

Associations between pre-pregnancy body mass index, gestational weight gain and preterm birth: a cohort study in Wuhan, China

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Research

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Abstract

Background Preterm birth (PTB) is the leading cause of neonatal mortality and morbidity worldwide.

Methods This cohort study aims to investigate the associations between pre-pregnancy BMI, total gestational weight gain (GWG), and the GWG during early pregnancy with PTB utilizing data of 83,096 Chinese women from the Wuhan Maternal and Children Healthcare Information Tracking System in China.

Results Women who were underweight, overweight or obese before pregnancy had an higher overall risk of PTB compared with the normal group. Women who with a total GWG below the IOM recommendation had an increased risk of PTB compared to women who had GWG within the recommendation, whereas increased weekly early pregnancy GWG had a significant impact on the increasing risk of PTB. When stratified by subtypes of PTB, pre-pregnancy underweight was associated with higher risk of spontaneous PTB, and pre-pregnancy overweight /obese increased the risk of both spontaneous PTB and medically indicated PTB. Women with total GWG below the IOM recommendation had elevated risk for spontaneous PTB and PROM, and women with GWG above the recommendation had decreased risk for all three subtypes of PTB, whereas risk for the three subtypes of PTB increased along with increasing weekly GWG of early pregnancy.

Conclusions Maternal underweight, overweight/obesity, total GWG, and GWG during early pregnancy should be considered in combination to reduce the risk of PTB, women should modify their weight gains during pregnancy according to the results.

Background

Preterm birth (PTB), defined as a delivery of live born infant before 37 completed gestational weeks[1], is the leading cause of neonatal mortality and morbidity worldwide[2], and has been reported to be strongly associated with long-term health problems such as neurological disabilities and various chronic diseases[3, 4]. During the recent decades, the burden of preterm birth is substantial and increasing[5]. Therefore, it is important to identify the potential modifiable risk factors for prevention of preterm birth. However, as a complex phenomenon, the etiology of preterm birth is not yet well understood to date.

Several previous studies have indicated that the maternal overweight/obesity is one potential modifiable risk factor for PTB[6, 7], and thus provided a target for intervention of PTB during pre-conception care. Besides, as weight control is considered to be more feasible during pregnancy than before conception, much attention has been drawn to the association of gestational weight gain (GWG) with PTB in recent years. However, conclusions of previous investigations have been inconsistent, as several studies reported an association between lower GWG and elevated risk of PTB[8], while some studies indicated that risk of PTB increased with higher GWG[9].

Most of the previous studies only evaluated the GWG by weight data throughout pregnancy, which may lead to biased associations because GWG differs by term and preterm birth[10], and is not linear throughout pregnancy[11]. GWG during early pregnancy was considered to be critical for embryogenesis and fetal growth[12], however, few studies have specifically examined GWG early in pregnancy related to PTB. Furthermore, PTB is a heterogeneous condition, but few studies have examined whether associations between pre-pregnancy BMI, GWG and PTB differ by different subtypes of PTB. Besides, most of previous studies were conducted in developed countries. Commonly, above 30% of reproductive age women generally have a high body mass index ($BMI \geq 23.0 \text{ kg/m}^2$) in western United States[13], however, this number in developing countries was only 8.5%¹⁴, and was less investigated.

Therefore, the magnitude and direction of the associations between pre-pregnancy BMI, GWG and PTB has not been well studied, especially in developing countries. Hence, a retrospective cohort study with the records of 83,096 women was conducted in China to investigate the independent as well as joint association of pre-pregnancy BMI, total GWG and early pregnancy GWG with the risk of subtypes of PTB in singleton pregnancies.

