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The association between inflammatory indices in early pregnancy and the risk of gestational diabetes mellitus in Chinese population

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Abstract

Background The association between inflammatory indices from peripheral blood cell in early pregnancy and the risk of gestational diabetes mellitus (GDM) is unclear.

Methods This was a retrospective study involving the medical data of 15,807 pregnant women who gave birth in 2019. Data were collected from the medical records and analyzed. The pregnant women's age, educational level, pre-pregnancy body weight, height, parity, family history of diabetes, lipid profile, blood pressure were recorded during $11\sim13^{+6}$ pregnancy weeks. We collected and measured several easily accessible systemic inflammatory indices from peripheral blood cell count, including Neutrophils, Lymphocytes, Monocytes, MHR (monocyte count/HDL-C), SII (platelet count ×neutrophil count/lymphocyte count) and SIRI (neutrophil count ×monocyte count/lymphocyte count), and we analyzed their association with the risk of developing GDM.

Results In the present study, a total of 15,807 women were included, including 2,355 (14.9%) women diagnosed with GDM. Women who were diagnosed with GDM showed markedly lower level of monocyte count and higher level of neutrophil and lymphocyte counts. The GDM group showed relatively lower level of SIRI, while no significant differences were found between GDM group and non-GDM group in MHR or SII. After adjusting for potential confounding factors, we observed a significant association between monocyte counts, MHR and the risk of developing GDM, and the risk tended to decrease with increasing levels of monocyte counts and MHR.

Conclusion The present study revealed that in early pregnancy, monocyte count and MHR have great potential as early diagnostic markers of GDM.

Keywords Gestational diabetes mellitus, Early pregnancy, Inflammation, Monocytes

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Background

Gestational diabetes mellitus (GDM) is the most common global metabolic disorder that manifest during pregnancy. GDM is defined as the hyperglycemia first detected during pregnancy and has been reported to affect 2–19% of all pregnancy women, particularly among Asian population [1, 2].

Diagnostic criteria for GDM are diverse across guidelines from different countries and regions. The Chinese guideline adopt GDM screening criteria based on the International Association of Diabetes in Pregnancy Study Group (IADPSG) [3], which means GDM cannot be diagnosed until late in the second trimester.

However, studies have shown that accelerated fetal growth occurs as early as 20 weeks gestation, and there is increased adiposity in the offspring of women with GDM in early infancy, despite good maternal glycemic control [4]. Therefore, detecting women at high-risk of GDM early in pregnancy is a desirable goal as lifestyle interventions such as diet and exercise can be applied early which can potentially reduce later development of GDM and its associated morbidities [5].

Evidence from literature suggests that a suitable method for identifying women in early pregnancy who may be at high risk of GDM has not been clearly established as there is no international consensus for accurate screening approach. However, racial group, maternal age, pre-pregnancy BMI, family history [6], first-trimester fasting plasma glucose [7, 8], abnormal lipid profile [9] and accelerated first trimester fetal heart rate [10]were considered as potential predictors in previous studies.

GDM is a complex disease with multiple etiologies, occurrence of GDM may be related to genetic susceptibility, inflammatory cytokines, adipokines, placental hormone and other risk factors such as obesity [11]. Metabolic regulation and immune response are highly integrated [12]. Multiple inflammatory factors are involved in the regulation of various metabolic products, such as lipids and glucose, and high-grade inflammation could lead to extensive accumulation of abnormal levels of lipids and glucose, eventually resulting in metabolic dysfunction and loss of homeostasis. Pregnancy itself is characterized by an altered inflammatory profile compared to the non-pregnant state and normal pregnancy is a pro-inflammatory, pro-thrombotic, highly insulin resistant and hyperlipidemic state [13].

Most of the current studies on inflammation and metabolism would appear have focused mainly on adipose tissue or immune cells, and at the individual level the interest has been limited to obesity and diabetes mellitus (DM), representing only a limited aspect of metabolic diseases. These have significant implications, especially among pregnancy women, leading to a limitation of epidemiological studies on inflammation and metabolic disorders.

The composite low-grade inflammatory indices, including monocyte-to-high density lipoprotein ratio (MHR), systematic immune inflammation index (SII) and systemic inflammation response index (SIRI), are novel type of parameters based on the traditional peripheral blood cell count. Previous studies have confirmed that these indices could reflect inflammation levels and were widely used in evaluating the risk of various chronic diseases [14, 15]. Therefore, our study enrolled and screened these 3 simple-to-calculate and several easily accessible systemic inflammatory indices during early pregnancy to assess their effectiveness in evaluating the risk of GDM.

