Body Mass Index and Blood Lipids Underpin The Correlation Between The Age At Menarche and Gestational Diabetes Mellitus

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Abstract

Background

The age of menarche affects the metabolic activities in pregnant women. However, data on the factors that define the association between age at menarche and gestational diabetes mellitus (GDM) remains scant.

Methods

Logistic regression models coupled with restricted cubic splines were used to analyze the effect of menarche on GDM. We stratified the participants by age at pregnancy, fetal gender, and parity. We interrogated the role of BMI before pregnancy, BMI gain during pregnancy, and blood lipids in early pregnancy in mediating GDM.

Results

With menarche age ≤ 12 years as the control, women with menarche ages of 13, 14, and ≥ 15 years had 0.91 (95%CI, 0.85 to 0.97), 0.87 (95%CI, 0.81 to 0.93), and 0.85 (95%CI, 0.79 to 0.91) odds ratio for GDM. There were similar and pronounced effects in advanced-age pregnancy, with male fetuses and primiparous women. We showed that pre-pregnancy BMI and blood lipids such as triglycerides, total cholesterol, and low-density lipoprotein in early pregnancy mediate the association between age at menarche and GDM.

Conclusion

Taken together, our data demonstrated that menarche at early ages fuels the development of GDM. For pregnant women with early menarche should reduce BMI and blood lipid levels before pregnancy.

Introduction

Gestational diabetes mellitus (GDM) is a common pregnancy complication, affecting between 1% and 30% of pregnant women worldwide¹. Women with GDM may suffer from many serious perinatal complications such as pregnancy-induced hypertension, cesarean section, preeclampsia or shoulder dystocia^{2–4}. GDM is associated with adverse fetal outcomes², increased risk for fetal macrosomia⁵, neonatal respiratory distress⁶, congenital abnormalities⁷, as well as increased rates of neonatal admissions and perinatal deaths³. Previous studies have shown a close correlation between the development of GDM and type 2 diabetes⁸. Women with hyperglycemia during pregnancy had a significantly increased risk of diabetes after index pregnancy⁹. Therefore, exploration of the underlying

mechanisms and risk factors would reduce the incidence and impact of GDM on the health of pregnant women and their children.

The GDM occurs mainly due to the inability of the pancreas to effectively respond to the increased insulin demand in pregnant women¹⁰. Menarche is the onset of ovarian and other endocrine functions relating to reproduction¹¹, which might be related to a variety of metabolic diseases^{12–14}. Age at menarche affects the women's hormone exposure and may have an impact on maternal lipid metabolism^{6,15–17}. Women with earlier menarche age have an increased odds ratio of GDM^{18,19}. However, there is limited data on the mechanisms of the association between GDM and age at menarche. Epidemiological studies have shown that BMI before pregnancy, weight gain during pregnancy, and hormone levels were the key risk factors for GDM^{20–24}. Here, we hypothesized lipid metabolism exposure might play a central role in the interplay between menarche age and GDM. We retrospectively interrogated the association between menarche age and GDM risks, and analyzed the role of pre-pregnancy weight and blood lipids in fuelling the GDM.

Methods

Study population

This retrospective cohort study was conducted at the International Peace Maternal and Child Health Hospital (IPMCHH), affiliated to the Shanghai Jiaotong University Medical College of. We collected electronic medical records of women who underwent routine prenatal examination at the IPMCHH from January 1, 2015, to December 31, 2019. Demographic data such as age, education level, BMI before pregnancy, gestational weight, smoking, drinking, and reproductive history were collected at admission. We excluded patients with multifetal pregnancy (2,047) polycystic ovary syndrome (n=214), previous GDM (n= 289), stillbirth or miscarriage (n= 271) to GDM (Supplemental Figure 1). The method in this study was carried out in accordance with guidelines of strengthening the reporting of observational studies in epidemiology (STROBE). This study was approved by the ethical committees of the International Peace Maternity and Child Health Hospital. The patient's written informed consent requirement was waived, due to the removal of sensitive information from participants in this retrospective study.