Methods

Study Population

This retrospective cohort study was conducted in Wuhan, China, using electronic medical record (EMR) data from the Wuhan Maternal and Children Healthcare Information Tracking System, which is a large integrated healthcare system including the information of maternal demographic characteristics, past histories, antenatal examinations and delivery information from 93 hospitals with obstetrics and gynecology departments and 121 primary health institutions in Wuhan. Eligible participants in this study should meet the following criteria: (1) women who delivered a live singleton newborn without any birth defect within 28-41 weeks' gestational age between June 1, 2015 and June 1, 2017; (2) lived in the urban area of Wuhan during the whole pregnancy and (3), at least had two weight records during early pregnancy, once earlier than 9 weeks of gestation and another should not later than 20 weeks of gestation. Women who were younger than 16 years or older than 50 years at delivery were excluded. Also, participants with unknown anthropometric data (i.e. maternal height, pre-pregnancy weight and weight at delivery) were excluded.

A total of 110,078 electronic medical records were conducted and 83,096 participants met the eligibility criteria and were included in the study. 68,527 of them had at least two weight measurement records during 8-20 gestational weeks.

Assessment of study variables

Gestational age was calculated from the delivery date and the date of the last recorded normal menstrual period. Preterm delivery was defined as a delivery between 28 weeks 0 days and 36 weeks 6 days of gestation. We excluded very preterm deliveries (<28 weeks gestation) as there were few in this cohort.

We additionally categorized preterm term subtype as either spontaneous preterm birth, premature rupture of membranes (PROM), or medically indicated preterm birth, based on the records of clinical diagnosis reported by the obstetrician at birth. Medically indicated preterm birth was defined by either induction or caesarean section without uterine contractions or rupture of membranes prior to delivery. PROM was defined as birth with premature rupture of membranes, and spontaneous preterm birth was identified as early onset of delivery and no identifiable medical indication, without a PROM diagnosis.

Gender of the infants was obtained from birth records. Pre-pregnancy weight and height were self-reported at the first prenatal check up (usually in the first trimester). BMI before pregnancy was calculated by weight (kg) /height (m²) and then divided into four groups according to the recommendations of the Institute of Medicine (IOM) (2009): (1) underweight (<18.5 kg/m²); (2) normal weight (18.5-24.9 kg/m²); (3) overweight (25.0-29.9 kg/m²); and (4) obese (≥30 kg/m²)[11].

Maternal weight at delivery was measured within 3 days before the delivery day, and the calculation of GWG was to subtract the maternal pre-pregnancy weight from the weight at delivery, and then classified according to the recommendations of the Institute of Medicine (IOM) (2009). GWG within the IOM recommendations was defined as 12.5-18 kg, 11.5-16 kg, 7-11.5 kg, and 5-9 kg respectively for underweight, normal weight, overweight, and obese women.

According to evidence from previous studies, the gestational BMI gain was divided into minimal (<5 kg/m²), moderate (5-10 kg/m²) and excessive (> 10 kg/m²)[13]. Every increase in BMI by 1 point is roughly equivalent to 2.5 kg in weight gain, using the average female weight and height at reproductive age (158 cm, 54 kg) in China [14].

We used average weekly weight gain between 8-20 weeks gestation to evaluate GWG during early pregnancy, which was calculated as the latest prenatal care weight before 20 weeks of gestation minus the first prenatal care weight (before 9 weeks) divided by gestation age of the latest prenatal care (up to 20 weeks of gestation) and classified as class I (<200 g/week), class II (200-400 g/week), class III (400-600 g/week), and class IV (> 600 g/week). [15]

Statistical Analysis

Unconditional logistic regression was used to calculate odds ratios (ORs), and 95% confidence intervals (CIs) to evaluate the association between PTB and pre-pregnancy BMI, GWG and gestational BMI gain. Models were adjusted for some potential confounders, including infant gender, birth weight, maternal age, parity, education level and models that evaluated maternal pre-pregnancy BMI and BMI/weight gain during pregnancy were mutually adjusted.

