Association Between Maternal Weight Gain in Different Periods of Pregnancy and the Risk of Venous Thromboembolism: A Retrospective Matched Case-Control Study

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Abstract

Objective To explore the incidence of pregnancy-related VTE in China and to assess the associations of maternal weight gain in different periods of pregnancy with VTE. Design Retrospective case-control study. Setting Shanghai, China Participants 151 cases (11.7 per 10000) of pregnancy-related venous thromboembolism (VTE) and 302 controls. Methods GWG was standardized into gestational age-specific z-scores stratified by body mass index (BMI) and categorized as low (< -1), normal (-1 to 1), and high (>1). The adjusted odds ratios (aORs) and 95% confidence intervals (CIs) were estimated through log-binomial regression models. Main outcome measures Pregnancy-related VTE Results There were 65.6% of pulmonary embolus (PE) and 34.4% of deep venous thrombosis (DVT) alone or combined with PE. Among normal-weight women, there was observed protective effects of low weight gain (aOR 0.79; 95% CI 0.37–1.68) and significantly increased risks of high weight gain (aOR=1.47; 95% CI: 1.03-2.09) for PE in early pregnancy. Similarly, a tendency towards decreased risk at lower weight gain throughout pregnancy (aOR 0.79; 95% CI 0.37–1.68) and significantly increased risk at higher values (aOR=1.52; 95% CI: 1.01-2.31) for PE was observed. As for underweight and overweight women, results from the categorical model for early, late or total pregnancy weight gain indicated an increased risk in PE at both low and high weight gain, but confidence intervals were wide. Conclusion Maternal weight gain in total or early pregnancy is an important risk factor for PE. Intensive weight management that continues through pregnancy may be indispensable to effectively improve pregnant outcomes.

Introduction

Deep vein thrombosis (DVT) and pulmonary embolism (PE) are collectively referred to as venous thromboembolic disease (VTE). Although the rate of maternal mortality has declined over the past few decades, PE remains an important cause of maternal deaths[1,2]. During pregnancy, a women's risk of VTE is increased by 6 times, with reported incidence ranging from 0.5 to 2.0 per 1000 deliveries[3,4]. Approximately 75–80% of cases of pregnancy-associated VTE are caused by DVT, and 20–25% of cases are caused by PE[5]. However, few studies have examined trends in the incidence of pregnancy-related VTE in China.

Several studies have already identified risk factors for pregnancy-related VTE, including advanced maternal age, greater body mass index (BMI), cesarean delivery, preeclampsia, postpartum hemorrhage and newborns with low birth weight[1,6-11]. They help care providers to target the use of thromboprophylaxis to women at risk to maximize its benefit[12]. However, few studies have evaluated gestational weight gain (GWG) as a risk factor for VTE[13]. Although insufficient and excessive maternal weight gain has been linked with

increased risks of VTE[13], they have often not accounted for the effects of weight gain during certain periods of pregnancy. Furthermore, the associations of specific periods of GWG with detailed PE and DVT has not been reported. In addition, few studies have examined trends in the incidence of pregnancy-related VTE in China, and these studies have shown variable results[14,15].

For this retrospective case–control study of women, our objective was to explore the incidence of pregnancy-related VTE in China, and evaluate the association of maternal weight gain in different periods of pregnancy with detailed pulmonary embolism (PE) and deep vein thrombosis (DVT).

Materials and Methods

Study design

We performed a retrospective case–control study, using data on all prenatal visit and discharges from Shanghai First Maternity and Infant Hospital for the period of January 1st, 2017 to July 31th, 2021 to evaluate the effect of maternal weight gain in different periods of pregnancy on VTE at any site. Written informed consent was obtained from the participants. The data including maternal demographical characteristics, reproductive history, as well as clinical information related to this pregnancy were collected. This study was approved by Ethics Committee of Shanghai First Maternity and Infant Hospital (reference number: KS2057).

Study population

Women with a diagnosis of DVT or PE, which combined VTE in pregnancy or in the first 6 postnatal weeks were identified by search for selected ICD-9 or 10 codes in the Hospital Information System. 192 women were registered with a diagnosis of VTE in 129443 pregnancies. We excluded 3 cases wrongly diagnosed with VTE in index and subsequent pregnancies, 3 cases with thrombotic events in association with miscarriage, induced abortion, or ectopic pregnancy terminated before gestational week 28. In addition, we excluded possible cases with a diagnosis of amniotic fluid embolism (n=7). Further exclusions were applied to women who started antenatal care after 18 week's gestation (n=2) and women with missing data for pre-pregnancy, delivery weight and height information (n=26). Finally, we excluded 3 cases with server heart/liver/kidney disease, malignancy or history of VTE. The eligible case population comprised 151 women (Figure 1).

