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ORIGINAL RESEARCH

Independent and Joint Associations of Age, Pre-pregnancy BMI, and Gestational Weight Gain with Adverse Pregnancy Outcomes in Gestational Diabetes Mellitus

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ABSTRACT

Introduction: To explore the independent and combined effects of maternal age, pre-pregnancy body mass index (BMI), and gestational weight gain (GWG) on pregnancy outcomes in gestational diabetes mellitus (GDM).
Methods: A total of 2171 pregnant women with GDM attending the Women's Hospital of Zhejiang University were retrospectively included. We compared pregnancy outcomes in different age, BMI, and GWG groups after adjusting for confounding variables.
Results: Results showed that (1) advanced maternal age increased the risk of primary Cesarean section and hypertensive disorders of pregnancy (HDP) in normal weight; (2) independent of age and GWG, high BMI significantly increased the risk of HDP, primary Cesarean section, and macrosomia; (3) Women with excessive GWG had a higher risk of primary Cesarean section and HDP, even they were $\leq$ 29 years old or normal weight, respectively; (4) Pregnant women with inadequate GWG had a higher risk of preterm birth and a lower risk of macrosomia in both the 30–34 age group and the normal weight group; (5) BMI was a better predictor of HDP than GWG among women younger than 30.
Conclusions: Among the GDM population, women over the age of 35, overweight and obese, or with an excessive GWG were more prone to adverse pregnancy outcomes, especially primary Cesarean delivery and HDP.

Keywords: Gestational diabetes mellitus; Maternal age; Pre-pregnancy BMI; Gestational weight gain; Pregnancy outcomes

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Key Summary Points

Primary Caesarean birth and hypertensive disorders of pregnancy are more probable in women over the age of 35, as well as those who were overweight or obese or who had an abnormal gestational weight gain.

Overweight and obese pregnant women had the highest prevalence of excessive gestational weight gain while underweight and normal weight pregnant women had the highest prevalence of inadequate gestational weight gain.

High pre-pregnancy body mass index and high gestational weight gain were determined to be significant risk factors for higher HbA1c.

The pre-pregnancy body mass index and gestational weight gain of pregnant women are the main modifiable risk factors.

INTRODUCTION

The effects of physiological and psychological factors on maternal reproductive function and pregnancy complications and comorbidities will increase as maternal age increases [1, 2]. The term "advanced maternal age" (AMA) traditionally refers to childbearing in women older than 35 who are at higher risk of adverse pregnancy outcomes [3, 4]. However, the evidence for the negative effects of AMA on pregnancy outcomes is still inconclusive [5, 6].

Obesity is a worldwide issue, caused by a variety of factors, including genetics, diet, social and psychological factors, and lack of exercise [7]. Obesity has nearly tripled since 1975, and it is estimated that 51% of the population will be obese by 2030 [8]. Between 1999 and 2004, nearly two-thirds of women of childbearing age were overweight or obese, and nearly one-third were obese, according to the National Center for Health Statistics (NCHS). Obesity not only raises the risk of gestational diabetes, hypertension, Cesarean section, macrosomia, neonatal hypoglycemia, and perinatal death, but also increases the risk of chronic diseases such as cardiovascular disease and type 2 diabetes in the long term [9, 10].

Gestational weight gain (GWG) is monitored as a part of pregnancy care. The standards for GWG, various adverse pregnancy outcomes, and the mechanisms that contribute to these outcomes have become hotspots of research recently, owing to the increasing phenomenon of excessive gestational weight gain (EGWG) [11]. Weight gain is influenced by a variety of factors, including physiological, psychological, behavioral, family, social, cultural, and environmental factors [12].

Empirical studies have found that gestational diabetes mellitus (GDM) can result in a variety of adverse pregnancy outcomes, which is still one of the factors seriously endangering maternal and infant health. Pregnant women with GDM had a higher incidence of preeclampsia, polyhydramnios, Caesarean delivery, preterm birth, macrosomia and fetal growth restriction, whose newborns are also at risk of hypoglycemia, jaundice, congenital malformations, and erythrocytosis [13].

AMA, obesity, and EGWG are three independent risk factors for adverse pregnancy outcomes. Despite this, there is limited evidence to support the correlation between these three risk factors and pregnancy outcomes in GDM.

The aim of this retrospective study was to analyze the risk factors of interest (maternal age, body mass index, and GWG) associated with adverse pregnancy outcomes, and assess the correlation between adjustable risk factors (body mass index, GWG) and non-adjustable risk factors (age) and pregnancy outcomes in pregnant women with gestational diabetes.