Methods

The current study was carried out within the framework of a historical cohort of 15,948 pregnant women who gave birth in 2019 at a maternal hospital in Shanghai, China. The retrospective desensitization data used in this study were exempted from the informed consent of participants. Ethical approval for the current study was obtained from Clinical Research Ethics Committee of the International Peace Maternity and Child Health Hospital, School of Medicine, Shanghai Jiao Tong University [(GKLW)2018-29]. Individuals were excluded if they had a history of pre-pregnancy diabetes mellitus or any infectious disease. Ultimately, we obtained a target population of 15,807 women.

Baseline characteristics of the mothers' early-pregnancy health status were obtained from the computerized medical records. At the first prenatal visit, the pregnant women's age, educational level, pre-pregnancy body weight, height, parity, family history of diabetes were either measured or obtained from the patients and written in the medical history.

Diagnosis of GDM was based on IADPSG criteria [3]. Pregnant women attending the clinic visit at 24 ~ 28 weeks were given a 75 g oral glucose tolerance test (OGTT) after overnight fasting. GDM would be diagnosed if any of the glucose level was equal to or greater than the cut-off value of 5.1 mmol/l (fasting), 10.0mmol/l (1 h) or 8.5 mmol/l (2 h) after the test, and results were recorded in the medical history. The blood samples were collected to gather data on blood biochemistry and perform blood routine examinations during $11 \sim 13^{+6}$ pregnancy weeks. The whole blood counts were determined by the Sysmex XE-2100 Hematology Automated Analyzer (Sysmex, Kobe, Japan) at our hospital's laboratory. Lipid profile, including total cholesterol (TC), triglyceride (TG), low-density lipoprotein (LDL) and high-density lipoprotein-cholesterol (HDL-C) were determined using commercially available kits (Roche Diagnostics).

In the current study, we analyzed 6 inflammatory indices: Neutrophils, Lymphocytes, Monocyte, MHR, SII and SIRI. The inflammatory indices were calculated as follows: MHR = monocyte count/HDL-C; SII = platelet count ×neutrophil count/lymphocyte count; SIRI = neutrophil count ×monocyte count/lymphocyte count.

We also converted the three inflammatory indices into four levels by quartile values and the lowest level was set as a reference. The detailed intervals of the three indices were as follows: MHR (Q1:≤0.29; Q2:0.30–0.37; Q3:0.36–0.45; Q4:≥0.46); SII(Q1:≤723.40; Q2:723.41-906.68; Q3:906.69-1130.69; Q4:≥1130.70); SIRI (Q1:≤1.98; Q2: 1.99–2.61; Q3:2.62–3.39; Q4:≥3.40).

Statistical analysis

We used SPSS software and R language for statistical analysis. Descriptive statistics were calculated for each variable, with GDM as a binary outcome variable. The comparison between the two groups (GDM Versus Non-GDM) was done using an independent sample t-test or χ2-test. Logistic regression was used to examine independent associations with GDM. Odds ratios and 95% confidence intervals were calculated for each variable. $P<0.05$ indicated that the difference was statistically significant.

Results

Demographic characteristics of pregnant women

Table 1 summarized characteristics of women with and without GDM. In the present study, a total of 15,807 women were included, including 2,355 (14.9%) women diagnosed with GDM. Women with GDM were more likely to have obesity, elevated BP level, higher fasting plasma glucose and hyperlipidemia.

In terms of inflammatory indices, we found that women who were diagnosed with GDM showed markedly lower level of monocyte count and higher level of neutrophil and lymphocyte counts. The GDM group showed relatively lower level of SIRI, while no significant differences were found between GDM group and non-GDM group in MHR or SII.