The Hospital Information System selected first two women without VTE in pregnancy or the first 6 weeks following delivery, who gave birth at Shanghai First Maternity and Infant Hospital at the same time as the case, as possible controls. If these women did not meet the criterions above, we included the 3rd or 4th selection as controls. In total 302 controls were identified.

Weight measurements

Gestational age was estimated based on the date of last menstruation period and confirmed by first trimester ultrasound date. Pre-pregnancy weight (kg) was based on self-reporting, while weight at every prenatal visit and at delivery was routinely measured to the nearest 0.1 kg using the available electronic weighing device in the prenatal care clinics. Height (cm) at the first prenatal visit was routinely measured to the nearest 0.1 cm using the available electronic stadiometer in the hospital. Pre-pregnancy body mass index (BMI; kg/m^2) was calculated as pre-pregnancy weight (kg) divided by height (m)^2 and categorized as underweight (<18.5 kg/m^2), normal weight (18.5 to 24.9 kg/m^2), overweight (25.0 to 29.9 kg/m^2), and obese ([?] 30.0 kg/m^2)[16]. However, due to the sporadic number of obese women, we analyze them together with overweight women in this study.

We defined the following 3 gestational intervals: [?]14, 24 to 28, >28 weeks. If a woman had more than 1 antenatal visit within an interval, we took her last weight measurements for that interval. GWG in early pregnancy was calculated as the antenatal weight up to [?]14 weeks minus the pre-pregnancy weight; GWG in mid pregnancy was calculated as the weight measured in 24 to 28 weeks' intervals minus the last weight measured [?]14 week, and late pregnancy as last measurement of weight prior to delivery minus the weight measured in 24 to 28 weeks' intervals. Total GWG was calculated as last measurement of weight before

delivery minus pre-pregnancy weight. All GWG values were standardized into z-scores by gestational age, stratified by BMI categories. The means and standard deviations (SD) of GWGs in early, mid, late and whole pregnancy were used to convert the GWG values into z-scores. All GWG z-scores were first examined as continuous variables, and then categorized as < -1.0 (below), -1.0 to +1.0 (average) and > +1.0 (above) in data analyses.

Exposure and other variables

Maternal demographics and lifestyle characteristics included maternal age ([?]35 years or no), parity (0 or no), education (university degree and above or no), ART (intrauterine insemination (IUI); IUI with ovulation induction but without in-vitro fertilization (IVF); IVF; IVF with intracytoplasmic sperm injection (ICSI); ovulation induction without IVF and vaginal insemination), pre-pregnancy body mass index (BMI) categories (underweight, normal, overweight/obese).

Maternal pregnancy characteristics and complications included gestational age at delivery, delivery mode (vaginal delivery, either spontaneous or by vacuum extraction or forceps, and cesarean section, either planned or by emergency), multiple pregnancy, gestational diabetes mellitus (GDM), pregnancy induced hypertension (PIH), hypothyroidism, preterm birth (<37 week), postpartum hemorrhage (>500 mL after vaginal delivery, blood loss >1000 mL after cesarean delivery), premature rupture of membranes, ischemic placental diseases (composite of preeclampsia, intrauterine growth retardation (IUGR), placental abruption and stillbirth), placenta previa, abruptio placentae and postpartum transfusion.

Newborn characteristics included fetal sex, birthweight, small for gestational age (SGA) [?]10^{th}, large for gestational age (LGA) [?]90^{th} according to Chinese sex- and gestational age-specific birth weight standards[17], macrosomia (>4000 g), low birthweight (<2500 g), very low birthweight (<2500 g), sentinel congenital anomalies (atrial septal defect, ventricular septal defect, esophageal fistula, hypospadias), respiratory distress syndrome and hyperbilirubinemia (>12 mg/dL).

Statistical analyses

Maternal demographic characteristics and clinical factors were compared between venous thrombosis cases and control groups. Continuous variables were described by mean with standard deviation (SD) or median with interquartile range (IQR). Categorical variables were described by frequencies (%). Analysis of variance or Kruskal-Wallis H tests were performed for continuous data, and chi-square tests or Fisher's exact tests were performed for categorical data.

Multivariate log-binomial regression models were used to estimate the adjusted odds ratios (aORs) and 95% confidence intervals (CIs) for separately PE alone, DVT (including DVT and concomitant PE) and all VTE events across GWG in different periods of pregnancy. Regression model were adjusted for only co-variables with p <0.2 (maternal age, parity, ART, delivery mode, fetal number, birthweight, PIH, GDM and postpartum hemorrhage). Interaction effects between GWG and other covariates (parity, birthweight, maternal age and delivery mode) on venous thrombosis were also tested.