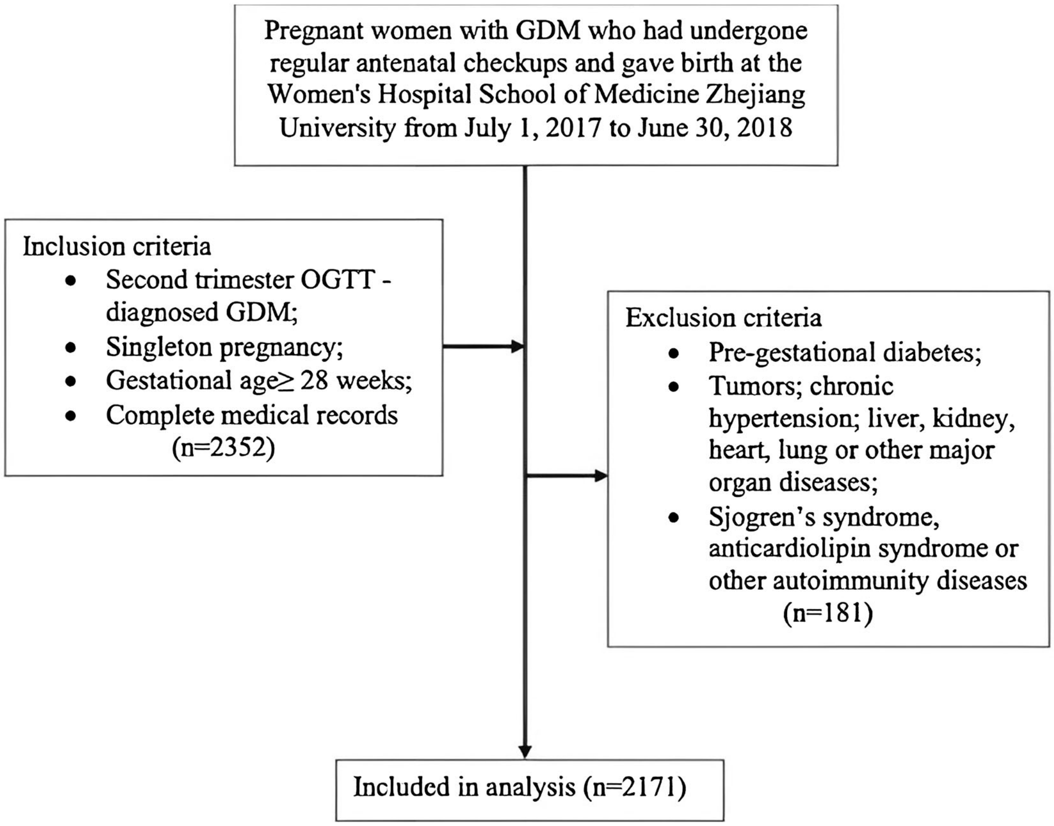

Fig. 1 Participant flow chart

METHODS

Study Design and Data Sources

This was a retrospective cohort study of 2171 pregnant women who have undergone prenatal care and delivered in the Women's Hospital School of Medicine Zhejiang University from July 1, 2017 to June 30, 2018. Inclusion criteria were (1) GDM diagnosed by oral glucose tolerance test (OGTT); (2) singleton pregnancy; (3) gestational age at birth $\geq$ 28 weeks; (4) complete medical records. Exclusion criteria were (1) pregestational diabetes mellitus; (2) coupled with chronic hypertension or liver, kidney, heart, lung and other major organ diseases or tumors; (3) coupled with Sjögren's syndrome, anticardiolipin syndrome or other autoimmunity diseases (Fig. 1).

Maternal and neonatal information, as recorded in the electronic medical record system, included maternal characteristics and obstetrical history such as age, height, pre-pregnancy weight (within 1 month before pregnancy), GWG, pregnancy parity, OGTT value (fasting, 1 h and 2 h after oral glucose load), second-trimester glycated hemoglobin, and mode of delivery. Pregnancy complications evaluated included hypertensive disorders of pregnancy (HDP) (including gestational hypertension, preeclampsia, eclampsia), postpartum hemorrhage, intrahepatic cholestasis of pregnancy, amniotic fluid abnormalities, etc. Neonatal outcomes included gestational age at birth and birth weight.

This study was approved by the Human Ethics Committee at Women's Hospital, School of Medicine, Zhejiang University. The Human Research Ethics Committee agreed that this study is exempt from informed consent because there will be no additional adverse effects on participants, and the investigator will strictly observe the principle of confidentiality, and the relevant study information will only be accessible to the investigator. The methods were performed in accordance with the relevant guidelines and regulations.

Measurements and Calculations

Maternal age was stratified into the following age categories: ≤ 29 years; 30–34 years; and ≥ 35 years [14]. Body mass index (BMI) is defined as weight divided by square of height (kg/m^2) and is categorized into underweight (≤ 18.5 kg/m^2), normal weight (18.5–24.9 kg/m^2), overweight (25.0–29.9 kg/m^2), and obese (≥ 30.0 kg/m^2) groups. GWG (kg) is the difference between the weight before delivery and the weight before pregnancy. According to the 2009 IOM guidelines in the United States, the suggested GWG is 12.7–18.1 kg, 11.3–15.8 kg, 6.8–11.3 kg, and 5.0–9.1 kg for pregnant women with pre-pregnancy BMI underweight, normal weight, overweight, and obese, respectively [15], and falling below the thresholds was defined as inadequate GWG, while exceeding the thresholds was defined as excessive GWG.

