Contents available at ScienceDirect

Diabetes Research and Clinical Practice

journal homepage: www.elsevier.com/locate/diabres

Excessive gestational weight gain and the risk of gestational diabetes: Comparison of Intergrowth-21st standards, IOM recommendations and a local reference

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ARTICLE INFO

Article history:
Received 17 September 2019
Received in revised form
22 October 2019
Accepted 29 October 2019
Available online 1 November 2019

Keywords:
Gestational diabetes
Gestational weight gain
Intergrowth-21st standards
IOM recommendations

ABSTRACT

Aims: To compare the abilities of Intergrowth-21st standards, Institute of Medicine (IOM) recommendations and a Chinese reference on gestational weight gain (GWG) to identify women at risk of gestational diabetes (GDM) and GDM-related adverse outcomes.
Methods: A retrospective cohort study was conducted on 13,366 women delivering live singleton infants between 2013 and 2017 in Tongzhou district of Beijing, China. Poisson regression with robust error estimates was used to estimate risk ratios (RRs) of GDM in different GWG groups according to three standards.
Results: There were 39.97%, 46.31% and 30.03% of women gaining weight above Intergrowth-21st standards, IOM recommendations and the Chinese reference respectively. Women with GWG above Intergrowth-21st standards and the Chinese reference had 27% (aRR, 1.27 95% CI, 1.18–1.37) and 30% (aRR, 1.30; 95% CI, 1.21–1.40) increased risks of GDM respectively, as compared to 22% (aRR, 1.22; 95% CI, 1.13–1.32) for IOM recommendations. GWG above either of these three standards was associated with macrosomia and cesarean delivery ($P < 0.05$).
Conclusion: Compared with IOM recommendations, GWG above Intergrowth-21st standards or the Chinese reference was associated with higher risks of GDM and GDM-related adverse outcomes. Furthermore, these two prospective standards could additionally assess the severity of abnormal GWG and are feasible for dynamic monitoring.

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https://doi.org/10.1016/j.diabres.2019.107912
0168-8227/

1. Introduction

Gestational diabetes mellitus (GDM) is defined as "a carbohydrate intolerance resulting in hyperglycaemia of variable severity with onset or first recognition during pregnancy" [1]. A worldwide estimate showed approximately 1 in 7 live births to women are affected by GDM [2]. GDM has significant adverse impact on both mother and offspring, such as the increased risks of macrosomia and caesarean section [3]. In the long term, GDM could increase the likelihood of subsequent maternal type 2 diabetes and metabolic diseases in the offspring [3–5]. Potentially via the pathway of increased risk of infant macrosomia, GDM could contribute to future generation risks of childhood and adolescent obesity, making prevention of GDM an important goal in preventing offspring obesity [6].

Excessive gestational weight gain (GWG) is an important controllable risk factor of GDM. A recent meta-analysis showed excessive GWG prior to GDM screening had a 40% increase in risk of developing GDM [6]. Meanwhile, Excessive GWG also contributes to other adverse outcomes including macrosomia, large for gestational age, and cesarean delivery [7]. Many recommendations and standards have been established for GWG [8–10]. Few of them, however, included GDM as one of the main outcomes. The Institute of Medicine (IOM) recommendations, which was first developed in 1990 and then updated in 2009, is the most commonly used GWG standard [8]. According to IOM recommendations, a range of absolute weight gain in the first trimester and a range of rate of weight gain per week for the second and third trimesters were recommended for women in different pre-pregnancy body mass index (BMI) categories. However, although the trade-offs between abnormal GWG and some important adverse health outcomes were well addressed, GDM wasn't given full consideration because the research of the association between GWG and GDM by then had inconsistent results. A new multi-ethnic international GWG standards, called Intergrowth-21st, selected healthy, well-nourished and educated mothers with uncomplicated pregnancies in 8 countries, including China, and created a prescriptive GWG reference chart [9]. Besides, a Chinese GWG reference for gestational age has been established recently, based on 132 thousand pregnant women in 12 districts/counties of 6 provinces in China [11]. However, the abilities of these two prospective standards on GWG to identify pregnant women at risk of GDM as well as GDM-related adverse pregnancy outcomes have not been reported.