All analyses were performed using the Statistical Analysis System (SAS) for Windows, version 9.4 (SAS Institute, Cary, NC). P<0.05 was considered statistically significant.

Results

Study population and characteristics

A total of 129443 women gave birth in Shanghai First Maternity and Infant Hospital between January 1^{st}, 2017 and July 31^{th}, 2021 and 151 (11.7 per 10000) women experienced VTE in pregnancy or in the first 6 postnatal weeks. Of these, 65.6% (99 of 151) was PE alone and 34.4% (52 of 151) was DVT alone or combined with PE. 302 women who did not experience a VTE were selected as control. The prevalence of known risk factors for VTE was significantly higher in cases than controls (Table 1). In particular, cases were more likely to be of advanced age (23.2% versus 14.3%), to be overweight or obese (19.3% versus 11.0%), to have multiple birth (6.6% versus 2.7%), pregnancy-induced hypertension (PIH) (17.9% versus 6.0%),

hypothyroidism (9.3% versus 3.7%), preterm birth (17.3% versus 5.0%), postpartum hemorrhage (14.6% versus 5.0%), abruptio placentae (4.0% versus 1.0%), ischemic placental diseases (26.5% versus 12.0%), delivery via cesarean delivery (81.5% versus 46.3%), newborns with low birth weight (15.2% versus 4.3%) and respiratory distress syndrome (6.6% versus 1.7%).

Total Weight gain during pregnancy

In normal-weight women, total GWG was 14.6±4.7 kg for PE, 12.3±4.2 kg for DVT, 13.9±4.7 kg for all VTE and 13.2±4.3 kg for control (Table S1), and did significantly differ between PE and control group (adjusted estimated mean difference combined 0.06 kg, 95% CI 0.01-0.13 kg) (Table 2). A tendency towards decreased risk at lower total weight gain (aOR 0.85; 95% CI 0.43–1.69) and significantly increased risk at higher values (aOR=1.52; 95% CI: 1.01-2.31) for PE was observed in normal-weight women, whereas there was no clear association between total weight gain and DVT or all VTE. As for underweight and overweight women, results from the categorical model for total weight gain indicated an increased risk at both low (aOR 1.85; 95% CI 0.28–12.08 and aOR 1.23; 95% CI 0.46–3.27, respectively) and high weight gain (aOR 2.31; 95% CI 0.44–12.16 and aOR 2.13; 95% CI 0.67–6.79, respectively), but confidence intervals were wide. In addition, total GWG was not significantly associated with DVT or all VTE (Table 3).

Weight gain during early pregnancy

The pattern for early pregnancy weight gain showed similar results as those in total pregnancy: In normal-weight women, early GWG was 1.5±2.7 kg for PE, 0.7±1.6 kg for DVT, 1.3±2.4 kg for all VTE and 0.6±2.3 kg for control (Table S1), and did significantly differ between PE or all VTE and control group (adjusted estimated mean difference combined 0.03 kg, 95% CI 0-0.10 kg, p=0.0087 and 0.02 kg, 95% CI 0-0.08 kg, p=0.0235, respectively) (Table 2). There was observed protective effects of low weight gain (aOR 0.79; 95% CI 0.37–1.68) and significantly increased risks of high weight gain (aOR=1.47; 95% CI: 1.03-2.09) for PE in normal-weight women. As for underweight women, weight gain above average was associated with an increased risk of PE (aOR=2.50; 95% CI: 0.29-21.40), so was for overweight and obese women (aOR=2.13; 95% CI: 0.52-8.79), but estimates were not statistically significant. In contrast, associations of weight gain above or below average with DVT or all VTE were not significant, included the null (Table 4).

Weight gain during mid and late pregnancy

The associations of higher GWG with PE for normal-weight women attenuated towards non-significant in mid and late pregnancy. Similarly, within the range of mid and late weight gain, no significant associations between maternal GWG and increased risk for DVT or all VTE were present, regardless of maternal BMI (Table 5 and 6).

Discussion

Main Findings

In this study, we found different associations of gestational stage-specific weight gain with venous thrombosis. Of those, higher GWG in total or early pregnancy was associated with higher risks of PE in normal-weight women. As for underweight and overweight women, results from the categorical model for early or total pregnancy weight gain indicated an increased risk at both low and high weight gain for PE, but confidence intervals were wide.