Analyses were further stratified by maternal pre-pregnancy BMI categories, and effect modifications with these variables were evaluated by including the relevant cross-product terms in the regression models. Linear trends were tested using the Wald test. Statistical analyses were conducted with SAS, version 9.4, (SAS Institute, Inc., Cary, North Carolina) and P values < 0.05 was considered statistically significant.

Results

Table 1 lists the selected characteristics of the participants in the cohort. 3,983 out of 83,096(4.79%) women delivered a preterm birth infant. Among all the preterm births, 1,569 (39.39%) were spontaneous preterm births, 1,337 (33.57%) were premature rupture of membranes and 1,077 (27.04%) were medically indicated preterm births. Women over the age of 30, multiparous women, women who gave birth to a male infant, and were overweight or obese before pregnancy were more likely to have preterm birth. The mean total GWG among women who had preterm birth was $14.87\pm 5.99\text{kg}$, lower than that of women with term birth ($17.57\pm 6.94\text{kg}$).

Table1. Distribution of selected characteristics among full term births and preterm births

Maternal characteristic	Full term births (n=79,113)	Preterm births (n=3,983)		
n	%	n	%	
<i>Age at delivery (years)</i>				
<25	14897	96.05	613	3.95
25-29	41044	95.78	1809	4.22
30-34	18135	94.10	1138	5.90
≥35	5037	92.25	423	7.75
<i>Education Level</i>				
Less than high school	9043	95.48	428	4.52
High school	35587	95.10	1834	4.90
College	30533	95.25	1522	4.75
Advanced Degree	3950	95.20	199	4.80
<i>Gravidity</i>				
1	40853	95.12	2097	4.88
2	20448	95.63	934	4.37
≥3	17812	94.93	952	5.07
<i>Parity</i>				
Nulliparous	65981	95.33	3231	4.67
Multiparous	13132	94.58	752	5.42
<i>Offspring Gender</i>				
Male	41859	94.56	2406	5.44
Female	37254	95.94	1577	4.06
<i>Pre-pregnancy BMI(kg/m²)</i>				
Under weight (<18.5)	13453	95.32	661	4.68

Normal (18.5–24.9)	60755	95.33	2973	4.67
Overweight (25-29.9)	4365	93.43	307	6.57
Obese(≥ 30)	540	92.78	42	7.22

Table 2 shows the relationships between pre-pregnancy BMI, gestational BMI gain, total GWG, GWG during early pregnancy and PTB. Compared with women of normal pre-pregnancy BMI, women who were underweight [Adjusted OR:1.05 (1.03-1.27)], overweight[Adjusted OR:1.28 (1.12-1.43)] or obese [Adjusted OR:1.50 (1.11-1.98)] prior to pregnancy had an raised risk of PTB. Compared with women who had a total GWG within the IOM recommendation, women with a total GWG below the recommendation had an increased risk of PTB[Adjusted OR:1.11 (1.02-1.21)], while those with a total GWG above the recommendation had a lower risk of PTB [Adjusted OR:0.45 (0.42-0.49)].Further, decreased risk of PTB was observed for women with greater BMI gain during pregnancy (p for trend <0.01).The adjusted OR for women who had a gestational BMI gain more than 10 kg/m² was 0.29(CI:0.25-0.33) compared with women who gained less than 5 kg/m² during pregnancy.

The association between early pregnancy GWG and PTB in the first trimester shown different trends. As average GWG increased during early pregnancy, an elevated risk of PTB was observed (p for trend < 0.01). Compared with women who gained less than 200 grams per week before 20 weeks of pregnancy, women who gained greater than 400 grams per week had a significantly higher risk of PTB [Adjusted OR:1.50 (1.33-1.69)]. It was worth noting that women who gained more than 600 grams per week at the beginning of pregnancy had the highest risk of PTB, and the adjusted OR was 2.23 (CI: 2.01-2.48).

