

Original Research

# The Rate of Gestational Weight Gain are Associated with Preterm Birth in Pregnant Women at Low Risk for Preterm Birth: A Single-Center, Observational Study

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Academic Editor: Paolo Ivo Cavoretto

Submitted: 19 September 2022 Revised: 21 November 2022 Accepted: 21 November 2022 Published: 5 January 2023

## Abstract

**Background:** Preterm birth (PTB) is the main cause of infant disease and death worldwide. Approximately 70% of neonatal deaths and 36% of infant deaths worldwide are caused by premature birth. Gestational weight gain (GWG) is associated with adverse pregnancy outcomes. This study explored the relationship between the rate of GWG and PTB among pregnant women at low risk of preterm birth.

**Methods:** Our study used a cohort of mother-child pairs with a one-and-a-half-year follow-up from January 2020 to June 2021. We excluded pregnant women with undisputed high-risk factors for PTB and the remaining women were considered the low-risk group. The average rate of GWG was utilized in this research as the measure of GWG. Multivariate logistic regression was used to evaluate the relationship between GWG and PTB among pregnant women at low risk for preterm birth. **Results:** The final cohort study of mother-child pairs included 3480 pregnant women in the low-risk group. Women with low GWG had a higher possibility of PTB than those with adequate GWG. Comparing underweight women with an adequate GWG rate to underweight women with a low GWG rate, PTB risk increased by 2.52-fold with a low GWG rate. Compared to women with adequate GWG, underweight women with excessive GWG had significantly higher odds of PTB. No significant results were observed for pregnant women classified as overweight or obese.

**Conclusions:** A reasonable GWG during pregnancy can effectively reduce the risk of PTB, especially for pregnant women with low pre-pregnancy body mass index. Low or excessive GWG may lead to an increased risk of PTB.

**Keywords:** preterm birth; pregnancy; rate of gestational weight gain; risk factors

## 1. Introduction

Preterm birth (PTB), defined as gestational age less than 37 weeks, is the main cause of infant disease and death worldwide [1]. Approximately 70% of neonatal deaths and 36% of infant deaths worldwide are caused by premature birth [2]. Epidemiological studies have identified several risk factors for PTB, including a history of PTB and late abortion in previous pregnancies, short cervical length (measured between 16 and 24 weeks of gestation), history of cervical surgery, ethnic groups, PTB at <12 months inter-pregnancy interval, and *in vitro* fertilization (IVF) [3,4].

PTB can lead to low birth weight, anemia, infection, cerebral palsy, mental retardation, and various functional abnormalities in adulthood [5–7]. This can cause high consumption of medical resources, and a heavy burden to families and society. According to a 2006 survey report of the American Institute of Medicine (IOM), the annual medical expenses of premature infants in the United States (USA) amounted to USA \$26.2 billion, with an average of USA \$51,000 per person [8]. Therefore, identifying modifiable risk factors for PTB has become a necessary and worthwhile task for researchers.

Gestational weight gain (GWG) can reflect the nutritional status of women during pregnancy, which is important for women and their fetuses. Low and excessive GWG is associated with adverse pregnancy outcomes [9,10]. In a retrospective cohort study in Puerto Rico, women with low GWG had an increased risk of PTB (odds ratio (OR): 1.34, 95% confidence interval (CI): 1.30–1.37) [11]. However, studies examining the relationship between GWG and PTB have revealed a conflicting correlation [12]. For example, excessive GWG was associated with a 17% reduction in PTB risk among women in the USA and Europe [13]. In comparison, excessive GWG among Chinese women was significantly correlated with PTB (OR: 1.93, 95% CI: 1.29–2.88) [14]. Most of these studies were retrospective and included all pregnant women [15,16], which may have led to research bias caused by high-risk factors of PTB. There are also differences in the population included in these studies, which may have contributed to inconsistency in the correlation between PTB and GWG. Meanwhile, women who delivered preterm had less time to gain weight, which may lead to a lower GWG, and hence a confounded association between GWG and PTB.

Therefore, to eliminate this confounding, we used the rate of GWG in our study. In addition, we used a cohort of



mother-child pairs with a one-and-a-half-year follow-up to investigate the relationship between GWG and PTB among pregnant women at low risk for preterm birth.