Strengths and limitations

There are strengths in our study. Due to the detailed clinical data, such as pre-pregnancy weight, weight measurements at every prenatal visit and weight measurements before delivery beyond the registry, it was possible for us to study both weight gain in different periods of pregnancy and to take the differences in types of VTE (eg, DVT as well as PE) into account. Moreover, use of weight gain z-scores instead of weight gain in kilograms helped to disentangle the effects of pregnancy weight gain on VTE from the effects of gestational duration, because GWG is highly correlated to the gestational duration. Our cohort study extends previous

studies by accounting for effect modification by pre-pregnancy BMI and using a gestational age-independent measure of pregnancy weight gain.

There are also limitations in our study. The number of VTE was decreased when stratified by BMI-categories, especially among obese women. For this reason, we analyze the effect of weight gain during pregnancy on VTE in obese together with overweight women. Furthermore, the incidence of VTE might be underestimated in this study, since women who have high risks of VTE during pregnancy typically receive low-molecular-weight heparin (LMWH) and are often not switched to VTE in the postpartum period, which is inevitable.

Interpretation

GWG has been associated with subsequent risks of adverse pregnancy outcomes, such as preterm birth, pre-eclampsia and caesarean section, has been suggested[18,19], but evidence to clarify the relationship between gestational weight gain and maternal VTE have been sporadic[13,20]. A Norwegian hospital-case control study reported that large weight gains (>p90 or >21.0kg) were associated with 60% increased odds of postpartum VTE, while small maternal weight gain is an independent antenatal risk factor for VTE[13]. In a Washington State, USA population-based, case-control study, women with large weight gains during pregnancy (>22kg), independently of BMI, were more likely to have VTE (1.5, 95%CI 1.2-2.1)[20]. In line with these studies, we observed that higher GWG in whole pregnancy was associated with higher risk of PE. Over weight gain during pregnancy accompanied with increased intraabdominal pressure can encourage blood stasis through iliac vessels compression. Furthermore, elevated inflammatory cytokines and adipokines with increased fat deposition promote endothelial dysfunction and platelet hyperreactivity. Fat deposition also skews the hemostatic-fibrinolytic balance through elevation of procoagulant factors including von Willebrand factor, fibrinogen, factor VII, factor VIII, issue factor, and impairment of fibrinolysis by elevation of plasminogen activator inhibitor[21]. On top of differential inflammatory responses, women with high weight have longer durations of labor, greater rates of chorioamnionitis, postpartum hemorrhage and surgical complications, which may all lead to the observed greater risk of VTE after delivery[22].

There is growing recognition that the impacts of gestational stage-specific weight gain on pregnancy outcomes may vary[23-27]. GWG in early pregnancy largely reflects maternal fat deposition, whereas GWG in mid and late pregnancy is also attributed to maternal and amniotic fluid expansion, and growth of the fetus, placenta and uterus[28]. In this study, we found that higher GWG in early pregnancy was associated with higher risks of PE in normal-weight women. As for underweight and overweight women, results from the categorical model for early pregnancy weight gain indicated an increased risk at both low and high weight gain for PE. Studies have found that mothers with increased fat deposition during early pregnancy may involve the multifactorial engagement of alterations to blood flow, hypercoagulability, chronic low-grade inflammation and endothelial dysfunction, which may lead to PE[21,29]. Therefore, GWG in early pregnancy, prior to the development of pregnancy outcomes, might be as or more important than GWG in late pregnancy with respect to pregnancy outcomes.

GWG below average in overweight and obese mothers were also at an increased risk of PE in our analysis. This finding, if true, could result from low amniotic fluid volume and fetal weight by ischemic placental disease (including preeclampsia, intrauterine growth retardation, stillbirth, and placental abruption), perhaps a potential for embolism, leading to PE[1]. Blondon et al found that the delivery of a newborn with low birth weight is associated with a 3-fold increased risk of maternal postpartum VTE[1]. In another Norwegian hospital-based, case–control study, mothers of newborns with IUGR were at 3.8-fold risk of postpartum VTE[13]. Moreover, hypertension during pregnancy and preeclampsia are also associated with an increased VTE risk during pregnancy and postpartum period[9,30]. However, a randomized clinical trial indicated that pre-pregnancy weight loss intervention has favorable effects on the early intrauterine environment[31]. Lifestyle intervention during pregnancy could to some extent limit GWG and improve maternal and infant health[32]. Therefore, pre-pregnancy weight interventions integrated into intensive weight management that continues through pregnancy may be indispensable to decrease the risks of PE.