Outcome and covariates

The oral glucose tolerance test (OGTT) was used to evaluate GDM at 24 - 28 weeks of pregnancy, according to the recommendations of the International Association for Diabetes Research. The pregnant women took 75 grams of glucose after fasting overnight, and then their blood glucose levels were measured between 1 and 2 hours. GDM was defined as fasting blood glucose (FBG) ≥ 5.1 mmol/L, or/and 1-hour postprandial blood glucose (1h PBG) ≥ 10 mmol/L, or/and 2-hour postprandial blood glucose (2h PBG) ≥ 8.5 mmol/L.

Covariates included sociodemographic characteristics (age at pregnant, fetal gender, and education level), anthropometric indicators (pre-pregnancy weight, second-trimester weight, and height), lifestyle (smoking, drinking), serum biochemical index, reproductive history (parity, gravidity) and past medical history (Table 1).

Mediating factors

We interrogated the mediating role of BMI before pregnancy, BMI gain during pregnancy and blood lipids in early pregnancy in GDM. The pre-pregnancy BMI was calculated from self-reported pre-pregnancy weight and height, after the first clinic visit during pregnancy and were reviewed by a doctor. BMI gain was calculated by subtracting the BMI before pregnancy from the BMI in the second trimester, divided by gestational week. We evaluated blood lipids such as triglycerides (TG), total cholesterol (TC), low-density lipoprotein (LDL), and high-density lipoprotein (HDL) in early pregnancy, which were measured in the first trimester (9-13 weeks). In addition, the blood glucose level of GDM was analyzed to explore the stability of the effect of age at menarche on blood glucose during pregnancy. We decomposed the total impact of age at menarche on GDM by assessing the natural direct or indirect impact. The natural direct impact of age at menarche on GDM was mediated through changes in BMI while the natural indirect impact was assessed through BMI before pregnancy and BMI gain during pregnancy. We obtained the total effect by summing up the natural direct and indirect effects. To explore the effects of estrogen exposure, we constructed an interaction network between age at menarche and pregnancy age or fetal gender.

Statistical analysis

Logistic regression was used to examine the association between age at menarche (categorized into ≤ 12 , 13, 14, ≥ 15 years) and GDM, with ≤ 12 years as the reference group. The models were adjusted for ethnicity (han and others), fetal gender (female and male), education levels (graduated from senior school or below, university graduate and master degree or above), ward types (general ward and senior ward), conception method (natural conception and assisted reproductive technology (ART)), insurance type (urban or employee, others), drinking, smoking, family history of hypertension or family history of diabetes. We further investigated the association by adjusting for age at pregnancy, parity (1 and ≥ 2), and gravidity (1, 2, and ≥ 3).

The restricted cubic splines were used to assess the relationships between GDM and pre-pregnancy BMI, BMI gain in pregnancy, blood lipids, and menarche age. Stratified analyses were performed to examine the heterogeneity in the associations of GDM with age at pregnancy, fetal gender, and parity. In addition, we estimated natural indirect or direct effects, as well as total effects using the interpolation-based method implemented in the 'medflex' R package^{25,26}. The missing values were filled by multiple imputation techniques. R software (version 3.6.3) was used for the statistical analyses.