## 2. Patients & Methods

### 2.1 Study Setting and Population

The cohort study of mother-child pairs was conducted at Women and Children's Hospital, School of Medicine, Xi'an University. This hospital is the leading provincial medical center for obstetrics referral center and has an average of 15,000 deliveries every year. Registered women with single pregnancy in first trimester were incorporated into the study cohort on an informed consent basis from 1 January 2020 to 30 June 2021. Pregnant women who did not participate in the whole process or have placenta previa or placental abruption were removed from the cohort study. These pregnant women were divided into two subgroups according to the existence of high-risk factors of preterm birth. All women were followed up until the end of pregnancy, including miscarriage, induced abortion, and delivery. In this study, the high risk group of PTB was defined as history of PTB and late abortion in previous pregnancies, a short cervical length (less than 25 mm, measured between 16 and 24 weeks of gestation), preterm birth at <12 months inter-pregnancy interval, and a history of cervical surgery (surgical treatment of dysplasia with cold-knife conization, loop electrosurgical excision), which are undisputed high risk factors for PTB according to the 2021 ACOG Guidelines [4]. The remaining the pregnant women were classified as the low-risk group for PTB. We included all mothers from the low-risk group of the cohort study who delivered a live singleton after more than 28 gestational weeks. This present study was conducted in accordance with the China approved guidelines.

### 2.2 Outcomes

The incidence of PTB, defined as delivery occurring before 37 weeks of gestation, was the primary outcome. The week of gestational was estimated by the last menstrual period. Early pregnancy ultrasound was used to verify gestational age.

### 2.3 Gestational Weight Gain and Pre-Pregnancy Body Mass Index (PP-BMI)

GWG recommendations updated by the IOM 2009 are based on PP-BMI from the World Health Organization (WHO) and are independent of parity, age, race, ethnicity, or smoking history [17]. The measure of GWG used in the study was average rate of GWG in second and third trimester, calculated by dividing the difference of weight between the last and first prenatal care visit in the second and third trimester by the corresponding difference of gestational weeks, respectively.

According to 2009 IOM standards, PP-BMI was classified into four subgroups: underweight (<18.5 kg/m<sup>2</sup>),

normal weight (18.5–24.9 kg/m<sup>2</sup>), overweight (25–29.9 kg/m<sup>2</sup>), and obese (≥30 kg/m<sup>2</sup>). Each category of PP-BMI has a recommendation for the range of GWG: underweight (0.44 to 0.58 kg/week); normal weight (0.35 to 0.50 kg/week); overweight (0.23 to 0.33 kg/week), and obese (0.17 to 0.27 kg/week). According to the range, the rate of GWG was categorized as: insufficient, adequate, and excessive.