There was no statistical association between maternal weight gain and DVT or all VTE across all BMI

categories. Similarly, Matthew et al retrospectively analyzed a large database from American found that only the risk of PE is elevated in patient classification as heavier categories after surgery, whereas there was no positive association between DVT and BMI[33,34]. Explanations for this observed association exist, of which anticoagulation used for VTE prophylaxis during pregnancy is most plausible. All pregnant women in Shanghai are managed based on RCOG Green-top Guidelines[35] and Quensland Clinical Guidelines[36,37]. Briefly, they will undergo a documented assessment of risk factors for VTE throughout pregnancy, intrapartum and the puerperium. Any woman with risk factors shown in Table S2 should be considered for prophylactic low-molecular-weight heparin (LMWH). Previous studies have evaluated the efficacy of LMWH for thromboprophylaxis, revealed that LMWH probably results in little to no difference in the incidence of PE in patients undergoing knee arthroscopy, but reduce the risk of asymptomatic DVT[38]. Similarly, eight RCTs showed no clear differences between the LMWH and no prophylaxis or placebo groups in patients with lower-limb immobilization for PE, but less DVT in the LMWH groups[39]. Therefore, aggressive pharmacologic anticoagulation regimens during pregnancy can decrease the DVT rate but have not been shown to affect the rate of PE. Meanwhile, common risk factors for DVT, like history of multiple deliveries, smoking, and obesity are less frequently observed in China[15,40]. These may be the reasons for the higher incidence of PE in this study. However, the evidence is very uncertain, and further high-quality very large-scale randomized trials are needed to determine effects of currently used treatments in women with different VTE risk factors.

Conclusion

The GWG associations with venous thrombosis differ at different periods of pregnancy. Of those, maternal weight gain in total or early pregnancy is an important risk factor for PE. In order to effectively improve maternal and child outcomes, pre-pregnancy weight interventions integrated into intensive weight management that continues through pregnancy may be indispensable.

Abbreviations

VTE: Venous thromboembolism; DVT: Deep venous thrombosis; PE: Pulmonary embolus; GWG: Gestational weight gain; BMI: body mass index; SD: Standard deviations; ART: Assisted reproductive technology; IUI: Intrauterine insemination; IVF: in-vitro fertilization; ICSI: Intracytoplasmic sperm injection; GDM: Gestational diabetes mellitus; PIH: Pregnancy induced hypertension; aORs: Adjusted odds ratios; Cis: Confidence intervals; IUGR: Intrauterine growth retardation; SGA: Small for gestational age; LGA: Large for gestational age; IQR: Interquartile range; SAS: Statistical Analysis System; LMWH: Low-molecular-weight heparin.

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Authors' contributions

YW and LD participated in interpretation of data and involved in drafting the manuscript. ZZ, TZ, XZ and JP analyzed the data and critically revised the manuscript. ZH and XH made substantial contributions to conception and design, interpreted the data and critically revised the manuscript. All authors read and approved the final manuscript.

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Availability of data and materials

The data that support the findings of this study are available from the corresponding author upon reasonable request.

Declaration

Ethics approval and consent to participate

This study was approved by Ethics Committee of Shanghai First Maternity and Infant Hospital (reference number: KS2057).

Consent for publication

Not applicable.

Competing interest

The authors declare that they have no known competing financial interests or personal relationships that may have influenced the work reported in this paper.

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Table 1. Characteristics of cases and controls.

Characteristic	**Controls (n=302)**	**Cases (n=151)**	***P* value**
Maternal age(y)	30.8±6.0	32.1±4.3	<0.0001
Maternal age [?]35 years, n (%)	43 (14.3)	35 (23.2)	0.0184
Nulliparous, n (%)	212 (70.9)	112 (74.2)	0.4658
Education, university degree and above, n (%)	276 (91.4)	136 (90.1)	0.6728
ART, n (%)	36(12.0)	4(2.7)	0.0010
Pre-pregnancy BMI (kg/m^2), mean±SD	21.6±2.8	22.0±3.0	0.3725
Pre-pregnancy BMI categories, n (%)	**Pre-pregnancy BMI categories, n (%)**	**Pre-pregnancy BMI categories, n (%)**	**Pre-pregnancy BMI categories, n (%)**
Underweight (< 18.5 kg/m2)	31 (10.3)	9 (6.0)	0.0074
Normal weight (18.5-24.9 kg/m2)	237 (78.7)	112 (74.7)	
Overweight and obese ([?] 25 kg/m2)	33 (11.0)	29 (19.3)	
Gestational age at delivery (week), median (IQR)	39 (38, 40)	38 (37, 39)	<0.0001
Mode of delivery	**Mode of delivery**	**Mode of delivery**	**Mode of delivery**
Spontaneous labor	161(53.6)	28(18.5)	<0.0001
Caserean section	139(46.3)	123 (81.5)	