Results

Characteristics of the study participants

A total of 60,189 pregnant women were included in this study. The mean age of pregnancy was 30.69 years (SD: 3.92), and the mean reported age at menarche was 13.7 years (SD:1.37). Our data showed that 18.76%, 26.22%, 30.95%, and 24.07%, of the participants reported menarche at ≤ 12 , 13, 14, and ≥ 15 years old respectively. The proportion of women who conceived through ART were higher among women who experienced menarche at 14 years, compared to those with earlier or later menarche ages. Women with earlier menarche were more likely to have been diagnosed with GDM in the second trimester. We further show that pregnant women with earlier age menarche (≤ 12) were more likely to be primiparas (parity = 1). The proportion of pregnant women who had later menarche with bachelor's degree or above was lower. On the other hand, women with aged ≤ 12 years at menarche had higher pre-pregnancy BMI and higher proportions of primipara. The prevalence of GDM was highest among pregnant women who experienced early menarche and lowest among pregnant women whose menarche age was 14 years (Table 1). In addition, pregnant women with early menarche age had the highest FBG, 1h PBG, and 2h PBG, as well as the levels of HDL, LDL, TC and TG in the first trimester, which decreased with the increase of the age at menarche.

The relationship between age at menarche and GDM

Our multivariate logistic models showed that the women with menarche at ≤ 12 years of age had the highest risk of GDM (Figure 1, Supplement Table 1). Compared with pregnant women with a menarche age ≤ 12 , the risks of GDM were significantly decreased with later ages at menarche, with menarche at 13, 14, and ≥ 15 years being associated with risks of 0.91 (95% CI, 0.85 to 0.97), 0.88 (95%CI, 0.82 to 0.94), and 0.90 (95%CI, 0.84 to 0.96), respectively. The risks were adjusted for ethnicity, fetal gender, education level, ward type, conception method, insurance type, drinking, smoking, as well as family history of hypertension or diabetes (Figure 1). The risk estimates for the development of GDM with menarche ages of 13, 14, and ≥ 15 were 0.91 (95% CI, 0.85 to 0.97), 0.87 (95% CI, 0.81 to 0.93), and 0.85 (95% CI, 0.79 to 0.91), respectively. Compared with the lowest age at menarche, menarche ages of 14 and ≥ 15 had more pronounced effects on GDM. We then used the age of menarche as a continuous variable to perform restricted cubic spline analysis. The data showed that delayed menarche age was associated with reduced incidence of GDM, levels of 1h PBG and 2h PBG (Supplemental Figure S2).

However, adjustment for potential mediating factors (BMI before pregnancy, weight gain during pregnancy and blood lipids in early pregnancy) attenuated the risk for age at menarche, and changed the risks (Supplemental Table S1).

Stratified analyses by maternal age, fetal gender, and parity

We then investigated the association between age at menarche and GDM in subgroups of maternal age, fetal gender, and parity (Figure 2, Supplemental Table S2). When stratified by maternal age, age at menarche was significantly associated with GDM in pregnant women aged ≥ 30 years (OR: 0.86, 95% CI: 0.79 to 0.94 for 13 years of age, OR: 0.86, 95% CI: 0.79 to 0.94 for 14 years of age and OR: 0.83, 95%CI: 0.76 to 0.91 for ≥ 15 years of age). For women aged <30 years, the association of age at menarche with GDM was less significant (Figure 2A). According to Figure 2B, the association of age at menarche with

GDM was stronger in women with male fetuses. Besides, there is a stronger correlation between the age of menarche and GDM in primiparous women (Figure 2C). Collectively, our results showed that the effect conferred by increased menarche age on GDM was more significant in women aged ≥ 30 years, women with male fetuses, and primiparas (Supplemental Figure S3).

The mediating effects of pre-pregnancy BMI, BMI gain, and blood lipids in the relationship between age at menarche and GDM

We first analyzed the effect of pre-pregnancy BMI, BMI gain during pregnancy, and blood lipids in early pregnancy on GDM (Supplemental Figure S4 and S5). Our results showed that incidence of GDM increased with the pre-pregnancy BMI or BMI gain (Supplemental Figure S4). Besides, the incidence of GDM increased with LDL, TC, or TG, but not HDL (Supplemental Figure S5).

