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Early pregnancy hemoglobin is associated with the risk of gestational diabetes mellitus: a retrospective cohort study

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Abstract

This study aimed to determine the association between hemoglobin (Hb) concentration and Hb change, during early to mid-pregnancy with the risk of gestational diabetes mellitus (GDM). This was a clinic-based retrospective cohort study of 1951 healthy pregnant women (18–45 years old) with a singleton gestation attending antenatal care at government health clinics. Hb concentration at first prenatal visit and each trimester was extracted from the antenatal cards. Hb changes from first prenatal visit to first and second trimester as well as from second to third trimester were calculated. Multivariate logistic regression was used with adjustment for covariates. Women with GDM had significantly higher Hb concentrations (Hb 1) at first prenatal visit (< 12 weeks) compared with non-GDM women (11·91 g/dl *v.*11·74 g/dl). Hb 1 and Hb changes (Hb change 2) from first prenatal visit to the second trimester (23–27th weeks) were significantly associated with GDM risk, with an adjusted OR of 1·14 (95 % CI 1·01, 1·29) and 1·25 (95 % CI 1·05, 1·49), respectively. The significant associations between Hb 1 and Hb change 2 with the risk of GDM were found among non-Malays, overweight/obese and women aged 35 years and above. Women with higher Hb concentrations in early pregnancy were at higher risk of GDM, and such association was significant among women aged 35 years and above, non-Malays and overweight/obese. This raises a potential concern for elevated Fe status in early pregnancy as a risk factor of GDM among Fe-replete women.

Key words: **Hg: Hb change: Gestational diabetes mellitus: Pregnancy**

Gestational diabetes mellitus (GDM), an increasingly common type of hyperglycaemia during pregnancy, follows the increasing trends of obesity and type 2 diabetes mellitus (T2DM). Globally, the prevalence of GDM is on the rise, particularly in the developing countries. The reported prevalence ranged from 1 to 14 %, depending on the study design and definition of GDM[1]. The Malaysian National Obstetric Registry (NOR) reported that the number of GDM cases reported in 2015 (11 111 cases) showed an increase when compared with 2009 with 6829 cases (9·3 %) of all reported pregnancies[2]. Advanced maternal age, height, parity, ethnicity, BMI, family history of diabetes, history of GDM and history of other insulin-resistant conditions, such as metabolic syndrome and polycystic ovary syndrome, are established risk factors for GDM[3,4].

Evidence suggests that the primary defect in the pathogenesis of GDM is relatively diminished insulin secretion coupled with pregnancy-induced insulin resistance[5]. There is increasing evidence to support that Fe status may play a role in the development of GDM[6,7]. Previous retrospective and prospective studies found that high maternal Hb (more than 13 g/dl) in the first trimester[8], and at 28–30th weeks of gestation[9] are independent risk factors for GDM. Similarly, systematic review and meta-analysis studies of Fe status and risk of GDM also showed that higher Hb or ferritin concentrations in the first and third trimester, as well as higher dietary heme intake, were associated with an increased risk of GDM[6,10]. A recent review on Fe status, Fe intake and pregnancy outcomes found that Fe supplementation in Fe-deficient women in early pregnancy appears to protect against adverse outcomes; conversely, Fe supplementation in

Abbreviations: AOR, adjusted odds ratios; FPG, fasting plasma glucose; GDM, gestational diabetes mellitus; 2hPG, 2-h plasma glucose; MCH, maternal child health; MOH, Ministry of Health; NOR, National Obstetric Registry; OGTT, oral glucose tolerance test; T2DM, type 2 diabetes mellitus.

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Fe replete women (Hb > 13·2 g/dl) during second trimester leads to even higher Hb concentrations, greater risk of fetal growth restriction and GDM[11].

The association between excess Fe and GDM is biologically plausible, although the underlying mechanisms are still unclear. Fe overload could promote the formation of hydroxyl radicals and subsequently oxidative stress[12]. Elevated oxidative stress could damage pancreatic beta cells and consequently impair insulin synthesis and secretion[13–15]. In the liver, high Fe stores may induce insulin resistance via impaired insulin signalling, as well as by attenuating the capacity of the liver to extract insulin. Excess Fe deposition in the muscles may enhance non-esterified fatty acids oxidation and interfere with glucose uptake or disposal. Fe accumulation may also impair the action of insulin and interferes with insulin-induced glucose transport in the adipocytes[16,17].