Characteristic	**Controls (n=302)**	**Cases (n=151)**	***P* value**
Multiple pregnancy	9(2.7)	10(6.6)	0.0284
Pregnancy complications	**Pregnancy complications**	**Pregnancy complications**	**Pregnancy complications**
GDM	30(10.0)	19(12.6)	0.3993
PIH	18(6.0)	27(17.9)	<0.0001
Hypothyroidism	11(3.7)	14(9.3)	0.0138
Preterm birth	15 (5.0)	26 (17.3)	<0.0001
Postpartum hemorrhage	15(5.0)	22(14.6)	0.0005
Ischemic placental diseases	36(12.0)	40(26.5)	<0.0001
Premature rupture of membranes	55 (18.3)	31 (20.5)	0.5646
Placenta previa	3 (1.0)	4 (2.7)	0.1801
Abruptio placentae	3 (1.0)	6 (4.0)	0.0328
Postpartum transfusion	6(2.0)	5(3.3)	0.3916
Infant Gender (female)	153 (50.8)	87 (57.6)	0.1732
Birth Weight (gm) (Mean±SD)	3246±449	3168±663	<0.0001
SGA [?]10th	19(6.3)	10(6.6)	0.8991
LGA [?]90th	17(5.7)	16(10.6)	0.0568
Macrosomia (>4000 g)	11(3.7)	8(5.3)	0.4120
Low birthweight (<2500 g)	13(4.3)	23(15.2)	<0.0001
Very low birthweight (<2500 g)	2(0.7)	4(3.3)	0.0824
Sentinel congenital anomalies	7(2.3)	6(4.0)	0.3233
Hyperbilirubinemia	32(10.6)	24(15.9)	0.1096
Respiratory distress syndrome	5(1.7)	10(6.6)	0.0055

Abbreviations: BMI: body mass index; GDM: gestational diabetes mellitus; PIH: pregnancy induced hypertension; SGA: small for gestational age; LGA: large for gestational age; IQR: median with interquartile range.

Table 2 Absolute effect size of gestational weight gain at different periods of pregnancy.

	PE Adjusted effect size (95% CI) (n=99)	*P* **value**	**DVT with PE or without PE Adjusted effect size (95% CI) (n=52)**	*P* **value**	**All VTE Adjusted effect size (95% CI) (n=151)**	*P* **value**
Total GWG in pregnancy by BMI categories	**Total GWG in pregnancy by BMI categories**	**Total GWG in pregnancy by BMI categories**	**Total GWG in pregnancy by BMI categories**	**Total GWG in pregnancy by BMI categories**	**Total GWG in pregnancy by BMI categories**	**Total GWG in pregnancy by BMI categories**
Underweight (< 18.5 kg/m2)	-0.04 (0, 0.26)	0.2645	**0.31 (0, 0.57)** *	**0.0063**	0.03 (0, 0.31)	0.0516
Normal weight (18.5-24.9 kg/m2)	**0.06 (0.01, 0.13)***	**0.0149**	0.05 (0.01, 0.12)	0.2752	0.05 (0.01, 0.11)	0.1191
Overweight and obese ([?] 25 kg/m2)	0.06 (0, 0.31)	0.7018	0.02 (0, 0.27)	0.4258	0.07 (0, 0.27)	0.6870
GWG in early pregnancy by BMI categories	**GWG in early pregnancy by BMI categories**	**GWG in early pregnancy by BMI categories**	**GWG in early pregnancy by BMI categories**	**GWG in early pregnancy by BMI categories**	**GWG in early pregnancy by BMI categories**	**GWG in early pregnancy by BMI categories**
Underweight (< 18.5 kg/m2)	0.30 (0, 0.59)	0.0542	0.33 (0, 0.63)	0.0596	0.29 (0, 0.59)	0.0542
Normal weight (18.5-24.9 kg/m2)	**0.03 (0, 0.10)** *	**0.0087**	-0.01 (0, 0.04)	0.7320	**0.02 (0, 0.08)** *	**0.0235**
Overweight and obese ([?] 25 kg/m2)	-0.05 (0, 0.27)	0.4264	-0.08 (0, 0.24)	0.1886	0.01 (0, 0.26)	0.1424
GWG in mid pregnancy by BMI categories	**GWG in mid pregnancy by BMI categories**	**GWG in mid pregnancy by BMI categories**	**GWG in mid pregnancy by BMI categories**	**GWG in mid pregnancy by BMI categories**	**GWG in mid pregnancy by BMI categories**	**GWG in mid pregnancy by BMI categories**
Underweight (< 18.5 kg/m2)	0.09 (0, 0.46)	0.3084	0.01 (0, 0.41)	0.0797	**0.14 (0, 0.50)** *	**0.0065**
Normal weight (18.5-24.9 kg/m2)	0.00 (0, 0.06)	0.4225	0.00 (0, 0.07)	0.3731	0.01 (0, 0.07)	02473
Overweight and obese ([?] 25 kg/m2)	0.15 (0, 0.44)	0.1499	-0.02 (0, 0.31)	0.5082	0.11 (0, 0.37)	0.1470