Considering that excessive GWG is associated with GDM and the prevalence of excessive GWG is notably high [12], it is necessary to determine which standards could be best used to describe the appropriate weight gain prior to glucose screening to prevent GDM. The objective of the current study was to compare the abilities of Intergrowth-21st standards, IOM recommendations and the Chinese reference on GWG to identify women at risk of developing GDM and GDM-related adverse outcomes.

2. Methods

2.1. *Study population*

A retrospective cohort study was conducted and women who delivered a live singleton infant between April 2013 and December 2017 in Tongzhou Maternal and Child Health Hospital of Beijing were included in this study. Their demographic data, pregnancy history and current pregnancy information were collected from the hospital information system. Participants' heights and weights were measured and recorded during the first prenatal visit and their weights were also routinely measured in each following prenatal examination. To enhance reliability, we restricted to women with weight measurements within 2 weeks before oral glucose tolerance test (OGTT). Only women with normal pre-pregnancy BMI (18.5–24.9 kg/m^2) were included because of the scope of application of Intergrowth-21st standards. Among 15,211 eligible women, we excluded those who have heart disease (n = 8) or chronic renal disease (n = 12), who have GDM history (n = 300), and who didn't take OGTT between 24 and 28 weeks of gestation (n = 1,525), which left 13,366 women included in the final analysis. This study was approved by the institutional review boards at Peking University (reference number IRB00001052-18003; date of approval 4 February 2018).

2.2. *Gestational weight gain*

GWG before OGTT was calculated as weight measured at or before (within 2 weeks) OGTT minus self-reported pre-pregnancy weight. GWG was standardized into gestational age-specific Z-scores according to the Intergrowth-21st standards by using their excel-based GWG calculator [13] and the Chinese reference by using the equations provided in their paper [11]. Since both of them didn't provide cut-off values, we calculated the sensitivity, specificity and Youden index of different cutoff points for prediction of GDM (Z-scores equal to 0.5, 1, 1, 5, 2). Both standards had relatively higher Youden Index when Z-scores equal to 1 (**supplement** Table 1). Thus, we set appropriate GWG as Z-scores between −1 to 1. Accordingly, pregnant women were classified as below (Z-scores <−1), within (Z-scores between −1 to 1) or above (Z-scores > 1) the Intergrowth-21st standards or the Chinese reference. For IOM recommendations, a range of absolute weight gain in the first trimester (0.5–2 kg) and a range of rate of weight gain per week for the second and third trimesters (0.35–0.50 kg/week) were recommended for normal-weight women [8]. Thus, we used the formulas below to calculate the range of weight gain that meets the IOM recommendations and then compared it with exact weight gain to determine each women's GWG category (below, within or above).

$$\text{GWG lower limit} = 0.5\text{ kg} + 0.35\text{ kg/week} \times (\text{Gweek-13})$$
$$\text{GWG upper limit} = 2.0\text{ kg} + 0.50\text{ kg/week} \times (\text{Gweek-13})$$

2.3. Gestational diabetes mellitus

Participating women without preexisting diabetes underwent a routine 75 g OGTT between 24 and 28 weeks of gestation. According to the World Health Organization-endorsed criteria of the International Association of Diabetes and Pregnancy Study Group [14], those with fasting glucose value ≥5.1 mmol/L, 1-hour post glucose ≥10.0 mmol/L or 2-hour post glucose ≥8.5 mmol/L were diagnosed as GDM.