Table 1 The characteristics of GDM and Non-GDM patients

Characteristic	Overall (*N* = 15807)	GDM (*N* = 2355)	Non-GDM (*N* = 13452)	χ^2 or z	*P*
Age, year	31.26 ± 3.98	31.38 ± 3.98	31.23 ± 3.97	-1.67	0.10
Pre-pregnancy BMI, kg/m^2	21.24 ± 2.79	22.21 ± 3.12	21.07 ± 2.69	-17.62	<0.001*
Systolic BP, mmHg	110.87 ± 12.34	114.53 ± 12.56	110.22 ± 12.19	-14.92	<0.001*
Diastolic BP, mmHg	69.10 ± 9.86	71.49 ± 10.05	68.68 ± 9.76	-12.16	<0.001*
Family history of diabetes					
No	14,665(92.8%)	2057	12,608	121.7	<0.001*
Yes	1142(7.2%)	298	844		
Gravida	1.83 ± 1.09	1.97 ± 1.17	1.81 ± 1.07	-6.10	<0.001*
Primiparous					
No	4874(30.8%)	823	4051	21.95	<0.001*
Yes	10,933(69.2%)	1532	9401		
In-vitro fertilization	1380(8.7%)	308	1072	65.66	<0.001*
Fasting plasma glucose(Early pregnancy), mmol/L	4.58 ± 0.37	4.72 ± 0.44	4.56 ± 0.35	-17.35	<0.001*
HbA1C (Early pregnanc), mmol/L	5.27 ± 0.28	5.42 ± 0.34	5.24 ± 0.26	-24.60	<0.001*
Total cholesterol, mmol/L	4.47 ± 0.74	4.60 ± 0.78	4.44 ± 0.73	-9.40	<0.001*
Total triglyceride, mmol/L	1.42 ± 0.60	1.66 ± 0.73	1.38 ± 0.56	-17.74	<0.001*
High-density lipoprotein, mmol/L	1.98 ± 0.42	1.93 ± 0.44	1.99 ± 0.41	6.67	<0.001*
Low-density lipoprotein, mmol/L	2.47 ± 0.64	2.57 ± 0.66	2.45 ± 0.63	-7.95	<0.001*
RBC, *10^9/L	9.11 ± 1.72	4.30 ± 0.35	4.23 ± 0.35	-9.66	<0.001*
Hemoglobin, g/L	125.37 ± 11.64	128.02 ± 10.71	124.91 ± 11.73	-12.8	<0.001*
WBC, *10^9/L	9.12 ± 1.72	9.23 ± 1.81	9.09 ± 1.70	-3.62	<0.001*
Neutrophils, *10^9/L	7.26 ± 1.49	7.33 ± 1.50	7.24 ± 1.49	-2.60	0.009*
Lymphocytes, *10^9/L	2.00 ± 0.48	2.04 ± 0.51	1.99 ± 0.47	-0.50	<0.001*
Monocyte, *10^9/L	0.73 ± 0.21	0.72 ± 0.20	0.74 ± 0.21	4.11	<0.001*
MHR, *10^9/L	0.39 ± 1.55	0.39 ± 0.15	0.39 ± 0.16	-1.70	0.09
SII, *10^9/L	951.98 ± 329.53	962.22 ± 361.06	950.18 ± 323.65	-1.64	0.10
SIRI, *10^9/L	2.80 ± 1.15	2.70 ± 1.13	2.81 ± 1.15	5.46	<0.001*

BMI, body mass index; RBC: Red blood cell; WBC, White blood cell; MHR: monocyte count/ High-density lipoprotein; SII, platelet count ×neutrophil count/lymphocyte count; SIRI, neutrophil count ×monocyte count/lymphocyte count

*, $P<0.05$

The associations between inflammation and GDM

It seems that levels of inflammatory parameters, including neutrophils, lymphocytes and monocyte were closely associated with risk of having GDM. To reveal the association between inflammation and GDM, logistic regression analysis was performed (Table 2). Model 1 was unadjusted for clinical factors and showed that very few inflammatory parameters were associated with the risk of GDM. After adjusting for potential confounding factors, including fasting plasma glucose, HbA1c, RBC, TG in Model 2 and Model 3, the risk for development of GDM in women with lower monocyte count or MHR during early pregnancy increased.

Overall, we observed a significant association between monocyte counts, MHR and the risk of the development of GDM, and the risk tended to decrease with increasing levels of monocyte counts and MHR.

The dose-response relationship between monocyte counts/MHR and the risk of GDM

The dose-response relationship between monocyte counts/MHR and the risk of GDM is shown by cure fitting. After adjusting for confounders, the restricted cubic spline function was fitted to present the nonlinear association (Fig. 1A and B). The results showed that the incidence of GDM increased significantly with decreased monocyte count and MHR.

Sub-group analysis of logistic regression modelling

Subgroup analysis of logistic regression modelling based on demographic factors and presentation of subgroup correlations showed that decreased monocyte count/MHR levels were particularly risk factors for the development of GDM in a population of pregnant women with family history of diabetes (Fig. 2a & b).

The relationship between monocyte counts/MHR, and OGTT values

To further evaluating the relationship between monocyte counts/MHR, and OGTT values (FBG, 1 h BG, 2 h BG) for predicting GDM, we also performed the RCS plots (Fig. 3).