The normal values of fasting, 1 h and 2 h 75 g OGTT, according to National Health Commission 2011, are less than 5.1, 10.0, and 8.5 mmol/l, respectively. Any abnormal blood glucose level should be diagnosed as GDM. Preterm infants are those who were born between 28 weeks' and 37 weeks' gestational age. Oligohydramnios refers to amniotic fluid volume < 300 ml, while amniotic fluid volume > 2000 ml is considered polyhydramnios. Macrosomia is defined as newborns with a birth weight ≥ 4000 g. Gestational hypertension is the first incidence of high blood pressure at ≥ 20 weeks of gestation, with systolic blood pressure of 140 mmHg and/or diastolic blood pressure of 90 mmHg in the absence of proteinuria or new signs of end-organ dysfunction. Preeclampsia is defined as a combination of one or more of the following conditions based on the diagnosis of gestational hypertension: proteinuria or other target organ dysfunction or uteroplacental function obstacle, while eclampsia is a seizure that occurs as a result of preeclampsia and cannot be explained by other factors. Postpartum hemorrhage is defined as bleeding more than 500 ml after vaginal birth or more than 1000 ml after Cesarean delivery within 24 h of the fetus's birth. Intrahepatic cholestasis of pregnancy is a pregnancy problem that manifests clinically as skin pruritus and increased bile acids in the second and third trimesters.

Statistical Analysis

The data of the normal distribution was expressed as $x \pm s$. Count data were expressed in frequency and rate. Characteristics and pregnancy outcomes were compared using Student's t test or chi-square (χ^2) test as appropriate. Multivariate logistic regression analysis was used to estimate adjusted odds ratios (aORs) with 95% confidence intervals and p values for pregnancy outcomes for (1) maternal age categories adjusting for gravidity, parity, pre-pregnancy BMI, GWG, and OGTT levels; (2) pre-pregnancy BMI categories adjusting for maternal age, gravidity, parity, GWG, and OGTT levels; (3) GWG categories adjusting for maternal age, gravidity, parity, pre-pregnancy BMI, and OGTT levels. $P < 0.05$ was considered statistically significant. All statistical analyses were conducted using SPSS Statistics 25.0.

RESULTS

Independent Associations of Maternal Age, Pre-pregnancy Body Mass Index, and Gestational Weight Gain with Adverse Pregnancy Outcomes

The proportion of pregnant women using insulin and other drugs was only 1.8% in our study. The mean 0-, 1-, and 2-h values on OGTT are 4.67, 10.00, and 8.68 mmol/l. In this study, we found that there were significant differences in maternal age, pre-pregnancy BMI, and GWG among three different categories, respectively (all $p < 0.05$), which indicated that these three factors might have a potential interaction, respectively or jointly affect the occurrence of adverse outcomes. Further analysis revealed that OGTT fasting plasma glucose levels increased significantly with maternal age, pre-pregnancy BMI, and GWG. OGTT1h levels were lowest in pregnant women with normal pre-pregnancy BMI or appropriate GWG. Pregnant women who were underweight or obese had the highest mean OGTT2h levels. Surprisingly, the OGTT2h levels decreased as GWG increased. On the other hand, with the increase of pre-pregnancy BMI, the proportion of elevated HbA1c increased significantly, which was 0.04, 1.9, 4.5, and 15.1 in underweight, normal, overweight and obese people, respectively. Besides, the prevalence of HDP, primary Cesarean section, and macrosomia differed significantly between pre-pregnancy BMI groups and GWG groups, with an increasing tendency proportionately. Furthermore, the prevalence of preterm birth differed significantly between GWG groups, with the inadequate group having the highest risk of preterm birth (Additional file 1a, 1b and 1c).

The Association of Maternal Age and Adverse Pregnancy Outcomes in Different Pre-pregnancy Body Mass Index Groups and Gestational Weight Gain Groups

In the normal pre-pregnancy BMI group, pregnant women ≥ 35 years old had significantly higher risks of primary Cesarean section and HDP than pregnant women ≤ 29 years old (aOR = 1.55, 95% CI 1.10–2.17, and aOR = 2.15, 95% CI 1.23–3.76, respectively). Among pregnant women who were overweight and obese instead, those in the ≥ 35 age group were less likely to have a preterm birth (aOR = 0.27, 95% CI 0.08–0.85).

Using 29-year-old or younger age group as a reference, the risk of primary Cesarean section was significantly higher in advanced age groups among women who gained appropriate weight during pregnancy. The adjusted odds ratios were 1.52 (95% CI 1.03–2.23) for women 30–-34 years old and 2.04 (95% CI 1.28–3.25) for women ≥ 35 years old. Besides, in excessive GWG group, 35-year-old or older pregnant women were more likely to have amniotic fluid abnormalities (aOR = 4.82, 95% CI 1.08–21.50) (Additional file 2a and 2b).

The Association of Pre-pregnancy Body Mass Index and Adverse Pregnancy Outcomes in Different Maternal Age Groups and Gestational Weight Gain Groups

Overweight and obese pregnant women had a significantly higher risk of HDP than those with normal weight regardless of age and GWG (Fig. 2). The risks of primary Cesarean section (aOR = 1.78 95% CI 1.12–2.84) and macrosomia (aOR = 2.14 95% CI 1.08–4.24) were significantly higher in the overweight and obese groups only for pregnant women aged 30 to 34 years old (Table 1a, b).