### 2.4 Data Analysis

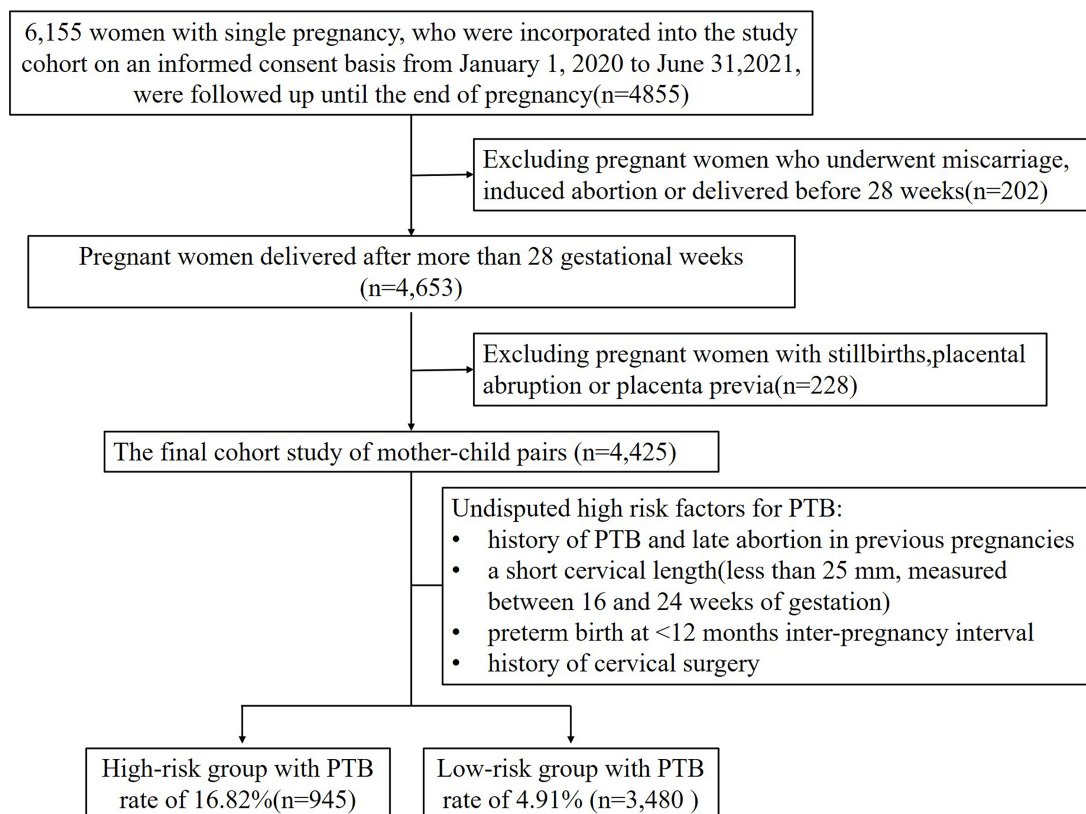
Maternal and neonatal demographic and clinical features are reported as frequency (%) or means (± Standard deviation (SD)). To compare the maternal sociodemographic characteristics, pregnancy history, and GWG between the preterm birth and normal group, univariate logistic regression analysis was utilized. Logistic regression models were performed to estimate the odds ratios (ORs) and 95% confidence interval (CI) for preterm birth and its subgroups. Maternal pre-pregnancy BMI, maternal age, education level, type of resident, parity, gravidity, and infant sex were adjusted in our analyses. All statistical tests were conducted by the two-tailed test, and  $p < 0.05$  was considered significant. All statistical analyses were done with SPSS 21.0 software (IBM Corp., Chicago, IL, USA).

## 3. Results

Fig. 1 shows the flow diagram of the study. From 1 January 2020 to 30 June 2021, we enrolled 4855 eligible pregnant women. The final cohort study of mother-child pairs included a total of 4425 pregnant women with complete data. According to undisputed high risk factors for PTB, 945 pregnant women were divided into high-risk group with a PTB rate of 16.82%, and 3480 pregnant women were divided into low-risk group with a PTB rate of 4.91%.

Table 1 shows the information on the basic characteristics of the included population. Baseline characteristics such as maternal age, education level, type of resident, parity, gravidity, and infant sex were not significantly different between low-risk and high-risk groups. The proportion of births that were preterm was significantly higher among high-risk group than low-risk group (16.82% vs 4.91%). In the low-risk group, 491 (14.11%) women were underweight, 2199 (63.19%) were normal weight, 699 (20.09%) were overweight, and 91 (2.61%) were obese. During pregnancy, 895 (25.55%), 1669 (47.96%), and 916 (26.49%) women had insufficient, adequate, and excessive GWG rates, respectively.

We further analyzed the characteristics, rate of GWG, and PP-BMI associated with preterm birth in the low risk group (Table 2). The proportion of births that were preterm was significantly higher among underweight women than those with normal weight. Women with a low rate of GWG had a higher prevalence of preterm birth compared with women with adequate GWG ( $p = 0.008$ ). Education level,



**Fig. 1. Flow diagram of the study.** PTB, preterm birth.

type of resident, gravidity, PP-BMI, and gate of GWG were significantly associated with preterm birth ( $p = 0.027$ ,  $p = 0.023$ ,  $p = 0.000$ ,  $p = 0.022$ , and  $p = 0.008$ , respectively). No differences were observed regarding maternal age, parity, and infant sex.