Table 2 Logistic analysis of incidence of GDM

			Model 1		Model 2		Model 3	
	group	ranges	OR (95CI%)	*P*	OR (95CI%)	*P*	OR (95CI%)	*P*
Neutrophils	Q1	≤ 6.17	1 (Reference)		1 (Reference)		1 (Reference)	
	Q2	6.18 ~ 7.22	1.00(0.88 ~ 1.15)	0.99	0.95(0.83 ~ 1.10)	0.49	0.90(0.78 ~ 1.04)	0.15
	Q3	7.23 ~ 8.36	1.02(0.98 ~ 1.17)	0.74	0.95(0.83 ~ 1.10)	0.46	0.86(0.75 ~ 0.10)	0.05
	Q4	≥ 9.37	1.07(0.94 ~ 1.23)	2.99	1.02(0.89 ~ 1.17)	0.78	0.90(0.78 ~ 1.04)	0.14
Lymphocytes	Q1	≤ 1.65	1 (Reference)		1 (Reference)		1 (Reference)	
	Q2	1.66 ~ 1.93	1.06(0.93 ~ 1.22)	0.40	0.99(0.86 ~ 1.15)	0.93	0.96(0.83 ~ 1.10)	0.54
	Q3	1.94 ~ 2.26	1.05(0.91 ~ 1.20)	0.52	0.97(0.84 ~ 1.12)	0.66	0.91(0.79 ~ 1.05)	0.21
	Q4	≥ 2.27	1.17(1.03 ~ 1.34)	0.02*	0.99(0.86 ~ 1.14)	0.89	0.89(0.77 ~ 1.02)	0.10
Monocyte	Q1	≤ 0.58	1 (Reference)		1 (Reference)		1 (Reference)	
	Q2	0.59 ~ 0.70	0.88(0.78 ~ 1.00)	0.05	0.83(0.72 ~ 0.95)	0.07	0.80(0.70 ~ 0.91)	0.001*
	Q3	0.71 ~ 0.84	0.82(0.72 ~ 0.93)	0.002*	0.75(0.65 ~ 0.86)	<0.001*	0.71(0.62 ~ 0.81)	<0.001*
	Q4	≥ 0.85	0.78(0.69 ~ 0.90)	< 0.001*	0.72(0.63 ~ 0.83)	<0.001*	0.66(0.58 ~ 0.76)	<0.001*
MHR	Q1	≤ 0.29	1 (Reference)		1 (Reference)		1 (Reference)	
	Q2	0.30 ~ 0.37;	0.85(0.74 ~ 0.96)	0.20	0.82(0.71 ~ 0.94)	0.005*	0.77(0.67 ~ 0.89)	<0.001*
	Q3	0.36 ~ 0.45	0.85(0.75 ~ 0.97)	0.15	0.79(0.69 ~ 0.91)	0.001*	0.73(0.63 ~ 0.84)	<0.001*
	Q4	≥ 0.46	0.89(0.78 ~ 1.02)	0.09	0.82(0.71 ~ 0.94)	0.003*	0.68(0.59 ~ 0.79)	<0.001*
SII	Q1	≤ 723.40	1 (Reference)		1 (Reference)		1 (Reference)	
	Q2	723.41 ~ 906.68	1.01(0.89 ~ 1.16)	0.84	0.99(0.86 ~ 1.14)	0.86	0.98(0.85 ~ 1.13)	0.82
	Q3	906.69 ~ 1130.69	1.05(0.92 ~ 1.19)	0.52	1.01(0.88 ~ 1.16)	0.90	0.99(0.86 ~ 1.13)	0.83
	Q4	≥ 1130.70	0.99(0.86 ~ 1.31)	0.87	0.92(0.80 ~ 1.06)	0.25	0.90(0.78 ~ 1.03)	0.13
SIRI	Q1	≤ 1.98	1 (Reference)		1 (Reference)		1 (Reference)	
	Q2	1.99 ~ 2.61	0.91(0.80 ~ 1.03)	0.14	0.90(0.79 ~ 1.03)	0.13	0.89(0.77 ~ 1.02)	0.08
	Q3	2.62 ~ 3.39	0.90(0.79 ~ 1.02)	0.11	0.88(0.77 ~ 1.01)	0.07	0.85(0.74 ~ 0.97)	0.02*
	Q4	≥ 3.40	078(0.68 ~ 0.89)	<0.001*	0.80(0.69 ~ 0.98)	0.002*	0.75(0.65 ~ 0.86)	<0.001*