The Association of Gestational Weight Gain and Adverse Pregnancy Outcomes in Different Maternal Age Groups and Pre-pregnancy Body Mass Index Groups

Among pregnant women who were less than or equal to 29 years old, those with excessive GWG had significantly higher risks of primary Cesarean section, HDP, and macrosomia (aOR = 1.81 95% CI 1.12–2.93, aOR = 2.42 95% CI 1.16–5.05, and aOR = 2.38 95% CI 1.09–5.18, respectively), while pregnant women with inadequate GWG had significantly lower risks of postpartum hemorrhage (aOR = 0.21 95% CI 0.05–0.93). Women in 30–34 age group with excessive GWG were more likely to have a primary Cesarean section (aOR = 1.57 95% CI 1.00–2.47), and inadequate GWG was a protective factor for macrosomia (aOR = 0.26, 95% CI 0.12–0.59). Furthermore, when compared to the appropriate GWG group, pregnant women aged 30 or older were more likely to have a preterm birth when they gained inadequate GWG.

Moreover, in normal pre-pregnancy BMI group, significant increased risks of primary Cesarean section (aOR = 1.67 95% CI 1.19–2.33) and HDP (aOR = 2.24 95% CI 1.35–3.72) were seen in pregnant women with excessive GWG. Pregnant women who gained inadequate GWG on the other hand, had a higher risk of preterm

Hypertensive disorders in Overweight and Obese women	aOR (95%CI)	P value
Maternal age, y		
≤29	3.800 (1.802-8.013)	<.001
30–34	5.576 (3.036-10.240)	<.001
≥35	2.112 (1.079-4.134)	.029
Gestational weight gain		
Inadequate	6.538 (2.706–15.797)	<.001
Appropriate	2.531 (1.375–4.658)	.003
Excessive	1.965 (1.070–3.608)	.029

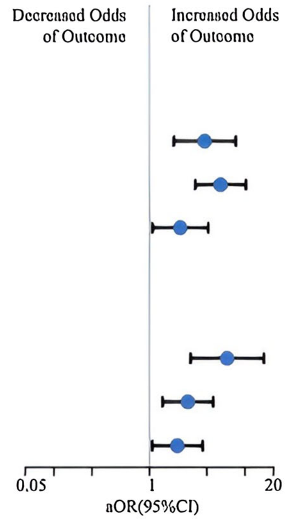

Fig. 2 Forest plot of hypertensive disorders in overweight and obese women

birth but a lower risk of macrosomia than those with appropriate GWG (aOR = 1.96 for preterm birth, 95% CI 1.35–2.86; aOR = 0.60 for macrosomia, 95% CI 0.36–0.98) (Table 2a, b).

DISCUSSION

In our study of pregnant women with GDM, we found that women over the age of 35, or who were overweight or obese, or who have an inappropriate GWG, are more likely to have a negative pregnancy outcome.

Existing studies showed that women of advanced age had a higher risk of Cesarean delivery [16, 17], which is consistent with our results. Our results confirm that, even when the pre-pregnancy BMI and GWG were both appropriate, maternal age still had an impact on the pregnancy outcome of pregnant women with GDM. The possible reason for this is that women of advanced age who are affected by a variety of factors such as psychological and environmental factors have an increased incidence of pregnancy comorbidities, which increases the risk of adverse pregnancy outcomes. Obesity, on the other hand, not only inhibits normal ovulation, reducing fertility, but also increases the risk of IVF failure as BMI rises. However, the precise mechanisms underlying the influences of high pre-pregnancy BMI and GWG on negative pregnancy outcomes are still unknown. Therefore, more epidemiological studies and evidence-based research are required to shed light on the impact of advanced age, high pre-pregnancy BMI, and excessive GWG on pregnancy outcomes, as well as the mechanisms underlying these effects.

Our findings further proved that pre-pregnancy BMI is an independent risk factor for HDP, Cesarean delivery, and macrosomia among pregnant women with GDM. Besides, previous research has illustrated a significant link between maternal obesity and HDP, Cesarean delivery, and macrosomia in the GDM population [18]. Aside from that, few previous studies found results that were similar to the relationship between GWG and adverse pregnancy outcomes that we investigated [19, 20]. However, despite previous research indicating that excessive GWG increased the risk of postpartum hemorrhage in the general population [21], there is limited evidence to support such correlation in the GDM population.