Multivariate logistic regression (Table 3) was performed to further explore the relations between GWG and preterm birth after adjusting for maternal age, education level, type of resident, parity, gravidity, and infant sex. Women with low GWG as compared to adequate GWG showed a higher risk of PTB (OR: 1.49, 95% CI: 1.11–2.09) in adjusted models that were not restricted to the strata of PP-BMI. No significant results were observed among pregnant women with low GWG compared to those with excessive GWG. In order to further investigate the impact of weight gain across different PP-BMIs, we performed stratified analysis. We found that a low rate of GWG was also related with higher risks of PTB among pregnant women who were classed as underweight and normal weight. Underweight women with a low GWG rate had a 2.52 increase in odds of PTB (95% CI: 1.20–6.02) compared to underweight women with adequate GWG rates. The adjusted OR for normal weight women with low GWG compared to normal women with an adequate GWG was 1.77 (95% CI: 1.16–2.78). Compared to women with adequate GWG, underweight women with excessive GWG had significantly higher odds of PTB (OR: 1.92, 95% CI: 1.10–5.11). No sig-

nificant results were observed among the pregnant women classified as overweight or obese.

## 4. Discussion

### 4.1 Interpretation of Findings

Contradictory results between PP-BMI, GWG, and PTB have been reported previously. We used a cohort study of mother-child pairs with a one-and-a-half-year follow-up to assess the relationship between PP-BMI, GWG, and PTB in women at low risk for preterm birth. The results demonstrated that pregnant women with a low rate of GWG had an increased risk of PTB compared to women with an adequate rate of GWG. These associations were more obvious in pregnant women classified as underweight or normal weight. We did not find an association between excessive rate of GWG and PTB risk, which is inconsistent with previous studies [14,18]; however, the risk increased if those women had a low PP-BMI, which indicated that the association between GWG and PTB varies according to PP-BMI. Our analysis identified low GWG and excess GWG with low PP-BMI as important and modifiable risk factors for PTB.

Although the biological mechanisms linking GWG to PTB are not fully understood, some pathogenic mechanisms have been postulated. Maternal weight change may be a marker of nutritional status and is also consid-

**Table 1. Basic characteristics of the included population.**

Variables	Low-risk group	How-risk group	OR (95% CI)
	(n = 3480)	(n = 945)	
Maternal age (years), mean $\pm$ SD	30.7 $\pm$ 4.35	31.16 $\pm$ 4.43	/
Education level, n (%)			
Primary	87 (2.5)	33 (3.49)	0.736 (0.49, 1.11)
Secondary	1860 (53.44)	519 (54.93)	Ref
College or graduate school	1544 (44.36)	393 (41.58)	1.10 (0.95, 1.27)
Type of resident, n (%)			
Local	2560 (73.56)	661 (69.95)	Ref
Non-local	920 (26.44)	284 (30.05)	0.84 (0.71, 0.98)
Parity, n (%)			
Nulliparous	1569 (45.08)	435 (46.04)	Ref
Multiparous	1911(54.92)	510 (53.96)	1.04 (0.90, 1.2)
Gravidity, n (%)			
0	1074 (30.86)	290 (30.68)	1.01 (0.86, 1.20)
1–2	1860 (53.45)	509 (53.86)	Ref
>2	546 (15.69)	146 (15.44)	1.02 (0.83, 1.26)
Infant sex, n (%)			
Male	1893 (54.39)	501 (53.02)	Ref
Female	1587 (45.61)	444 (46.98)	0.95 (0.82, 1.10)
Gestational age at delivery, n (%)			
Full-Term	3309 (95.09)	786 (83.17)	3.91 (3.11, 4.92)
Preterm	171 (4.91)	159 (16.83)	Ref
PP-BMI, n (%)			
Underweight (<18.5 kg/m <sup>2</sup> )	491 (14.11)	171 (18.10)	0.73 (0.60, 0.89)
Normal weight (18.5–24.9 kg/m <sup>2</sup> )	2199 (63.19)	561 (59.36)	Ref
Overweight (25–29.9 kg/m <sup>2</sup> )	699 (20.09)	180 (19.05)	0.99 (0.82, 1.20)
Obese ( $\geq$ 30 kg/m <sup>2</sup> )	91 (2.61)	33 (3.49)	0.70 (0.47, 1.06)
Gate of GWG, n (%)			
Insufficient	895 (25.55)	221 (23.39)	1.04 (0.87, 1.25)
Adequate	1669 (47.96)	430 (45.50)	Ref
Excessive	916 (26.49)	294 (31.11)	0.80 (0.68, 0.95)

Note: Adequate is the reference group for odds ratios.