2.4. Statistical analysis

The differences of characteristics of the study population with and without GDM were examined. Variance analysis was used to evaluate differences in continuous variables across groups and chi-square tests were used for categorical variables. The differences in distributions and incidence rate of GDM between different weight gain groups according to Intergrowth-21st standards, IOM recommendations and the Chinese reference were also examined by using chi-square tests. Considering odds ratio (OR) cannot provide accurate estimates for the relative risk (RR) in cohort studies, we used univariate and multivariate Poisson regression with robust error estimates to estimate crude risk ratios (cRRs) and adjusted risk ratios (aRRs) of GDM in relation to different weight gain groups according to three standards [15,16]. The robust error variance makes estimates to be relatively robust to omitted covariates in contrast to logistic regression [15]. Women with GWG within these standards were used as the reference group respectively. Variables evaluated for confounding included maternal age (years, continuous), pre-pregnancy BMI (kg/m^2, continuous), parity (childbirth numbers: 0, ≥1), maternal education (≤12 years, >12 years), occupation (employed, unemployed), family history of diabetes (yes, no), and history of macrosomia (yes, no). In addition, considering that women with higher GWG are at risk of developing preeclampsia, which is defined as the occurrence of hypertension and proteinuria in a previously healthy woman on or after the 20th week of gestation [17], and preeclampsia is also more frequent in women with GDM [18], a sensitivity analysis was conducted after excluding women with preeclampsia. SAS 9.4 was used to carry out all analyses and a two-sided value of $P < 0.05$ was considered statistically significant.

3. Results

Among 13,366 participants, mean age was 29.74 ± 3.93 years, mean pre-pregnancy BMI was 21.4 ± 1.72 kg/m^2, mean GWG before OGTT was 8.44 ± 3.77 kg, mean gestation at the first antenatal visit was 12.48 ± 3.68 weeks. The incidence of GDM was 18.05%. The characteristics of the pregnant women with and without GDM were shown in Table 1. Women with GDM were older, shorter, and had higher pre-pregnancy weight, BMI, GWG, and lower proportion of primipara.

Incidence rate of GDM and GDM-related adverse outcomes in different weight gain groups according to three standards were shown in Table 2. There were 39.97%, 46.31% and 30.03% of women gaining weight above Intergrowth-21st standards, IOM recommendations and the Chinese reference respectively. Compared with women gaining weight within Intergrowth-21st standards, women with GWG above Intergrowth-21st standards had significantly higher incidence rates of GDM (20.96% vs 16.54%), macrosomia (10.76% vs 6.51%), and cesarean delivery (42.88% vs 36.70%). Meanwhile, women gaining weight above IOM recommendations and the Chinese standard also had significantly higher incidence rate of GDM, macrosomia, and cesarean delivery.

As shown in Table 3, after adjustment for maternal age, pre-pregnancy BMI, parity, maternal education, occupation, family history of diabetes, and history of macrosomia, women with GWG above Intergrowth-21st standards, IOM recommendations and the Chinese reference had 27% (aRR, 1.27 95% CI, 1.18–1.37), 22% (aRR, 1.22; 95% CI, 1.13–1.32) and 30% (aRR, 1.30; 95% CI, 1.21–1.40) increased risks of developing GDM respectively. Moreover, women with GWG above these standards also had increased risks of macrosomia and cesarean delivery. The results didn't change after the exclusion of women with preeclampsia (results shown in **Supplemental** Table 2).

The risk of GDM by GWG Z-score units according to Intergrowth-21st standards and the Chinese reference were shown in Fig. 1. For both standards, the risks increased apparently after gaining weight more than + 1 SD (Z-scores >1). Compared with women with GWG Z-scores between −1 to 1, according to Intergrowth-21st standards, women with Z-scores ≥3 had 54% (aRR, 1.54; 95% CI, 1.30–1.82) increased risks of developing GDM. However, according to the Chinese reference, women with Z-scores ≥3 didn't have significantly increased risks of GDM compared with women with Z-scores between −1 to 1.

4. Discussion

To our knowledge, this is the first study to evaluate the ability of Intergrowth-21st standards and the Chinese reference on GWG to identify pregnant women at risk of GDM and GDM-related adverse outcomes and compare these two prospective standards with IOM recommendations. We found that GWG above Intergrowth-21st standards or the Chinese reference was associated with higher risks of GDM and GDM-related adverse outcomes, as compared to IOM recommendations, and these two prospective standards are more practical for dynamic monitoring.