In our study, overweight and obese pregnant women had the highest prevalence of excessive GWG while underweight and normal weight pregnant women had the highest prevalence of inadequate GWG. Similar findings have been reported in other studies [22]. Hence, pre-pregnancy BMI is an important predictor of GWG. Pregnant women who are underweight or

Table 1 The association of pre-pregnancy BMI and adverse pregnancy outcomes in different (a) maternal age groups, (b) GWG groups

Adverse pregnancy outcomes	Pre-pregnancy BMI				
	Underweight	*p* value	Normal	Overweight and obese	*p* value
(a) Maternal Age					
≤ 29					
Preterm birth	0.764 (0.306, 1.903)	0.563	Ref	1.249 (0.568, 2.750)	0.580
Primary Cesarean section	0.719 (0.431, 1.198)	0.205	Ref	1.217 (0.681, 2.175)	0.507
ICP	1.146 (0.440, 2.988)	0.780	Ref	1.675 (0.597, 4.697)	0.327
Amniotic fluid abnormalities	0.732 (0.242, 2.221)	0.582	Ref	0.468 (0.101, 2.167)	0.332
Hypertensive disorders	0.451 (0.132, 1.543)	0.204	Ref	3.800 (1.802, 8.013)	< 0.001
Postpartum hemorrhage	0.811 (0.222, 2.965)	0.752	Ref	2.227 (0.702, 7.061)	0.174
Macrosomia	0.260 (0.060, 1.136)	0.073	Ref	1.653 (0.666, 4.099)	0.278
30–34					
Preterm birth	0.887 (0.363, 2.167)	0.887	Ref	1.745 (0.918, 3.318)	0.089
Primary Cesarean section	0.832 (0.481, 1.441)	0.512	Ref	1.782 (1.119, 2.839)	0.015
ICP	1.094 (0.406, 2.947)	0.859	Ref	0.796 (0.261, 2.430)	0.689
Amniotic fluid abnormalities	0.888 (0.258, 3.063)	0.851	Ref	0.535 (0.152, 1.885)	0.330
Hypertensive disorders	–	–	Ref	5.576 (3.036, 10.240)	< 0.001
Postpartum hemorrhage	0.735 (0.215, 2.513)	0.623	Ref	2.066 (0.860, 4.963)	0.105
Macrosomia	0.564 (0.168, 1.897)	0.355	Ref	2.142 (1.081, 4.242)	0.029
≥ 35					
Preterm birth	1.186 (0.471, 2.991)	0.717	Ref	0.425 (0.174, 1.035)	0.059
Primary Cesarean section	0.731 (0.322, 1.660)	0.454	Ref	1.610 (0.979, 2.649)	0.060
ICP	1.353 (0.29, 6.313)	0.701	Ref	1.030 (0.365, 2.903)	0.956
Amniotic fluid abnormalities	0.941 (0.207, 4.286)	0.937	Ref	1.812 (0.802, 4.093)	0.153
Hypertensive disorders	–	–	Ref	2.112 (1.079, 4.134)	0.029
Postpartum hemorrhage	0.648 (0.082, 5.102)	0.680	Ref	0.606 (0.163, 2.255)	0.455
Macrosomia	–	–	Ref	1.440 (0.646, 3.207)	0.372
(b) GWG					
Inadequate					
Preterm birth	0.900 (0.473, 1.715)	0.749	Ref	1.126 (0.450, 2.817)	0.800
Primary Cesarean section	0.781 (0.458, 1.331)	0.363	Ref	1.382 (0.672, 2.840)	0.379
ICP	0.942 (0.375, 2.365)	0.899	Ref	1.481 (0.424, 5.175)	0.538
Amniotic fluid abnormalities	0.584 (0.170, 2.000)	0.392	Ref	1.449 (0.410, 5.119)	0.565

Table 1 continued

Adverse pregnancy outcomes	Pre-pregnancy BMI				
	Underweight	*p* value	Normal	Overweight and obese	*p* value
Hypertensive disorders	0.264 (0.035, 2.007)	0.198	Ref	6.538 (2.706, 15.797)	< 0.001
Postpartum hemorrhage	0.668 (0.146, 3.053)	0.602	Ref	1.488 (0.322, 6.871)	0.611
Macrosomia	–	–	Ref	1.127 (0.249, 5.101)	0.877
Appropriate					
Preterm birth	0.643 (0.246, 1.680)	0.367	Ref	1.589 (0.804, 3.143)	0.183
Primary Cesarean section	0.896 (0.550, 1.460)	0.661	Ref	1.442 (0.898, 2.316)	0.130
ICP	1.121 (0.445, 2.824)	0.808	Ref	1.905 (0.818, 4.436)	0.135
Amniotic fluid abnormalities	0.700 (0.239, 2.056)	0.517	Ref	0.824 (0.303, 2.242)	0.704
Hypertensive disorders	0.289 (0.068, 1.225)	0.092	Ref	2.531 (1.375, 4.658)	0.003
Postpartum hemorrhage	0.866 (0.292, 2.570)	0.796	Ref	1.209 (0.473, 3.093)	0.692
Macrosomia	0.380 (0.114, 1.260)	0.114	Ref	1.263 (0.619, 2.578)	0.521
Excessive					
Preterm birth	–	–	Ref	1.337 (0.610, 2.930)	0.469
Primary Cesarean section	0.589 (0.192, 1.810)	0.356	Ref	1.128 (0.685, 1.858)	0.635
ICP	2.518 (0.261, 24.324)	0.425	Ref	1.787 (0.421, 7.593)	0.431
Amniotic fluid abnormalities	5.450 (0.908, 32.725)	0.064	Ref	1.982 (0.578, 6.794)	0.277
Hypertensive disorders	–	–	Ref	1.965 (1.070, 3.608)	0.029
Postpartum hemorrhage	0.714 (0.084, 6.067)	0.757	Ref	1.136 (0.420, 3.072)	0.801
Macrosomia	1.059 (0.222, 5.043)	0.943	Ref	1.073 (0.534, 2.154)	0.843

