3%)	0.02	1.19 (0.77–1.83)	1.20 (0.78–1.84)	1.30 (0.88–1.92)	1.30 (0.88–1.92)
Primiparity	145 (56.6%)	385 (54.8%)	0.62	0.88 (0.57–1.38)	0.91 (0.58–1.42)	0.98 (0.65–1.46)	0.97 (0.65–1.45)
Prior induced or spontaneous abortions	87 (34.0%)	227 (32.3%)	0.63	1.11 (0.71–1.75)	1.12 (0.72–1.75)	1.12 (0.78–1.75)	1.17 (0.78–1.75)
Prior fetal death	13 (5.1%)	10 (1.4%)	<0.01	2.88 (0.85–9.83)	2.70 (0.80–9.06)	2.50 (0.83–7.49)	2.52 (0.84–7.59)
Conception by reproductive technology	4 (1.6%)	2 (0.3%)	0.03	1.63 (0.48–5.51)	1.77 (0.52–6.02)	2.12 (0.64–7.03)	2.11 (0.64–6.99)
Family history of diabetes	13 (5.1%)	16 (2.3%)	0.03	2.18 (1.44–3.31)	2.16 (1.42–3.26)	1.90 (1.30–2.77)	1.90 (1.30–2.77)
Chronic hypertension	134 (53.0%)	266 (37.8%)	<0.01	3.93 (0.44–35.18)	4.18 (0.47–37.58)	6.97 (0.84–58.23)	6.97 (0.84–58.15)
Preeclampsia	8 (3.1%)	9 (1.3%)	0.06	2.18 (0.87–5.44)	2.08 (0.84–5.15)	2.89 (1.27–6.56)	2.90 (1.27–6.62)
First-trimester GWG > 90th percentile	22 (8.6%)	24 (3.4%)	<0.01	1.23 (0.60–2.52)	–	–	–
Second trimester GWG > 90th percentile	4 (1.6%)	2 (0.3%)	0.03	0.40 (0.13–1.25)	–	–	–
First-trimester GWG > IOM guidelines	22 (10.6%)	54 (9.9%)	0.78	–	1.19 (0.77–1.85)	–	–
Second trimester GWG > IOM guidelines	5 (2.4%)	38 (7.1%)	0.01	–	0.94 (0.54–1.63)	–	–
GWG before GDM test > 90th percentile	74 (35.7%)	170 (31.3%)	0.25	–	–	1.02 (0.43–2.43)	–
GWG before GDM test > IOM guidelines	34 (16.4%)	126 (23.5%)	0.04	–	–	–	0.97 (0.61–1.53)

Data presented as number (%); P value based on chi-square test or Fisher exact test. AOR, adjusted odds ratio; CI, confidence interval; GDM, gestational diabetes mellitus; GWG, gestational weight gain; IOM, Institute of Medicine. Variables including prior preterm birth (n = 6) and hyperthyroidism (n = 6) were not computed for adjusted odds ratio and associated 95% confidence intervals because of small case numbers.

GDM[12,23]. Together, these results suggest a causal relationship between excessive GWG prior to GDM screening and the development of GDM. It is proposed that a higher GWG can cause increased insulin resistance which leads to glucose intolerance and GDM.

Unlike the above studies, we and others did not find a positive association between excessive GWG throughout the first or second trimester (before GDM screening), and the later development of GDM[11,21]. Explanations for this discrepancy remain unclear. There are several possibilities. First, women who were prone to develop GDM (i.e., those with a high pre-pregnancy BMI or advanced maternal age) were more likely to be educated about appropriate weight gain throughout gestation to reduce the development of known pregnancy complications such as preeclampsia and fetal macrosomia at the antenatal examinations. As a result, these women might be more careful about their dietary habit and had more exercise and eventually had less GWG than women without GDM.

Second, some prior studies that reported on the associations between excessive GWG and GDM were based on comparisons of those with excessive GWG versus those with non-excessive GWG. Women with non-excessive GWG included not only adequate weight gain, but also insufficient weight gain during pregnancy (i.e., weight gain below the IOM recommendations). It has been noted that women with insufficient GWG before 24–28 weeks of gestation were less likely to have GDM than those with adequate GWG[21]. Therefore, the theory that excessive GWG affects the development of GDM may have been overestimated if the comparison was simply between excessive to non-excessive weight gain. Indeed, a meta-analysis including eight studies showed that excessive GWG before GDM screening increases the risk of GDM development by an odds ratio of 1.4[25]. However, when the analysis was confined to studies that adjusted for confounding factors, and that reported the odds ratio as a comparison between excessive and adequate GWG, the association was not statistically significant, with overlapping 95% confidence limits.