	PE Adjusted effect size (95% CI) (n=99)	*P* **value**	**DVT with PE or without PE Adjusted effect size (95% CI) (n=52)**	*P* **value**	**All VTE Adjusted effect size (95% CI) (n=151)**	*P* **value**
GWG in late pregnancy by BMI categories	**GWG in late pregnancy by BMI categories**	**GWG in late pregnancy by BMI categories**	**GWG in late pregnancy by BMI categories**	**GWG in late pregnancy by BMI categories**	**GWG in late pregnancy by BMI categories**	**GWG in late pregnancy by BMI categories**
Underweight (< 18.5 kg/m2)	-0.06 (0, 0.23)	0.3860	-0.02 (0, 0.31)	0.1161	-0.07 (0, 0.21)	0.6476
Normal weight (18.5-24.9 kg/m2)	0.03 (0, 0.09)	0.1246	**0.05 (0.01, 0.12)** *	**0.0295**	0.03 (0, 0.08)	0.8666
Overweight and obese ([?] 25 kg/m2)	-0.04 (0, 0.21)	0.4134	0.05 (0, 0.31)	0.0541	0.01 (0, 0.22)	0.1369

Abbreviations: BMI: body mass index; DVT: deep venous thrombosis; PE: pulmonary embolus; VTE: venous thromboembolism.

Table 3. Maternal total pregnancy weight gain by z-score categories with adjusted odds ratios for PE alone, DVT (including DVT and concomitant PE) and all VTE events.

BMI category	Total Weight Gain	Control	PE	Adjusted odds ratio (95% CI)	DVT with PE or without PE	Adjusted odds ratio (95% CI)	All VTE	Adjuste odds ra (95% C
	z-score category							
Underweight (< 18.5 kg/m2)	¡-1	4	1	1.85 (0.28, 12.08)	0	NA	1	0.87 (0.55, 1.38)
	-1 to 1	23	3	Ref	0	Ref	3	Ref
	¿1	4	2	2.31 (0.44, 12.16)	2	NA	4	0.66 (0.33, 1.30)
Normal weight (18.5-24.9) kg/m2	¡-1	28	7	0.85 (0.43, 1.69)	9	1.77 (0.92, 3.41)	16	1.00 (0.89, 1.13)
	-1 to 1	171	48	Ref	20	Ref	68	Ref
	¿1	34	19	1.52 (1.01, 2.31) *	4	0.81 (0.30, 2.16)	23	0.97 (0.87, 1.09)

BMI category	Total Weight Gain	Control	PE	Adjusted odds ratio (95% CI)	DVT with PE or without PE	Adjusted odds ratio (95% CI)	All VTE	Adjuste odds ra (95% C
Overweight and obese ([?] 25 kg/m2)	¡-1	7	3	1.23 (0.46, 3.27)	3	1.09 (0.44, 2.68)	6	0.98 (0. 1.37)
	-1 to 1	22	8	Ref	9	Ref	17	Ref
	¿1	4	4	2.13 (0.67,6.79)	1	0.67 (0.10, 4.43)	5	0.95 (0.70, 1.29)

Adjusted maternal age, parity, ART, delivery mode, fetal number, birthweight, gestational age, PIH, GDM and postpartum hemorrhage.

Abbreviations: BMI: body mass index; DVT: deep venous thrombosis; PE: pulmonary embolus; VTE: venous thromboembolism.

BMI category	Early Weight Gain	Control	PE	Adjusted odds ratio (95% CI)	DVT with PE or without PE	Adjusted odds ratio (95% CI)	All VTE	Adjuste odds ra (95% C
	z-score category							
Underweight (< 18.5 kg/m2)	¡-1	2	0	NA	0	NA	0	NA
	-1 to 1	18	2	Ref	1	Ref	3	Ref
	¿1	3	1	2.50 (0.29, 21.40)	0	NA	1	0.87 (0.43, 1.74)
Normal weight (18.5-24.9 kg/m2)	¡-1	19	4	0.79 (0.37, 1.68)	2	0.80 (0.21, 3.01)	6	1.02 (0. 1.22)
	-1 to 1	145	46	Ref	23	Ref	69	Ref
	¿1	23	15	1.47 (1.03, 2.09)*	1	0.41 (0.06, 2.91)	16	0.98 (0.85, 1.12)
Overweight and obese ([?] 25 kg/m2)	¡-1	2	0	NA	0	NA	0	NA
	-1 to 1	21	9	Ref	7	Ref	16	Ref
	¿1	1	2	2.13 (0.52, 8.79)	3	1.46 (0.46, 4.67)	5	0.78 (0.47, 1.30)

Table 4. Maternal early pregnancy weight gain by z-score categories with adjusted odds ratios for PE alone, DVT (including DVT and concomitant PE) and all VTE events.