Model 1 adjusted for maternal age, gravida, pre-pregnancy BMI, method of conception, family history of diabetes;

Model 2 adjusted for maternal age, gravida, pre-pregnancy BMI, method of conception, family history of diabetes, Systolic BP, Diastolic BP, fasting plasma glucose, HbA1c;

Model 3 adjusted for maternal age, gravida, pre-pregnancy BMI, method of conception, family history of diabetes, Systolic BP, Diastolic BP, fasting plasma glucose, HbA1c, RBC, TG;

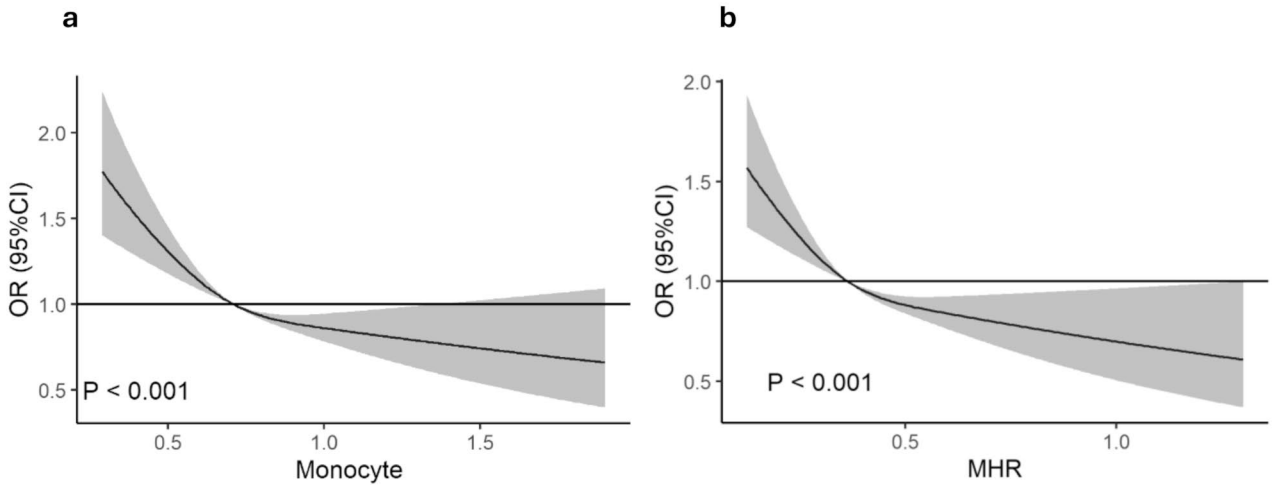

Fig. 1 Nonlinear association between monocyte counts/MHR and the risk of GDM. **A**: monocyte and GDM, **B**: MHR and GDM. Models adjusted for maternal age, gravida, pre-pregnancy BMI, method of conception, family history of diabetes, Systolic BP, Diastolic BP, fasting plasma glucose, HbA1c, RBC, TG

Discussion

In the present study, a total of 15,807 women were included, including 2,355 (14.9%) women diagnosed with GDM. Our study, for the first time, revealed the association between levels of inflammation during early pregnancy and the risk of GDM in a large-scale population in China.

We also compared and screened various inflammatory indices which can be easily measured from peripheral blood, and found that monocyte count and MHR demonstrated significant and effective indices in evaluating the risk of GDM. In this regard, a decreased level of monocyte count and MHR in early pregnancy was associated with higher risk of GDM, particularly among patients with family history of diabetes.

The placenta is an important immune-endocrine organ. The hormone released by placenta, increased with gestational age, plays important role in the etiology of GDM [16]. It has been suggested that there might be an association between GDM with the state of chronic, low-grade inflammation [17], while the increase in placental inflammatory mediatory maybe secondary to infiltration of the uterus by maternal macrophages, which are known to release pro-inflammatory cytokine [18].