normal weight are more likely to have inadequate GWG, whereas those who are overweight or obese are more likely to have excessive GWG. On the other hand, however, in our study population, pregnant women who gained inadequate GWG were twice as likely as those who gained excessive GWG. This is in contrast to most of the published research and data. According to a study conducted by Deputy N and his colleagues, the prevalence of excessive GWG was higher in every state in the United States than the prevalence of inadequate or appropriate GWG [23]. A retrospective cohort study of women who gave birth at UW Health between 2007 and 2012 discovered that more than half of the women gained excessive weight during pregnancy [24]. This could be due to two reasons: first, 86.3% of our study population was underweight or normal weight, and second, there are differences between Chinese and Western women in body shape, dietary structure, cultural beliefs, and pregnancy practices. As a result, domestic scholars developed the GWG range based on the classification of Chinese adult BMI. The Institute of Medicine (IOM) guidelines, however, are still followed in our study because a meta-analysis of over 1 million pregnant women with GDM discovered that the

Table 2 The association of GWG and adverse pregnancy outcomes in different (a) maternal age groups, (b) pre-pregnancy BMI groups

	GWG				
Adverse pregnancy outcomes	**Inadequate**	***p* value**	**Appropriate**	**Excessive**	***p* value**
(a) Maternal Age					
≤ 29					
Preterm birth	1.651 (0.866, 3.147)	0.128	Ref	0.638 (0.275, 1.483)	0.297
Primary Cesarean section	1.081 (0.707, 1.653)	0.719	Ref	1.813 (1.121, 2.934)	0.015
ICP	1.180 (0.538, 2.589)	0.680	Ref	0.633 (0.208, 1.928)	0.421
Amniotic fluid abnormalities	1.190 (0.518, 2.731)	0.682	Ref	0.362 (0.094, 1.393)	0.139
Hypertensive disorders	0.687 (0.282, 1.672)	0.408	Ref	2.416 (1.156, 5.049)	0.019
Postpartum hemorrhage	0.206 (0.046, 0.930)	0.040	Ref	0.605 (0.211, 1.734)	0.349
Macrosomia	0.526 (0.197, 1.402)	0.199	Ref	2.375 (1.088, 5.181)	0.030
30–34					
Preterm birth	2.173 (1.208, 3.908)	0.010	Ref	1.834 (0.881, 3.817)	0.105
Primary Cesarean section	0.772 (0.533, 1.118)	0.171	Ref	1.573 (1.002, 2.471)	0.049
ICP	1.033 (0.519, 2.055)	0.927	Ref	0.302 (0.068, 1.346)	0.116
Amniotic fluid abnormalities	0.542 (0.235, 1.250)	0.151	Ref	0.449 (0.142, 1.419)	0.172
Hypertensive disorders	0.700 (0.347, 1.412)	0.319	Ref	1.608 (0.808, 3.198)	0.176
Postpartum hemorrhage	0.930 (0.421, 2.054)	0.857	Ref	1.741 (0.728, 4.163)	0.213
Macrosomia	0.262 (0.117, 0.588)	0.001	Ref	0.925 (0.467, 1.834)	0.824
≥ 35					
Preterm birth	1.998 (1.185, 3.369)	0.009	Ref	0.859 (0.356, 2.074)	0.736
Primary Cesarean section	0.840 (0.565, 1.250)	0.391	Ref	1.031 (0.615, 1.724)	0.910
ICP	1.576 (0.694, 3.579)	0.277	Ref	0.743 (0.195, 2.829)	0.663
Amniotic fluid abnormalities	1.580 (0.742, 3.365)	0.236	Ref	1.595 (0.620, 4.106)	0.333
Hypertensive disorders	0.679 (0.362, 1.274)	0.228	Ref	1.361 (0.670, 2.762)	0.394
Postpartum hemorrhage	1.063 (0.439, 2.576)	0.892	Ref	1.071 (0.323, 3.546)	0.911
Macrosomia	1.139 (0.532, 2.438)	0.737	Ref	1.325 (0.575, 3.051)	0.509
(b) pre-pregnancy BMI					
Underweight					
Preterm birth	2.980 (0.997, 8.913)	0.051	Ref	–	–
Primary Cesarean section	0.801 (0.414, 1.547)	0.508	Ref	0.951 (0.300, 3.011)	0.932
ICP	1.048 (0.318, 3.458)	0.938	Ref	0.801 (0.085, 7.512)	0.846
Amniotic fluid abnormalities	0.921 (0.192, 4.418)	0.918	Ref	2.971 (0.402, 21.937)	0.286