The third possible explanation involves the components of GWG, which include the developing fetus and placenta, amniotic fluid, expansion of maternal blood volume and extracellular fluid, enlargement of the gravid uterus and mammary glands, and increased maternal adipose tissue. These components change over the course of pregnancy and to different extents in different individuals, therefore markedly affecting the interpretation of the relationship between GWG and risk of GDM. Little is known about which components of GWG relate to the development of GDM, though maternal fat mass is an important element as it may impair insulin sensitivity. It has been estimated that, for a normal term pregnancy characterized by a total GWG of 11 kg throughout gestation, maternal fat deposition accounts for only about 27% of GWG[26]. However, GWG before mid-gestation is essentially attributed to early placental development and the increase in maternal blood volume, rather than fat mass[27]. Furthermore, when considering the pre-

pregnant BMI, it was found that a gain of maternal truncal fat mass was a more potent predictor for GDM than the overall GWG from early pregnancy to late gestation[8]. The insignificance of GWG on the risk of GDM was further supported by a meta-analysis of 23 randomized controlled trials that concluded there was no effect on lowering the risk of GDM by reduction of weight gain throughout pregnancy with dietary and lifestyle modifications in obese women[28]. Together, this suggests that excessive GWG is likely to be a less significant risk factor for GDM than other factors such as pre-pregnancy overweight or obesity, advanced maternal age, and family history of type 2 diabetes mellitus, as revealed in this study.

The present study is strengthened by the adjustment for several major elements that may confound the effect of excessive GWG on the development of GDM, use of two classification methods for excessive GWG, and a subgroup analysis between different groups of pre-pregnancy BMIs. With these approaches, the association between excessive GWG and the risk of GDM can be effectively and comprehensively investigated. However, our study was not without limitations. First, the pre-pregnancy weight to calculate GWG and BMI was self-reported, which are subject to recall bias and likely to be underestimated. Second, due to the retrospective nature of the study, we were unable to obtain pertinent information regarding nutritional condition and physical activity during pregnancy, that may have affected GWG and the development of GDM, and therefore not examined. Furthermore, there remains a possibility of selection bias in the study population because the study was performed at a single tertiary care hospital with a retrospective and observational design. Finally, our analysis was carried out on a homogenous Taiwanese population and used IADPSG criteria to diagnose GDM, therefore the conclusions may not be applicable to other ethnicities/races and hospitals with different GDM diagnostic methods.

In summary, we found that there were no differences in GWG in the first trimester and before GDM screening, between women with and without GDM. We also failed to find a significant association between excessive GWG (weight gain above the 90th percentile of the study population or exceeding the upper range recommended by IOM) during the first and second trimesters, and up to GDM screening, and later development of GDM. Although women with excessive GWG are more susceptible to pregnancy complications such as preeclampsia, our results indicate that excessive GWG is not a significant risk factor for GDM. Further prospectively designed studies, particularly on Asian populations, and the use of IADPSG criteria for GDM are needed to confirm our findings.

ACKNOWLEDGMENTS

This work was supported by grants from Chang Gung Memorial Hospital (CMRPG1J0072) and the Ministry of Science and Technology, Taiwan (109-2314-B-182A-097-MY3). The authors are grateful to the Taipei Common Laboratory of Chang Gung Memorial Hospital for providing statistical assistance.

DISCLOSURE

The authors declare no conflict of interest.
Approval of the research protocol: The Institutional Review Board of Chang Gung Memorial Hospital approved this study on June 22, 2018.
Informed Consent: Requirement for informed consent was waived by the approval body since the study was retrospective and anonymous.
Approval date of Registry and Registration No. of the study/trial: June 22, 2018. Approval no. 201800894B0
Animal Studies: N/A.

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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section at the end of the article.

Table S1 | Trend analysis for the association between weight gain before gestational diabetes screening and risk of gestational diabetes.