The Intergrowth-21st Project was launched in 2009 with aims to extend the World Health Organization Child Growth Standards into the early neonatal and fetal period [19]. Up to now, a series of standards, including standards for pregnancy dating, fetal growth, maternal weight gain, newborn size, the postnatal growth of preterm infants, have been established [9]. Some previous studies have evaluated the accuracy of the standards for infant [16,20], whereas only one study used GWG standards to evaluate its ability to identify women at risk of excess interpregnancy weight gain [21]. The Chinese reference was set up in 2019, based on pregnant women with healthy pregnancy outcomes from 6 provinces in China. None of previous researches applied this standard to estimating the risks of adverse pregnancy outcomes. In our

Table 1 – Demographic characteristics of the pregnant women (n = 13,366).

Characteristic	Women with GDM N = 2,413	Women without GDM N = 10,953	P
Maternal age (y)	30.96 ± 4.14	29.47 ± 3.84	<0.0001
Education > 12 years (%)	1,699 (70.94)	7,534 (69.80)	0.2701
Employed (%)	1,702 (71.21)	7,674 (71.38)	0.8710
Parity (%)			<0.0001
0	1,531 (63.45)	7,605 (69.43)	
≥1	882 (36.55)	3,348 (30.57)	
Height (cm)	161.72 ± 4.62	162.00 ± 4.61	0.0058
Pre-pregnancy weight (kg)	57.30 ± 5.57	56.19 ± 5.51	<0.0001
Pre-pregnancy BMI (kg/m^2)	21.89 ± 1.71	21.39 ± 1.71	<0.0001
GWG before glucose screening (kg)	9.07 ± 3.92	8.30 ± 3.72	<0.0001

Data are presented as mean (SE) or n (%).
GDM, gestational diabetes mellitus. BMI, body mass index. GWG, gestational weight gain.
$P < 0.05$ was considered statistically significant.

Table 2 – Incidence rate of GDM and GDM-related adverse outcomes in different weight gain groups according to Intergrowth-21st standards, IOM recommendations and the Chinese reference.

	N (%)	GDM	P	Macrosomia	P	Cesarean delivery	P
Intergrowth-21st standards (Z-score)							
Below (<−1)	1,353 (0.12)	190 (14.04)	<0.0001	54 (3.99)	<0.0001	458 (33.85)	<0.0001
Within (−1–1)	6,670 (9.90)	1,103 (16.54)		434 (6.51)		2,448 (36.70)	
Above (>1)	5,343 (39.97)	1,120 (20.96)		575 (10.76)		2,291 (42.88)	
IOM recommendations							
Below	2,177 (16.29)	325 (14.93)	<0.0001	87 (4.00)	<0.0001	765 (35.14)	<0.0001
Within	4,999 (37.40)	834 (16.68)		337 (6.74)		1,806 (36.13)	
Above	6,190 (46.31)	1,254 (20.26)		639 (10.32)		2,626 (42.42)	
Chinese reference (Z-score)							
Below (<−1)	1,754 (13.12)	258 (14.71)	<0.0001	67 (3.82)	<0.0001	606 (34.55)	<0.0001
Within (−1–1)	7,598 (56.85)	1,276 (16.79)		539 (7.09)		2,829 (37.23)	
Above (>1)	4,014 (30.03)	879 (21.90)		457 (11.39)		1,762 (43.90)	

GDM, gestational diabetes mellitus. IOM, Institute of Medicine.
$P < 0.05$ was considered statistically significant.

Table 3 – Association between risks of GDM and GDM-related adverse outcomes and gestational weight gain before diagnosis according to Intergrowth-21st standards, IOM recommendations and the Chinese reference.

	GDM		Macrosomia		Cesarean delivery	
	Adjusted RR (95%CI)[a]	P	Adjusted RR (95%CI)[a]	P	Adjusted RR (95%CI)[a]	P
Intergrowth-21st standards (Z-score)						
Below (<-1)	0.82 (0.72–0.95)	0.0068	0.58 (0.44–0.76)	0.0001	0.90 (0.83–0.98)	0.0131
Within (-1–1)	ref		ref		ref	
Above (>1)	1.27 (1.18–1.37)	<0.0001	1.62 (1.44–1.83)	<0.0001	1.18 (1.13–1.23)	<0.0001
IOM recommendations						
Below	0.89 (0.79–0.99)	0.0337	0.56 (0.44–0.70)	<0.0001	0.95 (0.89–1.01)	0.1264
Within	ref		ref		ref	
Above	1.22 (1.13–1.32)	<0.0001	1.49 (1.31–1.69)	<0.0001	1.18 (1.13–1.24)	<0.0001
Chinese reference (Z-score)						
Below (<-1)	0.85 (0.75–0.96)	0.0091	0.51 (0.40–0.66)	<0.0001	0.91 (0.85–0.97)	0.0058
Within (−1–1)	ref		ref		ref	
Above (>1)	1.30 (1.21–1.40)	<0.0001	1.57 (1.40–1.77)	<0.0001	1.19 (1.17–1.24)	<0.0001