Table 2 continued

Adverse pregnancy outcomes	GWG				
	Inadequate	*p* value	Appropriate	Excessive	*p* value
Hypertensive disorders	0.694 (0.055, 8.797)	0.778	Ref	–	–
Postpartum hemorrhage	0.514 (0.088, 3.013)	0.461	Ref	1.271 (0.124, 13.023)	0.840
Macrosomia	–	–	Ref	7.114 (0.585, 86.548)	0.124
Normal					
Preterm birth	1.962 (1.348, 2.856)	< 0.001	Ref	1.105 (0.618, 1.973)	0.736
Primary Cesarean section	0.889 (0.687, 1.149)	0.368	Ref	1.667 (1.191, 2.332)	0.003
ICP	1.290 (0.778, 2.138)	0.323	Ref	0.523 (0.200, 1.373)	0.188
Amniotic fluid abnormalities	0.985 (0.597, 1.626)	0.953	Ref	0.509 (0.210, 1.233)	0.135
Hypertensive disorders	0.642 (0.398, 1.037)	0.070	Ref	2.240 (1.351, 3.715)	0.002
Postpartum hemorrhage	0.745 (0.415, 1.337)	0.323	Ref	1.196 (0.583, 2.455)	0.626
Macrosomia	0.598 (0.364, 0.983)	0.043	Ref	1.494 (0.883, 2.527)	0.135
Overweight and obese					
Preterm birth	1.087 (0.362, 3.268)	0.881	Ref	0.858 (0.376, 1.958)	0.717
Primary Cesarean section	1.037 (0.457, 2.353)	0.930	Ref	1.291 (0.730, 2.285)	0.380
ICP	0.961 (0.225, 4.099)	0.957	Ref	0.321 (0.089, 1.154)	0.082
Amniotic fluid abnormalities	2.099 (0.442, 9.977)	0.351	Ref	2.001 (0.552, 7.251)	0.291
Hypertensive disorders	1.462 (0.599, 3.569)	0.404	Ref	1.291 (0.668, 2.496)	0.448
Postpartum hemorrhage	0.865 (0.155, 4.834)	0.868	Ref	0.737 (0.234, 2.323)	0.603
Macrosomia	0.484 (0.099, 2.359)	0.369	Ref	1.579 (0.690, 3.611)	0.280

IOM guidelines applied to pregnant women in the United States, Western Europe, and East Asia [25].

In particular, high pre-pregnancy BMI and excessive GWG were found to be high-risk factors for elevated HbA1c (glycated hemoglobin) in our study. The HbA1c level of 6.5% as the reference diagnostic criterion for diabetes is still debatable. Previous research has linked higher HbA1c levels, even in non-diabetic range, to an increased risk of adverse pregnancy outcomes. Maresh et al. discovered that pregnant women with HbA1c levels between 6.0 and 6.4% of gestational age at 26 weeks had a significantly higher risk of having babies who were larger than gestational age, and pregnant women with HbA1c levels between 6.5 and 6.9% had higher risk of adverse pregnancy outcomes such as premature delivery, preeclampsia, and neonatal hypoglycemia [26]. According to a recent study, every 1% increase in HbA1c levels in pregnant women increased the risk of premature delivery by 1.58 times and the risk of macrosomia by 1.70 times [27]. Combined with our results, in order to more precisely define the HbA1c cut-off value for predicting adverse pregnancy outcomes in women with gestational diabetes, large-scale research is required, especially in those with a high pre-pregnancy BMI and excessive GWG, who are at higher risk of pregnancy complications.

As far as we know, it is the first to investigate the relationship of pregnancy outcomes with maternal age, pre-pregnancy BMI, and GWG among women with gestational diabetes. Nonetheless, this study is subject to some limitations. To begin with, because it is a retrospective study, selection and recall bias were unavoidable. Second, the study's population was pregnant women who had regular antenatal checkups and gave birth at a single center, implying a lack of representativeness. Third, the sample size was relatively small, for example, only 33 pregnant women were obese before pregnancy.

CONCLUSIONS

In conclusion, advanced-age pregnancy can increase the occurrence of adverse pregnancy outcomes in women with gestational diabetes. To improve the prognosis of mothers and children, we should advocate for age-appropriate pregnancy and provide comprehensive maternity care services for women with advanced-age pregnancy. The key modifiable risk factors for pregnant women are their pre-pregnancy BMI and GWG. Strict weight management during pregnancy to prevent excessive GWG in pregnant women with GDM may have a positive effect on improving neonatal outcomes and the long-term health of these people in adulthood.

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Compliance with Ethics Guidelines. This study was approved by the Human Ethics committee at Women's Hospital, School of Medicine, Zhejiang University.

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

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REFERENCES

1. Zhang X, Chen L, Wang X, et al. Changes in maternal age and prevalence of congenital anomalies during the enactment of China's universal two-child policy (2013–2017) in Zhejiang Province, China: an observational study. PLOS Med. 2020;17(2):e1003047.

2. Faddy MJ, Gosden RG, Gougeon A, et al. Accelerated disappearance of ovarian follicles in mid-life: implications for forecasting menopause. Human Reproduction. 1992;7(10):1342–6.