In the present study, we used six parameters to evaluate inflammatory status during early pregnancy. Previous studies have confirmed that these inflammatory markers were useful and effective indices in the diagnosis and prognosis of metabolic diseases, including GDM [19]. However, the relationship between circulating inflammatory cells and GDM are much more controversial. Several studies have demonstrated that circulating inflammatory cells were connected with development of GDM. One study investigated the neutrophil count of 258 women with GDM and 1,154 women without GDM, and found that elevated neutrophil count at 4–12 weeks of gestation was an independent risk factor for GDM, with a cut-off value of $5.0*10^9$/L [20]. In a separate cross-sectional study in China, involving patients at 4–20 weeks of gestation, it was shown that lymphocyte count was substantially higher in GDM patients [21]. The inconsistencies in the results of the studies might be due to different populations, study designs and methods used. Our study was a large retrospective cohort study of 15,807 women. Besides, to avoid biased results due to small sample size, our studies fully adjusted for various confounders related to GDM. In our study, although significant difference were observed between GDM and non-GDM group in neutrophils and lymphocytes, no significant association with predictive value of developing GDM in multiple regressive models were found.

Among these circulating inflammatory markers, we observed that monocyte count and MHR might have potential association with GDM based on regression models, possibly because the immune state represented by monocytes seemed to play a more important role in metabolic dysfunction [22, 23].

Monocytes are the main cells of the innate immune system of peripheral blood and are especially important in the maintenance of a normal pregnancy [24]. During normal pregnancy, an increase in the number of monocytes in blood and their activation were observed, and it seems GDM pathophysiology was associated with impaired monocyte profile in the peripheral blood [25]. Thus, the risk of GDM, which is related to insulin signaling and inflammatory responses of monocyte continuously increases with systemic insulin resistance in early pregnancy.

Consistent with our findings, several studies have demonstrated that monocyte count or MHR are associated