GDM, gestational diabetes mellitus. IOM, Institute of Medicine.
$P < 0.05$ was considered statistically significant.
[a] Adjusted for maternal age, pre-pregnancy BMI, parity, maternal education, occupation, family history of diabetes, and history of macrosomia.

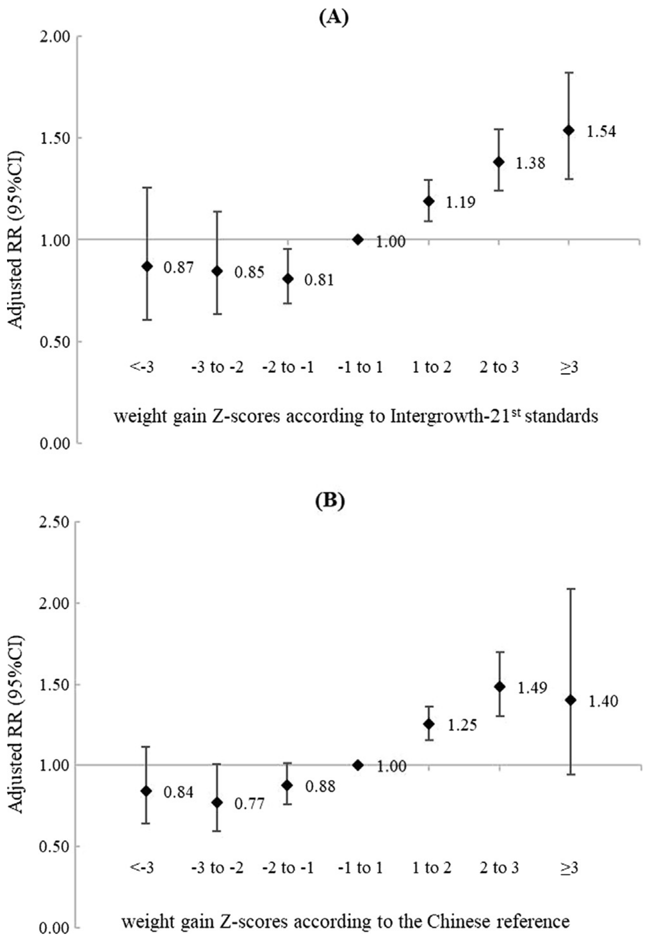

Fig. 1 – Relative ratios of the development of GDM by Z-scores of gestational weight gain before diagnosis according to Intergrowth-21st standards (A) and the Chinese reference (B). GDM, gestational diabetes mellitus.

study, we found that Intergrowth-21st standards and the Chinese reference had similar ability to identify women with normal pre-pregnancy BMI at risk of GDM and GDM-related outcomes. However, we couldn't compare these two standards among women in other BMI categories because of the limited scope of application of Intergrowth-21st standards. It's necessary to determine the optimal GWG among pre-pregnancy underweight, overweight and obese women in Intergrowth-21st standards, and further studies are need to evaluate which standard works best for women in other BMI categories.

Establishing explicit and uniform cutoff values for Intergrowth-21st standards and the Chinese reference is of great importance, otherwise it will be difficult for clinicians to identify abnormal GWG and take timely health interventions as appropriate. In our study, we found that the risk ratios started to increase apparently after Z-scores exceeding 1 for both standards. However, another recent study, which tried to link the Intergrowth-21st standards with the risk of excess maternal postpartum weight retention, found that the risks rose steadily with increasing weight gain Z-scores just above 0 [21]. None of previous studies assessed the association of Z-scores according to the Chinese reference with pregnancy outcomes. In our study, we set the cutoff points based on our main outcome, the incidence of GDM. More researches are needed to determine the optimal cutoff values after taking all important short- and long-term adverse outcomes into consideration.