3. Female age-related fertility decline. Fertil Steril. 2014;101(3):633–4.

4. Lean SC, Derricott H, Jones RL, et al. Advanced maternal age and adverse pregnancy outcomes: A systematic review and meta-analysis. PLOS ONE. 2017;12(10):e0186287.

5. Ziadeh SM. Maternal and perinatal outcome in nulliparous women aged 35 and older. Gynecol Obstet Investig. 2002;54(1):6–10.

6. Koo Y-J, Ryu H-M, Yang J-H, et al. Pregnancy outcomes according to increasing maternal age. Taiwan J Obstet Gynecol. 2012;51(1):60–5.

7. Khalil A, Syngelaki A, Maiz N, et al. Maternal age and adverse pregnancy outcome: a cohort study. Ultrasound in Obstetrics & Gynecology. 2013;42(6):634–43.

8. Ahmed B, Sultana R, Greene MW. Adipose tissue and insulin resistance in obese. Biomed Pharmacother. 2021;137: 111315.

9. Catalano PM, Shankar K. Obesity and pregnancy: mechanisms of short term and long term adverse consequences for mother and child. BMJ. 2017;356: j1.

10. Godfrey KM, Reynolds RM, Prescott SL, Nyirenda M, Jaddoe VWv, Eriksson JG, et al. Influence of maternal obesity on the long-term health of offspring. Lancet Diabetes Endocrinol. 2017;5(1): 53–64.

11. Galtier-Dereure F, Boegner C, Bringer J. Obesity and pregnancy: complications and cost. Am J Clin Nutr. 2000;71(5):1242S–8S.

12. Deputy NP, Sharma AJ, Kim SY, Hinkle SN. Prevalence and characteristics associated with gestational weight gain adequacy. Obstet Gynecol. 2015;125(4):773–81.

13. Wendland EM, Torloni MR, Falavigna M, Trujillo J, Dode MA, Campos MA, et al. Gestational diabetes and pregnancy outcomes—a systematic review of the World Health Organization (WHO) and the International Association of Diabetes in Pregnancy Study Groups (IADPSG) diagnostic criteria. BMC Pregnancy Childbirth. 2012;12(1):23.

14. Kenny LC, Lavender T, McNamee R, O'Neill SM, Mills T, Khashan AS. Advanced maternal age and adverse pregnancy outcome: evidence from a large contemporary cohort. PLoS ONE. 2013;8(2): e56583.

15. Pregnancy WGD. Washington. D.C.: National Academies Press; 2009.

16. Attali E, Yogev Y. The impact of advanced maternal age on pregnancy outcome. Best Pract Res Clin Obstet Gynaecol. 2021;70:2–9.

17. Sheen JJ, Wright JD, Goffman D, et al. Maternal age and risk for adverse outcomes. Am J Obstet Gynecol. 2018;219(4):390.e1-390.e15.

18. Owens OLA, O'Sullivan EP, Kirwan B, et al. ATLANTIC DIP: the impact of obesity on pregnancy outcome in glucose-tolerant women. Diabetes Care. 2010;33(3):577–9.

19. Gante I, Amaral N, Dores J, et al. Impact of gestational weight gain on obstetric and neonatal outcomes in obese diabetic women. BMC Pregnancy Childbirth. 2015;15:249 (**Published 2015 Oct 8**).

20. Liu L, Hong Z, Zhang L. Associations of prepregnancy body mass index and gestational weight gain with pregnancy outcomes in nulliparous women delivering single live babies. Sci Rep. 2015;5:12863.

21. Suliga E, Rokita W, Adamczyk-Gruszka O, et al. Factors associated with gestational weight gain: a cross-sectional survey. BMC Pregnancy Childbirth. 2018;18(1):465.

22. Jensen DM, Ovesen P, Beck-Nielsen H, et al. Gestational weight gain and pregnancy outcomes in 481 obese glucose-tolerant women. Diabetes Care. 2005;28(9):2118–22.

23. Deputy NP, Sharma AJ, Kim SY. Gestational weight gain—United States, 2012 and 2013. MMWR Morb Mortal Wkly Rep. 2015;64(43):1215–20.

24. Lindberg S, Anderson C, Pillai P, et al. Prevalence and predictors of unhealthy weight gain in pregnancy. WMJ. 2016;115(5):233–7.

25. Goldstein RF, Abell SK, Ranasinha S, et al. Gestational weight gain across continents and ethnicity: systematic review and meta-analysis of maternal and infant outcomes in more than one million women. BMC Med. 2018;16(1):153.

26. Maresh MJ, Holmes VA, Patterson CC, et al. Glycemic targets in the second and third trimester of pregnancy for women with type 1 diabetes. Diabetes Care. 2015;38(1):34–42.

27. Bi J, Ji C, Wu Y, et al. Association between maternal normal range HbA1c values and adverse birth outcomes [published correction appears in J Clin Endocrinol Metab. 2021 Jul 13;106(8):e3299]. J Clin Endocrinol Metab. 2020;105(6):dgaa127.