Abbreviations: SD, Standard deviation; OR, Odds ratio; CI, Confidence interval; Ref, Reference; PP-BMI, pre-pregnancy body mass indices; GWG, gestational weight gain.

ered to be a marker of many physiological processes. It has been suggested that low GWG may indirectly stimulate the production of corticotropin-releasing hormone and prostaglandins, which increases the sensitivity to uterine contraction [19]. Insufficient GWG may also reflect nutrient deficiency, which may be one of the pathways leading to PTB. Anorexia is associated with zinc deficiency, which leads to low GWG. Alternatively, low GWG may be due to maternal anemia during pregnancy. Both factors can lead to an increased risk of PTB [20]. A low GWG may also be associated with increased inflammation and poor plasma volume expansion, both of which are potential mechanisms of PTB [20].

#### 4.2 Comparison with Previous Studies

Twenty years ago, a few studies reported that low GWG increased the risk of PTB. However, some previous

studies have shown a conflicting correlation between excessive GWG and PTB [1,21]. Some scholars found the risk of PTB increased among pregnant women with excessive and low GWG [22]. Recent studies have also reported a positive correlation between excessive GWG and PTB [23,24]. Weight gain above target guidelines was associated with a reduced risk of PTB in the United States and Europe [13]. This controversial result may be due to different definitions of excessive and insufficient GWG and different analytical methods.

As in most previous studies, we found that insufficient GWG significantly increased the risk of PTB, especially among pregnant women classified as underweight or normal weight. We did not find an association between excessive rate of GWG and PTB risk; however, the risk increased if women had a low PP-BMI, which is consistent with some studies [11,25]. Although the biological mechanism is not

**Table 2. Characteristics, gate of GWG and PP-BMI of preterm birth in the low risk group.**

	Total	Preterm birth	<i>p</i> value
	(n = 3480)	(n = 171)	
Maternal age (years), mean ± SD	30.7 ± 4.35	30.2 ± 4.20	0.705
Education level, n (%)			0.027
Primary	87	8 (9.19)	
Secondary	1860	101 (5.43)	
College or graduate school	1544	62 (4.01)	
Type of resident, n (%)			0.023
Local	2560	113 (4.41)	
Non-local	920	58 (6.30)	
Parity, n (%)			0.152
Nulliparous	1569	68 (4.33)	
Multiparous	1911	103 (5.38)	
Gravidity, n (%)			0.000
0	1074	32 (2.97)	
1–2	1860	91 (4.89)	
>2	546	48 (8.79)	
Infant sex, n (%)			0.751
Male	1893	91 (4.80)	
Female	1587	80 (5.04)	
PP-BMI, n (%)			0.022
Underweight (<18.5 kg/m <sup>2</sup> )	491	35 (7.12)	
Normal weight (18.5–24.9 kg/m <sup>2</sup> )	2199	96 (4.36)	
Overweight (25–29.9 kg/m <sup>2</sup> )	699	32 (4.57)	
Obese (≥30 kg/m <sup>2</sup> )	91	8 (8.79)	
Rate of GWG, n (%)			0.008
Insufficient	895	61 (6.81)	
Adequate	1669	74 (4.43)	
Excessive	916	36 (3.93)	

Abbreviations: SD, Standard deviation; PP-BMI, pre-pregnancy body mass indices; GWG, gestational weight gain.

**Table 3. Association between rate of GWG and PTB-stratified by PP-BMI<sup>a</sup>.**

Rate of GWG	Total	Underweight		Normal		Overweight and Obese	
	OR (95% CI)	n1/n2	OR (95% CI)	n1/n2	OR (95% CI)	n1/n2	OR (95% CI)
<b>Unadjusted</b>							
Insufficient	1.58 (1.11, 2.24)	13/99	2.79 (1.23, 6.32)	36/532	1.67 (1.06, 2.65)	12/203	0.92 (0.44, 1.91)
Adequate	Ref	12/255	Ref	41/1013	Ref	21/327	Ref
Excessive	0.88 (0.59, 1.32)	10/102	2.08 (0.87, 4.97)	19/558	0.84 (0.48, 1.46)	7/220	0.50 (0.21, 1.19)
<b>Adjusted</b>							
Insufficient	1.49 (1.11, 2.09)		2.52 (1.20, 6.02)		1.77 (1.16, 2.78)		0.93 (0.47, 1.96)
Adequate	Ref		Ref		Ref		Ref
Excessive	0.92 (0.63, 1.40)		1.92 (1.10, 5.11)		0.88 (0.58, 1.55)		0.55 (0.22, 1.22)

<sup>a</sup> Adjusted for maternal pre-pregnancy BMI, maternal age, education level, type of resident, parity, gravidity, and infant sex.

n1/n2 represents the number of preterm/term births.