Table 2. Associations of pre-pregnancy BMI, gestational BMI gain, total GWG, and GWG during early pregnancy with risk of PTB^a

Variables	Full term births (n)	Preterm births (n)	Crude OR(95% CI)	Adjusted OR(95% CI)*
<i>Pre-pregnancy BMI(kg/m²)^b</i>				
Underweight (<18.5)	13453	661	1.02(0.93-1.13)	1.05(1.03-1.27)
Normal (18.5–24.9)	60755	2973	1.00 (ref)	1.00 (ref)
Overweight (25-27.9)	4365	307	1.51(1.36-1.71)	1.28(1.12-1.43)
Obese(≥30)	540	42	1.87(1.41-2.45)	1.50(1.11-1.98)
<i>Total GWG By IOM Recommendation^b</i>				
Below	12975	977	1.07(0.99-1.17)	1.11(1.02-1.21)
Within	23365	1640	1.00 (ref)	1.00 (ref)
Above	42773	1366	0.46(0.42-0.49)	0.45(0.42-0.49)
<i>Gestational BMI gain (kg/m²)^b</i>				
<5	18875	1468	1.00 (ref)	1.00 (ref)
5-10	51452	2322	0.58(0.54-0.62)	0.59(0.55-0.63)
≥10	8786	193	0.28(0.24-0.33)	0.29(0.25-0.33)
<i>P</i> for trend	<0.01			
<i>Average GWG up to 20 weeks(g/week)^c</i>				
<200	38408	1489	1.00 (ref)	1.00 (ref)
200-399	15048	627	1.08(0.98-1.18)	1.07(0.97-1.18)
400-599	6128	359	1.51(1.34-1.70)	1.50(1.33-1.69)
≥600	5950	518	2.25(2.03-2.49)	2.23(2.01-2.48)
<i>P</i> for trend	<0.01			

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1. Gestational BMI gain, total GWG, and GWG during early pregnancy were evaluated in separate models.
 2. Adjusted for maternal age at delivery, education level, gravidity, parity, parity and offspring sex. Additionally, pre-pregnancy BMI, and gestational BMI gain were mutually adjusted. Total GWG also adjusted for pre-pregnancy BMI.(n = 83,096)
 3. Adjusted for maternal age at delivery, education level, gravidity, parity, offspring sex, and pre-pregnancy BMI.(n = 68,527)

Results for the associations of evaluated variables with subtypes of PTB are presented in Table 3 (See additional file 1). After adjustment for potential confounders, pre-pregnancy underweight was associated with higher odds of spontaneous preterm birth [Adjusted OR:1.33 (1.17, 1.52)], and pre-pregnancy overweight and obese increased the risk of both spontaneous preterm birth [Adjusted OR for overweight: 1.32 (1.10, 1.59); obese:1.68 (1.10, 2.56)] and medically indicated preterm birth [Adjusted OR for overweight: 1.63 (1.33, 2.00); obese: Adjusted OR 1.77 (1.07, 2.93)]. Women with total GWG below the IOM recommendation had elevated risk for spontaneous preterm birth [Adjusted OR: 1.13 (1.00, 1.28)] and premature rupture of membrane [Adjusted OR: 1.18 (1.02, 1.36)], and women with GWG above the recommendation had decreased risk for all the subtypes of preterm birth. Adjusted odds for three subtypes of preterm birth decreased as gestational BMI gain increased (p for trend < 0.01), whereas the risk for three subtypes of preterm birth increased along with increasing weekly GWG of early pregnancy (p for trend < 0.01).

In addition, we examined the relationship between PTB stratified by pre-pregnancy BMI and the gestational BMI gain and GWG in the early pregnancy (See additional file 2, Table 4). Women with increased BMI during the entire pregnancy had a significantly lower risk of PTB in all pre-pregnancy BMI categories (p for trend < 0.01). In contrast, among women who were underweight/normal weight before pregnancy, as the average GWG during early pregnancy increased, the risk of PTB was observed to increase (p for trend < 0.01). In particular, women who were underweight before pregnancy and had the highest average GWG during the early pregnancy (≥ 600 g/week) had the highest risk of PTB [Adjusted OR:4.61 (3.68-5.77)], whereas the corresponding ORs were still elevated but not so strong in women who had normal weight before pregnancy [Adjusted OR:1.88 (1.66-2.14)]. However, no significant association of the risk of PTB and GWG during early pregnancy was observed among women who were overweight/obese before pregnancy (p for trend=0.79). There was significant heterogeneity between the pre-pregnancy BMI categories and the association between GWG during early pregnancy and PTB risk (P for heterogeneity<0.01).