*Adjusted maternal age, parity, ART, delivery mode, fetal number, birthweight, gestational age, PIH, GDM and postpartum hemorrhage.

Abbreviations: BMI: body mass index; DVT: deep venous thrombosis; PE: pulmonary embolus; VTE: venous thromboembolism.

Table 5. Maternal mid pregnancy weight gain by z-score categories with adjusted odds ratios for PE alone, DVT (including DVT and concomitant PE) and all VTE events.

BMI category	Mid Weight Gain	Control	PE	Adjusted odds ratio (95% CI)	DVT with PE or without PE	Adjusted odds ratio (95% CI)	All VTE	Adjuste odds ra (95% C
	z-score category							
Underweight (< 18.5 kg/m2)	¡-1	3	0	NA	0	NA	0	NA
	-1 to 1	17	0	Ref	0	Ref	0	Ref
	¿1	3	2	NA	1	NA	3	NA
Normal weight (18.5-24.9) kg/m2	¡-1	23	6	1.29 (0.84, 1.98)	3	0.96 (0.31, 3.00)	9	1.00 (0.88, 1.14)
	-1 to 1	128	46	Ref	19	Ref	65	Ref
	¿1	36	10	0.96 (0.56, 1.65)	2	0.44 (0.11, 1.81)	12	1.02 (0.90, 1.16)
Overweight and obese ([?] 25 kg/m2)	¡-1	4	1	0.78 (0.30, 3.02)	1	0.88 (0.16, 4.75)	2	1.08 (0. 1.63)
	-1 to 1	16	8	Ref	8	Ref	16	Ref
	¿1	4	2	1.44 (0.40, 5.25)	0	NA	2	1.07 (0.70, 1.63)

Adjusted maternal age, parity, ART, delivery mode, fetal number, birthweight, gestational age, PIH, GDM and postpartum hemorrhage.

Abbreviations: BMI: body mass index; DVT: deep venous thrombosis; PE: pulmonary embolus; VTE: venous thromboembolism.

Table 6. Maternal late pregnancy weight gain by z-score categories with adjusted odds ratios for PE alone, DVT (including DVT and concomitant PE) and all VTE events.

BMI category	Late Weight Gain	Control	PE	Adjusted odds ratio (95% CI)	DVT with PE or without PE	Adjusted odds ratio (95% CI)	All VTE	Adjuste odds ra (95% C
	z-score category							

BMI category	Late Weight Gain	Control	PE	Adjusted odds ratio (95% CI)	DVT with PE or without PE	Adjusted odds ratio (95% CI)	All VTE	Adjuste odds ra (95% C
Underweight (< 18.5 kg/m2)	¡-1	6	1	4.25 (0.83, 21.68)	0	NA	1	0.83 (0.54, 1.28)
	-1 to 1	19	2	Ref	1	Ref	3	Ref
	¿1	6	1	2.13 (0.25, 18.05)	1	2.86 (0.20, 39.83)	2	0.93 (0.64, 1.35)
Normal weight (18.5-24.9 kg/m2)	¡-1	37	9	0.86 (0.54, 1.35)	8	1.64 (0.78, 3.45)	17	1.01 (0.90, 1.14)
	-1 to 1	165	48	Ref	21	Ref	69	Ref
	¿1	32	13	1.01 (0.67, 1.52)	4	1.03 (0.38, 2.80)	17	0.99 (0.87, 1.12)
Overweight and obese ([?] 25 kg/m2)	¡-1	2	3	2.84 (0.57, 14.13)	2	1.01 (0.35, 2.93)	5	0.79 (0. 1.44)
	-1 to 1	24	8	Ref	10	Ref	18	Ref
	¿1	6	2	1.19 (0.36, 3.94)	0	NA	2	1.19 (0.65, 2.18)

Adjusted maternal age, parity, ART, delivery mode, fetal number, birthweight, gestational age, PIH, GDM and postpartum hemorrhage.

Abbreviations: BMI: body mass index; DVT: deep venous thrombosis; PE: pulmonary embolus; VTE: venous thromboembolism.

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