In the mediation analysis, we found that the association between age at menarche and GDM was indirectly mediated by BMI before pregnancy (Table 2). The indirect effect ORs were 0.94 (95% CI: 0.93 to 0.95) for 13 years of age, 0.90 (95% CI: 0.89 to 0.91) for 14 years of age and 0.87 (95%CI: 0.86 to 0.88) for ≥ 15 years of age. The evidence did not support mediation of the age at menarche-GDM association mediated by BMI gain.

In addition, mediation analysis of blood lipids in the first trimester showed that LDL, TC, and TG but not HDL had both direct and indirect effects on the relationship between age at menarche and GDM (Supplemental Table S3).

Discussion

Our study demonstrated there was a correlation between the ages at menarche and GDM after adjusting for confounding factors such as age at pregnancy, gravidity and parity. We found that the age at menarche-GDM association was mediated by blood lipid levels (LDL, TC, TG) in the first trimester and pre-pregnancy BMI.

Previous studies interrogated the relationship between age at menarche and GDM.

A meta-analysis of 315,428 women reported that the risk of type 2 diabetes was higher in women with early age at menarche²⁷. In pregnant women, the relationship between a recent meta-analysis found that age at menarche and GDM was curvilinear¹⁸. However, their study was limited due to the fact that it was based on only five studies and such potential covariates as maternal BMI and family history of diabetes were not adjusted for. In our study, we found consistent results that early age at menarche increased the risk of GDM. The mechanism by which menarche increase the risk of GDM is yet to be defined. Previous studies showed that early menarche was associated with the GDM risk factors such as obesity before pregnancy^{18,28,29}, insulin resistance^{30,31}, and age at menarche through hormonal changes. Early-age menarche leads to higher estrogen levels and reduced serum sex hormone binding globulin levels³².

Similarly, high plasma estradiol and testosterone levels and/or low sex hormone binding globulin levels were associated with a higher risk of GDM, but not obesity³³.

We performed a stratified analysis by pregnancy age, fetal sex, and parity. The effect of menarche age on GDM was not significant changes on addition of pregnancy age and/or parity to the model. Moreover, our results showed that the effects of age at menarche on GDM was stronger in women aged ≥ 30 years, women with male fetuses, and primiparas. We speculated that it might be associated with hormonal exposure. Earlier age at menarche increases cumulative exposure of estrogen, which might reduce the levels of serum sex hormone-binding globulin. It has been shown that patients with high plasma estradiol levels and low sex hormone-binding globulin levels may have increased risks of GDM^{34,35}. Accumulation of progesterone might affect the functions of insulin-secreting cells through oxidative stress³⁶, inhibit insulin release and glucose transporters³⁷, leading to insulin resistance³⁸, and diabetes. The cause of the adverse effect of fetal sex on pregnancy outcome is not clear. It was shown that there were differences in HCG expression and testosterone production between female and male fetuses, which may affect the pathogenesis of GDM^{39,40}. The greater sensitivity of primipara to hormone exposure may explain the interactive effects of parity.

The association of age at menarche and GDM became insignificant or reduced when adding pre-pregnancy BMI and pre-pregnancy blood lipids to the model. Early the age at menarche with increased chances of obesity⁴¹, the more the changes in the risks of GDM which affect energy metabolism before and during pregnancy. Our results emphasized the importance of monitoring the lifestyle and other health factors in preventing GDM. To assure the quality and stability of the results, our study used a relatively large sample size. Furthermore, we analyzed the factors that mediate the association between age at menarche and GDM, and discussed effects of BMI before pregnancy and blood lipid factors in early pregnancy. Finally, we explored the regulatory effects of pregnancy age, fetal sex and parity on the relationship between menarche age and GDM.

Abbreviations

GDM, gestational diabetes mellitus; BMI, body-mass index; TG, triglycerides; TC, total cholesterol; LDL, low-density lipoprotein; HDL, high-density lipoprotein; OGTT, the oral glucose tolerance test; PBG, postprandial blood glucose; ART, assisted reproductive technology; OR, odds ratio

Declarations

Declaration of Competing Interest

The authors declare no competing interest.