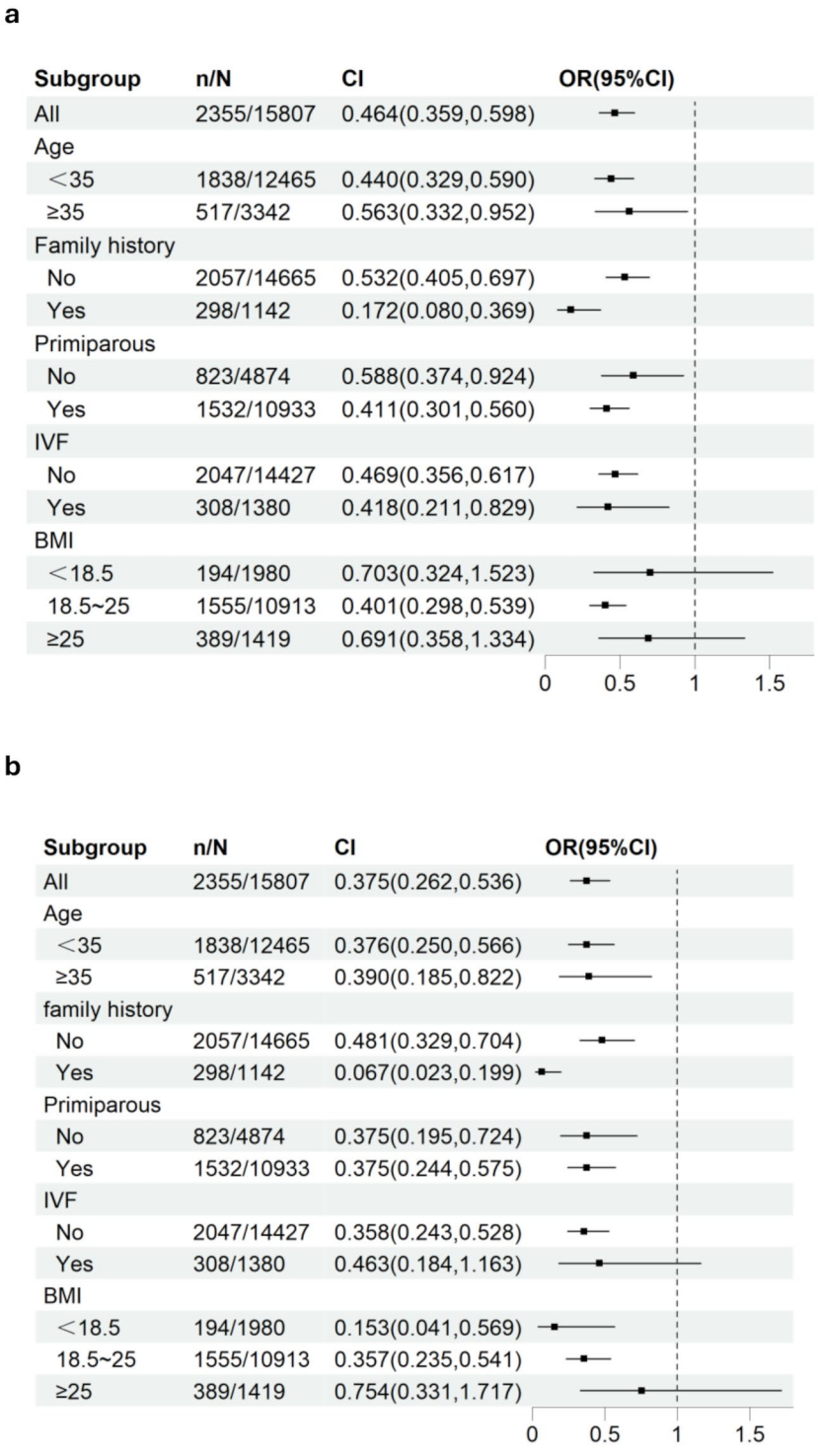

Fig. 2 Forest plot of logistic regression modelling based on demographic factors. **A**: monocyte and GDM, **B**: MHR and GDM. Models adjusted for maternal age, gravida, pre-pregnancy BMI, method of conception, family history of diabetes, Systolic BP, Diastolic BP, fasting plasma glucose, HbA1c, RBC, TG

with GDM. One case-control and cohort study including 1,418 women have shown that decreased monocyte count is associated with GDM development, and that the risk of GDM began to decrease rapidly when monocyte count exceeded $0.48*10^9$/L, indicating that decreased monocyte count may contribute to GDM development by mediating insulin resistance via down regulation of anti-inflammatory factors, up-regulation of inflammatory