Many prior studies have analyzed whether IOM recommendations could successfully recognize women with higher risk of developing GDM. A recent meta-analysis showed that GWG before GDM testing above IOM recommendations increases the risk of developing GDM by 40% [6], which was higher than our result (aRR, 1.27). The difference might because that we did not included women with inadequate weight gain in the reference group, whereas the meta-analysis included both adequate and inadequate weight gain in the reference group. Another more recent historical cohort study of 350 twin-conceiving Han women in a southern city in China found that the difference in GWG did not impact the incidences of GDM [22]. However, its results might be biased by using total weight gain over the entire pregnancy to predict GDM, as GWG after GDM diagnosis could be influenced by therapeutic intervention.

Intergrowth-21st standards and the Chinese reference are different from IOM recommendations in two aspects. First, they differ in methodology. IOM recommendations were developed by determining the optimal range of weight gain that minimized the aggregate risks of several adverse outcomes, while Intergrowth-21st standards and the Chinese reference created reference charts via describing the weight gain of a "healthy" population. Thus, compared with these two prospective standards, IOM recommendations are likely to be stricter. In our results, almost half of the subjects gained weight above IOM recommendations whereas 40% and 30% of the study population gained weight above Intergrowth-21st standards and the Chinese reference, with relatively higher risk of GDM as compared to IOM recommendations. Second, these two prospective standards are more practical. The degree of weight gain could be well demonstrated by using Z-scores, while IOM recommendations only have three categories failing to estimate the severity. Besides, IOM recommendations relatively lack precision on account of providing the same range of recommended weight gain rate for the second and third trimesters. By contrast, Intergrowth-21st standards and the Chinese reference depict the natural weight gain pattern throughout pregnancy and provide specific standards for every gestational week, thus they could be used as more precise tools for dynamic monitoring.

The following limitations of our study should be considered. First, only women with normal pre-pregnancy BMI were included in our study due to the application population of Intergrowth-21st standards. Therefore, our results cannot be generalized to women in other pre-pregnancy BMI categories. Future studies are still needed to determine GWG standards among pre-pregnancy underweight, overweight and obese women. Second, although women were diagnosed of GDM between 24 and 28 gestational weeks, it is unable to confirm the timing of the onset of GDM. However, we restricted to women with weight measurements within 2 weeks before OGTT, which could relatively guarantee the temporality of causal inference. In fact, many previous studies didn't report measures of GWG exactly at or before the GDM screening test [23], resulting in ambiguity when estimating the association between GWG and GDM. Third, pre-pregnancy weights were self-reported, because measured pre-pregnancy weights were difficult to obtain. However, many prior studies have found self-reported measurements were reliable [24,25]. Besides, there is no evidence that women who developed GDM would be more likely to underreport their weight. Thus, we believe any bias would only turn the results toward the null. Fourth, since Intergrowth-21st standards and the Chinese reference didn't provide cutoff values, we chose cutoff points based on our subjects. Thus, it's unknown whether these cutoff points could be applied to other population.

5. Conclusion

In conclusion, GWG above Intergrowth-21st standards or the Chinese reference was associated with higher risks of GDM and GDM-related adverse outcomes, compared with IOM recommendations. Furthermore, these two prospective standards could additionally estimate the severity of abnormal GWG and are practical for dynamic monitoring. Future prospective cohort studies are needed to evaluate the feasibility of Intergrowth-21st standards and local standards to identify women at risk of GDM.

Funding

This research was funded by National Natural Science Foundation of China [grant number 81703240].

Declaration of Competing Interest

All authors declare that they have no competing interests.

Acknowledgements

We sincerely thank staff in Maternal and Child Health Care Hospital of Tongzhou District for data collection.

Appendix A. Supplementary material

Supplementary data to this article can be found online at https://doi.org/10.1016/j.diabres.2019.107912.

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