Although the evidence on the association between Fe status and risk of GDM is somewhat convincing, most of the previous studies have been limited to Western countries. At present, there is increasing evidence on the association between Hb concentration at a single time period of pregnancy and GDM risk[5,10,18] but limited information on associations between Hb concentration at different trimester of pregnancy[14] and changes in Hb during pregnancy[19] with risk of GDM[8,14]. As GDM is on the rise in Malaysia, it is important to identify potential preventable risk factors. With the hypothesis that higher Fe status during pregnancy is associated with higher risk of GDM, this study aimed to determine whether Fe status, as indicated by Hb concentration and Hb change, during pregnancy is associated with the risk of GDM and to identify the cut-off value of Hb associated with GDM risk.

Materials and methods

This was a retrospective cohort study of healthy, non-diabetic pregnant women with a singleton gestation attending antenatal care at Senawang Maternal Child Health (MCH) clinic and Ampangan MCH clinic between January 2010 and December 2012. The sample size for this study was estimated using a statistical formula for retrospective cohort study[20]. Based on the assumption that women with higher Hb level are at a higher risk of GDM, the adjusted OR of developing GDM of 1·73 among women with Hb > 13·0 g/dl was applied to the sample size calculation[21]. A minimum of 1864 pregnant women were required for this study to achieve 80 % statistical power at 5 % significance to detect a significant association. The exclusion criteria for this study were women aged < 18 years old and women with abnormal glycaemia. Based on the Perinatal Care Guideline[22], as age < 18 years old is not a risk factor for GDM, women in this age group do not undergo a standard 2-h 75 g oral glucose tolerance test (OGTT) at 28 to 32nd weeks of gestation. Abnormal glycaemia was defined as having either or both fasting plasma glucose (FPG) ≥ 5·6 mmol/l or 2-h plasma glucose (2hPG) ≥ 7·8 mmol/l during OGTT in the early pregnancy[22]. A total of 2209 of pregnant women were initially identified for potential inclusion in this study. Two hundred and fifty-eight women were subsequently excluded from the analysis, based on age < 18 years old (*n* 16) and abnormal glycaemia (*n* 242). Subsequently, 1951 pregnant women were included in the final analysis (Fig. 1).

The source of data was antenatal clinic cards of pregnant women registered between January 2010 and December 2012. The clinic cards contained the patient's background, antenatal care information, demographic characteristics and obstetric history. Data were extracted from the antenatal clinic cards by trained enumerators.

The study protocol was approved by the Medical Research Ethics Committee (MREC), Universiti Putra Malaysia (UPM/FPSK/100–9/2-MJKEtika) and the Medical Research Ethics Committee (MREC), Ministry of Health Malaysia (KKM/NIHSEC/08/0804/P12–613). Informed consent was not required due to the retrospective study design, and all participants were anonymised before data analysis.

Haemoglobin

Data on Hb concentration at first prenatal visit as well as each trimester were extracted from the antenatal cards. Blood samples

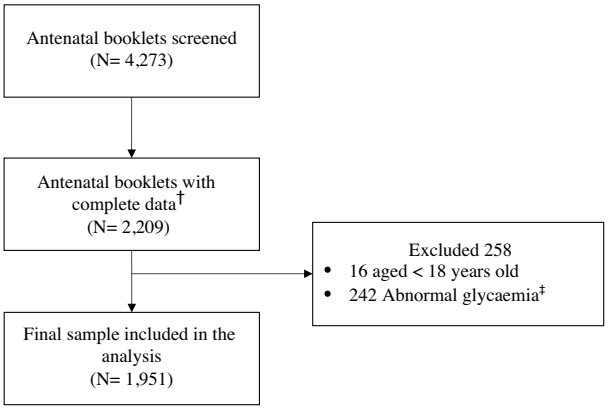

Fig. 1. Sampling procedure. †Complete data – complete all antenatal care visits. ‡Abnormal glycaemia was defined as either or both fasting plasma glucose ≥ 5·6 mmol/l or 2 h postprandial glucose ≥ 7·8 mmol/l that determined by an oral glucose tolerance test[22].

were collected by staff nurses at each antenatal visit for various biochemical parameters, including Hb[22]. The first sample was collected before 12 weeks of gestation (Hb 1–< 12th weeks of gestation), the second sample (Hb 2) between 12 and 14 weeks of gestation, the third sample (Hb 3) between 28 and 32 weeks of gestation and the fourth sample (Hb 4) between 37 and 40 weeks of gestation. Hb change 1 was defined as the difference between Hb 1 and Hb 2 (change in the first trimester). Hb change 2 was defined as the difference between Hb 1 and Hb 3 (change from early pregnancy to the time of GDM diagnosis), while Hb change 3 was defined as the difference between Hb 2 and Hb 3 (change in the second trimester).