Abbreviations: OR, Odds ratio; CI, Confidence interval; Ref, Reference; PTB, preterm birth; PP-BMI, pre-pregnancy body mass indices; GWG, gestational weight gain.

Note: Adequate is the reference group for odds ratios.

clear, it can be considered that a reasonable GWG during pregnancy can effectively reduce the risk of PTB, especially for pregnant women with low PP-BMI. Moreover, low or excessive GWG may lead to an increased risk of PTB.

#### 4.3 Advantages and Limitations

Our study had some advantages. First, given the potential confounding bias, our study used a cohort of mother-child pairs with a one-and-a-half-year follow-up, and only

women lacking undisputed high-risk factors for PTB were included in the study. Several studies used retrospective designs to investigate the association between GWG and PTB, which maybe a source of bias [25–27]. While most previous studies used statistical methods to correct for research bias caused by other high-risk factors of PTB, we excluded the PTB high-risk group from the beginning of the cohort study to accurately describe the relationship between GWG and PTB. Second, due to the different length of pregnancy in the study population, we used the GWG rate to correct the study bias. A key element cited in previous studies [21,23] on the relationship between GWG and PTB was total gestational weight gain, but women who delivered preterm had less time to gain weight, which may lead to less GWG. Finally, our data were robust. The research was carried out at a tertiary hospital that is the leading provincial medical center for obstetrics referral and has an average of 15,000 deliveries every year. Our hospital strictly implements common guidelines concerning pregnancy and delivery management and the cohort study was performed according to strict standards.

Our study had some limitations. First, it was a single-center design and the study population size may not be sufficient. Therefore, the findings may not be generalizable for all medical institutions. Hence, a continuous cohort study and a larger study population are necessary for future studies. Second, a recent study [28] proposed a generalized methodology with a hierarchical procedure (including multivariable machine learning statistics) assessing relative importance of risk factors and capable of selecting those which are essential for risk prediction vs those that are pleonastic and may be eliminated. This is the suggested method required to assess in future studies the importance of novel proposed risk factor. Finally, the uncertainty caused by COVID-19 pandemic contribute to the anxiety of pregnant women [29]. We did not consider the impact of the pandemic even though there were a few COVID-19 patients in the city of the study.

## 5. Conclusions

Our study further illustrated the relationship between low GWG and PTB and showed that the risk of PTB increased for those women with low PP-BMI, which indicated that the association between GWG and PTB varied by PP-BMI. It can be considered that a reasonable GWG during pregnancy can effectively reduce the risk of PTB, especially for pregnant women with low PP-BMI. A low or excessive GWG may lead to an increase in the risk of PTB.

## Availability of Data and Materials

The datasets generated during and/or analyzed during the current study are available from the corresponding author on reasonable request.

## Author Contributions

XZ designed the research study. XL, HL, and WW performed the research. WY analyzed the data. QW wrote the manuscript. All authors contributed to editorial changes in the manuscript. All authors read and approved the final manuscript.

## Ethics Approval and Consent to Participate

This study was approved by the Ethics Committee for Human Subjects Studies of Women and Children's Hospital, School of Medicine, Xiamen University (KY-2020-007), and written informed consent was obtained from each participant.

## Acknowledgment

This work was supported by the Xiamen Key Laboratory of Basic and Clinical Research on Major Obstetric Diseases and Department of Obstetrics, Women and Children's Hospital, School of Medicine, Xiamen University.

## Funding

This research was supported by grants from Xiamen health care projects (3502Z20191102, 3502Z20224ZD1221) and Key Research and Development Project of Shandong Province (2019GSF108073).

## Conflict of Interest

The authors declare no conflict of interest.

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