Discussion

In this cohort study of Chinese women, we found that pre-pregnancy overweight/obesity was independently associated with an increased overall risk of preterm birth, which is consistent with previous findings[6, 7]. When stratified by subtypes, pre-pregnancy overweight/obesity was observed to

significantly increase the risk of medically indicated preterm birth and spontaneous preterm birth in our study, but not the preterm caused by premature rupture of membrane.

The mechanisms linking pre-pregnancy overweight/obesity with risk of PTB is not well understood to date, but probably involves inflammatory, neuroendocrine and lifestyle factors[15]. Goldenberg and Culhane[16] have indicated that preterm birth is mediated by increased systemic inflammation due to a wide range of pre-pregnancy risk factors. Gestational diabetes, pre-eclampsia and obesity are also related to increased systemic inflammation, sometimes called the metabolic syndrome of pregnancy. Especially central obesity, which is more strongly related to insulin resistance than obesity *per se*, predisposes individuals to these diseases.[16, 17], which are known contributors to medically indicated preterm birth. Another previous study also suggested that the association between maternal overweight /obesity and excess risk of medically indicated preterm birth may largely be due to obesity-related pregnancy disorders[18].

On the other end of the pre-pregnancy BMI spectrum, pre-pregnancy underweight has been reported to be associated with an increased risk of PTB[8,19], though fewer studies have separated different subtypes of preterm birth. In this study, we found that women who were underweight before pregnancy were at greater risk of overall PTB. However, results for subtypes of PTB showed that pre-pregnancy underweight was associated with higher risk of spontaneous PTB, while no significant association of medically indicated PTB with pre-pregnancy underweight was found in our study. This result is consistent with a previous study from Boston Birth Cohort[20].

In contrast to the more consistent evidence linking pre-pregnancy BMI with PTB, studies for association of gestational weight gain (GWG) and PTB have yielded inconsistent results. Although some previous studies have shown an association between lower GWG and increased risk of preterm birth[8], some studies indicated a positive association between excessive GWG and elevated risk of preterm birth[9]. In our study, it was found that low GWG (below the IOM recommendation) throughout pregnancy had significant impact on the increased risk of Spontaneous PTB and PROM, while excessive GWG (above IOM recommendation) was found to be associated with decreased risk for all types of PTB. Since some studies believed that BMI is more representative of body fat than body weight alone[13], we also classified weight gain during pregnancy based on the net change in BMI. Similarly, excessively increase in BMI throughout pregnancy was also related to a decreased risk of all types of PTB. Rebecca et al. found a similar conclusion in a systemic review and meta-analysis of 1.3million pregnancies that gestation weight gain above recommendations was associated with lower risk of preterm birth[21]. According to a recent systematic review by McDonald et al[22]., women with high total GWG were observed to have lower risks of PTB, high weekly GWG was associated with increased PTB. This observation points to the need more study, although the effect may be due to the association of conditions such as preeclampsia, which is often accompanied by edema and significant short-term increased in weight.