Author contributions

DJ.Y. Y.Y. conducted the analyses. DJ.Y. and L.C. wrote the manuscript. XH.J., L.C., and XY.C. contributed to data collection. DJ.Y., L.C. and XH.J. contributed to study design. XH.J. edited the manuscript. All authors reviewed the manuscript.

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Tables

Table 1
Characteristics of study participants in IPMCHH by age at menarche

Characteristics	Age at menarche (Years)				
	≤ 12 (Mean = 11.78)	13	14	≥ 15 (Mean = 15.57)	All
Women, n (%)	11294(18.76)	15781(26.22)	18627(30.95)	14487(24.07)	60189(100)
BMI before pregnancy, mean (SD), kg/m ²	21.76(2.88)	21.32(2.76)	20.98(2.65)	20.78(2.66)	21.17(2.74)
GWG before GDM diagnosis, mean (SD), kg/week	0.28(0.18)	0.28(0.17)	0.28(0.17)	0.29(0.19)	0.28(0.18)
Age at pregnant, mean (SD), years	30.64(3.82)	30.55(3.86)	30.65(3.88)	30.93(4.09)	30.69(3.92)
Ethnicity, n (%)					
Han	11065(97.97)	15519(98.34)	18384(98.7)	14254(98.39)	59222(98.39)
Others	229(2.03)	262(1.66)	243(1.30)	233(1.61)	967(1.61)
Parity, n (%)					
1	8448(74.80)	11540(73.13)	13289(71.34)	9587(66.18)	42864(71.22)
≥ 2	2846(25.20)	4241(26.87)	5338(28.66)	4900(33.82)	17325(28.78)
Gravidity, n (%)					
1	6066(53.72)	8058(51.06)	9389(50.41)	6357(43.90)	29870(49.64)
2	3186(28.22)	4487(28.43)	5290(28.40)	4311(29.77)	17274(28.70)
≥ 3	2039(18.06)	3235(20.50)	3947(21.19)	3814(26.34)	13035(21.66)
Smoking, n (%)					
No	11167(98.88)	15615(98.95)	18448(99.04)	14348(99.04)	59578(98.98)
Yes	127(1.12)	166(1.05)	179(0.96)	139(0.96)	611(1.02)
Drinking, n (%)					
No	11262(99.72)	15723(99.63)	18551(99.59)	14420(99.54)	59956(99.61)
Yes	32(0.28)	58(0.37)	76(0.41)	67(0.46)	233(0.39)

Characteristics	Age at menarche (Years)				
	≤ 12 (Mean = 11.78)	13	14	≥ 15(Mean = 15.57)	All
Mode of conception					
Natural conception	9484(83.97)	13244(83.92)	15557(83.52)	12191(84.15)	50476(83.86)
Assisted Reproductive Technology (ART)	1810(16.03)	2537(16.08)	3070(16.48)	2296(15.85)	9713(16.14)
Ward types, n (%)					
General ward	10269(90.92)	14511(91.95)	17136(92.00)	13465(92.95)	55381(92.01)
Senior ward	1025(9.08)	1270(8.05)	1491(8.00)	1022(7.05)	4808(7.99)
Education level, n (%)					
Graduated from high school or below	478(4.25)	1022(6.50)	1373(7.40)	1821(12.61)	4694(7.82)
Collage graduated	7840(69.66)	11280(71.69)	13546(72.97)	10495(72.65)	43161(71.94)
Master degree or above	2936(26.09)	3432(21.81)	3646(19.64)	2129(14.74)	12143(20.24)
Medical insurance, n (%)					
Urban or employee	9185(81.33)	12753(80.84)	14896(80.00)	11379(78.57)	48213(80.13)
Others	2108(18.67)	3023(19.16)	3725(20.00)	3103(21.43)	11959(19.87)
Fetal gender, n (%)					
Female	5457(48.32)	7572(47.98)	9015(48.40)	7098(49.00)	29142(48.42)
Male	5837(51.68)	8209(52.02)	9612(51.600)	7389(51.00)	31047(51.58)
Family history of diabetes, n (%)					
No	10255(90.8)	14570(92.33)	17247(92.59)	13552(93.55)	55624(92.42)