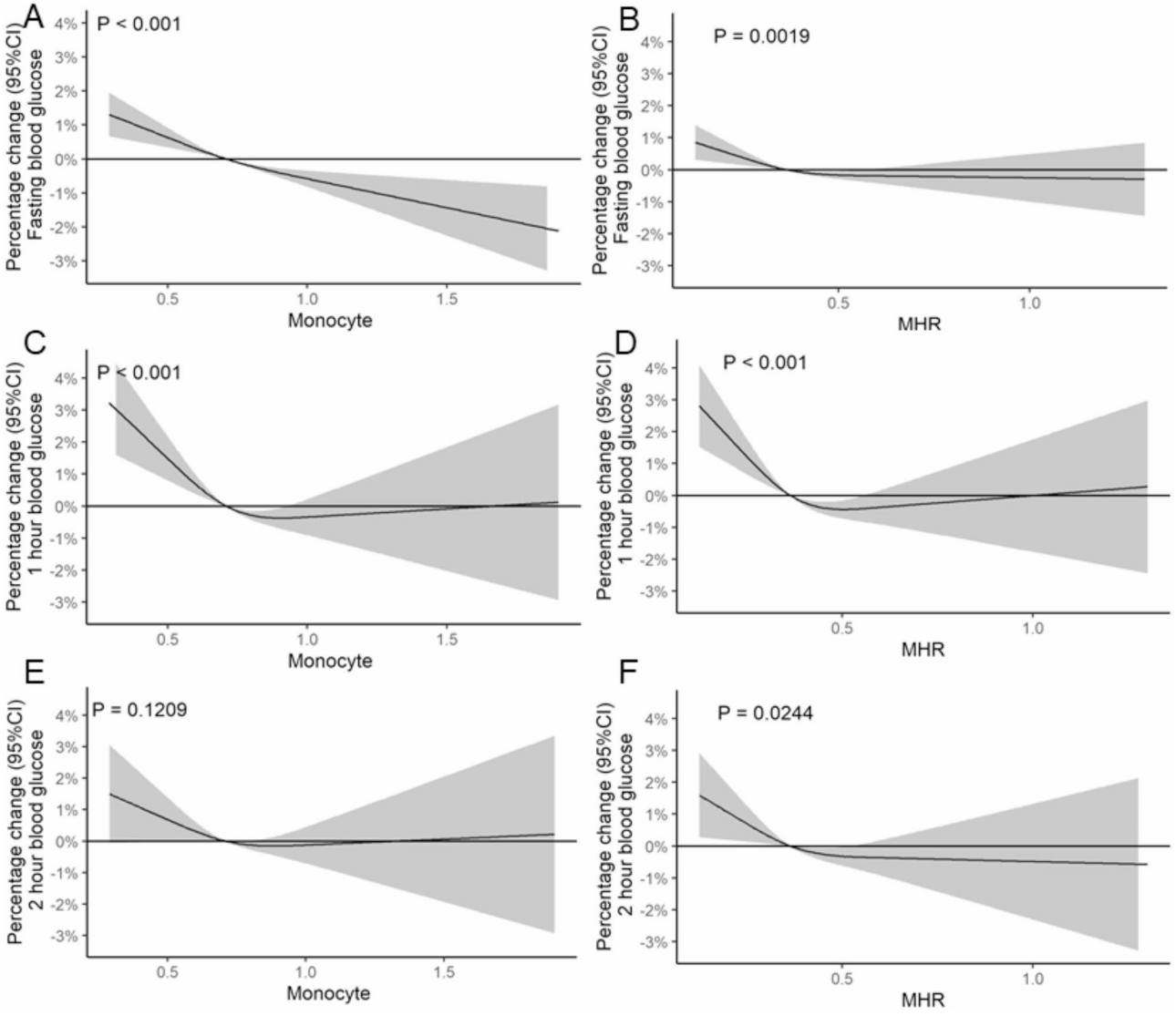

Fig. 3 RCS plots of association of monocyte counts/MHR with FBG, OGTT-1 h BG.OGTT-2 h BG. **A**: monocyte and FBG, **B**: MHR and FBG, **C**: monocyte and OGTT-1 h BG, **D**: MHR and OGTT-1 h BG, **E**: monocyte and OGTT-2 h BG, **F**: MHR and OGTT2-h BG. Models adjusting for maternal age, gravida, pre-pregnancy BMI, method of conception, family history of diabetes, Systolic BP, Diastolic BP, fasting plasma glucose, HbA1c, RBC, TG

factors and changing placenta-derived macrophage differentiation [26].

The genetic variations related to β-cell dysfunction and insulin resistance might also contribute to the development of GDM [27], thus the pregnant women with family history of diabetes got 2.77 to 3.46 times higher risk of developing GDM [28]. We further analyzed the predictive value of monocyte count and MHR in different subgroups, and the results suggest that women with family history of diabetes should pay more attention when they have decreased monocyte count or MHR. Therefore, we hypothesize that among these easily accessible maternal systemic inflammatory indices, both monocyte count and MHR might be potential predictive indices in the development of GDM, particularly among women with family history of diabetes.

As far as we know, this is one of the few reports that analyses the relationship between maternal systemic inflammatory indices from circulating blood cells in early pregnancy and the risk of developing GDM. Previous studies have usually used inflammatory markers, such as IL-1/6 and TNFα, to reflect inflammation levels, which seemed more suitable for molecular research, but difficult to be generalized due to technology and costs. Our finding is of great practical value in trying to use simple and easy methods to predict the risk of GDM in clinical or large-scale population screening.

There were some limitations in this study. Firstly, subjects were drawn from one center, other inflammatory

makers, such as CRP, TNF, and IL, and maternal socio-economic factors were absent from the records, which may have led to biased results. Secondly, the literature on the potential mechanism of the inflammatory indices are limited, therefore, more studies are required in the future.

Conclusion

The present study revealed that in early pregnancy, decreased monocyte count and MHR are possibly associated with an increased risk for developing GDM, which provides a new perspective on predicting GDM.

Abbreviations

GDM	Gestational diabetes mellitus
MHR	Monocyte-to-high density lipoprotein ratio
SII	Systematic immune inflammation index
SIRI	Systemic inflammation response index
IADPSG	International Association of Diabetes in Pregnancy Study Group
FBG	Fasting blood glucose
BG	Blood glucose
BMI	Body mass index
BP	Blood pressure
DM	Diabetes mellitus
OGTT	Oral glucose tolerance test
TC	Total cholesterol
TG	Triglyceride
LDL	Low-density lipoprotein
HDL-C	High-density lipoprotein-cholesterol
RBC	Red blood cell
WBC	White blood cell

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Not applicable.

Author contributions

All authors contributed to the study conception and design. Material preparation, data collection and analysis were performed by Jingbo Qiu, Rui Song, Lei Chen and Dongjian Yang. The first draft of the manuscript was written by Jingbo Qiu, Weiwei Cheng and Wei Zhu. All authors commented on previous versions of the manuscript. All authors read and approved the final manuscript.

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Data availability

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

Declarations

Ethics approval and consent to participate

Ethical approval for the current study was obtained from Clinical Research Ethics Committee of the International Peace Maternity and Child Health Hospital, School of Medicine, Shanghai Jiao Tong University [(GKLW)2018-29]

Consent for publication

Not applicable.

Competing interests

The authors declare no competing interests.

Consent to participate

Not applicable.

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