However, most of the previous studies evaluating the association of GWG with PTB relied on only two weight measures: weight near conception and weight at delivery, which may have biased associations

because GWG over gestational periods differs by term and preterm birth[10]. Furthermore, GWG during early pregnancy was considered to be critical for embryogenesis and fetal growth[12], however, few studies have specifically examined GWG early in pregnancy related to PTB. Therefore, in this study, we also investigated the association of average GWG during early pregnancy and PTB, and our results indicated that high weekly GWG of early pregnancy was significantly associated with higher risk of all types of PTB. While GWG in the first half of pregnancy is mainly the result of maternal tissues deposition and placental growth, gains from that point on until the end of pregnancy might be influenced by accumulation of amniotic fluid. As high GWG is associated with inflammatory up-regulation through increased production of adipokines by adipose tissue and augmented systemic secretion of pro-inflammatory cytokines, which may contribute to the biological pathway of PTB.

To explore whether the pre-pregnancy BMI would modify the association between GWG and PTB risk, we stratified the association according to pre-pregnancy BMI categories. We found that there was a significant correlation between the excessive increase of BMI throughout pregnancy and the reduction in PTB risk for all pre-pregnancy BMI categories, whereas the high weekly GWG during the early pregnancy is associated with a significantly elevated risk of PTB among women with underweight or normal weight in the early pregnancy. Interestingly, for women who were underweight before pregnancy, the association between high weekly GWG of early pregnancy and PTB was strongest. In contrast to our results, findings of Sharma et al. do not support any significant association between GWG in the first and second trimester and PTB among underweight and normal weight women[10]. Further prospective studies are needed to examine whether a causative relationship between pre-pregnancy BMI, GWG of different periods of pregnancy, and PTB exists, as well as the biological mechanisms underlying this relationship.

One of the strengths of this study is a large population-based cohort study which allowed us to evaluate the role of both total GWG and early GWG in PTB risk, because the anthropometric characteristics of participants during early pregnancy could be obtained easily. Also, we were able to identify subtypes of PTB in this study. To our knowledge, this is the first study investigating the association between pre-pregnancy BMI, total GWG as well as early pregnancy GWG and different subtypes of PTB among Chinese women. The potential limitation of the study is that our data relies on a self-reported pre-pregnancy weight, which may be underestimated and may have potential classification bias. However, previous researches has shown that BMI categories based on self-reported data rarely change, and it could be considered that self-reported weight could replace actual measurements[23, 24].

Conclusion

A population-based cohort study was conducted in China to explore the relationship between pre-pregnancy BMI, total GWG, early pregnancy GWG and the risk of PTB. We found that pre-pregnancy overweight and obesity were independently associated with the greater risk of medically indicated preterm birth and spontaneous preterm birth, whereas pre-pregnancy underweight was associated with higher risk of spontaneous PTB. High BMI gain during the whole pregnancy was shown to be related to a decreased risk of all types of PTB. In contrast, high weekly GWG of early pregnancy was significantly

associated with higher risk of all types of PTB. Our results indicate that maternal underweight, overweight/obesity, total GWG, and GWG during early pregnancy should be considered in combination to reduce the risk of PTB. Further prospective studies are needed to examine the relationship of trimester-specific GWG and PTB, as well as the underlying biological mechanisms.

Declarations

Ethics approval and consent to participate

The study was approved by the Institutional Review Board (IRB) of the School of Public Health, Tongji Medical College, Huazhong University of Science and Technology. And all methods were carried out according to the approved guidelines established by the IRB. Informed consent was obtained from all the participants when their EMR data was being typed into computers.

Consent for publication

Not applicable

Availability of data and materials

The datasets generated and/or analysed during the current study are available in the [Open Science Framework] repository, [<https://osf.io/vsprj/>]

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Competing interests

There are no conflicts of interest among the authors.

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Author Contribution

The first author Yiyang Guo contributed to the study design, data analysis, and manuscript preparation. Chao Xiong and Aifen Zhou contributed to the data analysis and manuscript revision. Ronghua Hu and Rong Yang revised the manuscript. The corresponding authors Yukai Du contributed to the conception of this study and revised the manuscript.

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Abbreviations

BMI: body mass index; PTB: preterm birth; GWG: gestational weight gain; IOM: Institute of Medicine

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