Characteristics	Age at menarche (Years)				
	≤ 12 (Mean = 11.78)	13	14	≥ 15 (Mean = 15.57)	All
Yes	1039(9.20)	1211(7.67)	1380(7.41)	935(6.45)	4565(7.58)
Blood sugar in the second trimester					
FBG, mean (SD), mmol/L	4.22(0.42)	4.2(0.40)	4.2(0.41)	4.21(0.41)	4.21(0.41)
1h PBG, mean (SD), mmol/L	8.04(1.39)	7.99(1.35)	7.97(1.34)	7.98(1.36)	7.99(1.36)
2h PBG, mean (SD), mmol/L	6.64(1.43)	6.57(1.39)	6.54(1.40)	6.52(1.43)	6.56(1.41)
Lipids in the first trimester					
HDL, mean (SD), mmol/L	1.84(0.40)	1.83(0.40)	1.83(0.40)	1.82(0.39)	1.83(0.40)
LDL, mean (SD), mmol/L	2.73(0.71)	2.70(0.70)	2.70(0.70)	2.68(0.69)	2.7(0.70)
TC, mean (SD), mmol/L	4.61(0.75)	4.58(0.76)	4.58(0.75)	4.55(0.74)	4.58(0.75)
TG, mean (SD), mmol/L	1.34(0.52)	1.33(0.53)	1.32(0.54)	1.32(0.58)	1.33(0.54)

Table 2

Odds ratio (95%CI) of incident GDM mediated by weight factors, by age at menarche(years) *

Age at menarche	Weight factors			
	BMI before pregnancy		BMI gains during pregnant	
	OR(95%CI)	<i>p</i>	OR(95%CI)	<i>p</i>
Direct effect				
≤ 12 years	Ref.		Ref.	
13 years	0.96(0.90 to 1.03)	0.300	0.91(0.85 to 0.97)	0.006
14 years	0.97(0.91 to 1.04)	0.349	0.871(0.81 to 0.93)	< 0.0001
≥ 15	0.98(0.91 to 1.05)	0.581	0.85(0.79 to 0.91)	< 0.0001
Indirect effect				
≤ 12 years	Ref.		Ref.	
13 years	0.94(0.93 to 0.95)	< 0.0001	1.00(1.00 to 1.00)	0.934
14 years	0.90(0.89 to 0.91)	< 0.0001	1.00(1.00 to 1.00)	0.891
≥ 15	0.87(0.86 to 0.88)	< 0.0001	1.00(1.00 to 1.00)	0.052
*: adjusted for ethnicity, fetal gender, education level, ward type, mode of conception, insurance type, drinking, smoking, family history of hypertension, family history of diabetes, age at pregnancy, gravidity and parity; Reference category is menarche at ≤ 12 years of age.				

Figures

Figure 1

Odds ratios (OR) and 95%CI of incident GDM by menarche age. Adjusted model 1: adjusted for ethnicity, fetal gender, education level, ward type, conception method, insurance type, drinking, smoking, family history of hypertension, family history of diabetes; Adjusted model 2: adjusted model 1 + maternal age; Adjusted model 3: adjusted model 2 + parity and gravidity. Reference category is menarche at ≤ 12 years of age.

Figure 2

Odds ratio (OR) and 95%CI confidence interval (CI) of incident GDM by age at menarche and risk factors for GDM (further details were given in Supplemental Table S1). Models were adjusted for ethnicity, fetal gender, education level, ward type, conception method, insurance type, drinking, smoking, family history of hypertension, family history of diabetes, age at pregnancy, gravidity and parity). Reference category is menarche at ≤ 12 years of age.

Supplementary Files

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