Maternal glucose level

All pregnant women were required to take a standard 2-h 75 g OGTT in between 28th and 32nd week of gestation[22]. GDM was diagnosed if either or both FPG ≥ 5·6 mmol/l or 2hPG ≥ 7·8 mmol/l according to the Ministry of Health Malaysia guideline[22].

Anthropometric measurements

Height and weight at the first prenatal visit were obtained from the antenatal cards. Height was categorised as < 1·56 m and ≥ 1·56 m. BMI at the first prenatal visit was calculated as weight at the first prenatal visit (kilogram) divided by the square of height (m^2) and further categorised into four groups: 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)[23].

Other variables

Information on demographic characteristics and obstetric history were obtained the antenatal cards. The variables were classified as follows: age (≤ 35, > 35 years old), ethnicity (Malay, others), education (lower-secondary, others), occupation (housewife, working) and parity (≤ 1, > 1).

Statistical analysis

All analyses were performed using SPSS version 25. Exploratory data analysis was conducted on all variables of interest. Normality of continuous data was estimated by skewness and kurtosis test, and homogeneity of variances was tested using the Levene's test. As all continuous variables were normally distributed, no data transformation was performed. Basic descriptive statistics were generated such as means and standard deviations for the continuous variables, while frequency and percentage distribution for categorical variables. χ^2 test for categorical variables and generalised linear mixed-effects models for continuous variables were used to compare Hb concentrations and Hb change between GDM and non-GDM (fixed effects) with the variable clinic as random effect. The mean Hb concentration from early pregnancy to the third trimester of pregnancy between GDM and non-GDM was plotted.

Multivariable logistic regression models were performed to estimate OR and 95 % CI for associations between Hb concentrations (continuous and categorical variables) and the risk of GDM, adjusted for the confounders. Non-GDM was used as the reference group with covariates included age (continuous), parity (continuous), ethnicity (categorical), BMI at first prenatal visit (continuous) and gestational weeks at OGTT performed (continuous). Separate models were performed to examine the associations between each Hb measure with GDM risk. Analyses for interaction effects between maternal characteristics (age, ethnicity, parity, height and BMI at first prenatal visit) and Hb concentrations in relation to the risk of GDM were performed. As age, ethnicity and BMI at first prenatal visit showed an interaction effect with Hb concentration, the associations between Hb concentration and risk of GDM were further stratified by age, ethnicity and BMI at first prenatal visit. Additionally, logistic regression model identified the Hb concentration categories at the first prenatal visit that was associated with the risk of GDM. Hb concentration at the first prenatal visit (Hb 1) was divided into quartiles (Q1, Q2, Q3 and Q4) using the visual binning tool in SPSS. Crude and adjusted odds ratios (AOR) were presented with statistical significant value was set at P-value of < 0·05 for main effects and interactions.

Results

Characteristics of subjects

Table 1 compares the characteristics of non-GDM (n 1696) and GDM (n 255) women. The age range of women in the sample was 18 to 45 years old with GDM women (30·23, SD 4·67 years) were significantly older than non-GDM women (28·91, SD 4·38 years). Majority of the women were Malay (80·0–84·4 %), had lower-secondary education level (59·6–61·2 %) and currently employed (60·8–61·0 %). GDM women had higher mean of parity (1·54, SD 1·42) than non-GDM women (1·41, SD 1·29). More than half of GDM women (51·3 %) were overweight/obese; meanwhile, most of non-GDM women (46·6 %) had normal BMI at first prenatal visit. GDM women had significantly higher Hb at first prenatal visit (Hb 1) (11·91, SD 1·20 g/dl) and Hb change from first prenatal visit to second trimester (Hb change 2) (1·11, SD 0·07 g/dl) compared with non-GDM women (Hb 1 = 11·74, SD 1·14 g/dl; Hb change 2 = 0·91, SD 0·02 g/dl). No significant differences were observed in Hb 2, Hb 3, Hb 4, Hb change 1 and Hb change 3 between GDM and non-GDM women.

The mean Hb concentration at each trimester of GDM and non-GDM women is shown in Fig. 2. Overall, both GDM and non-GDM women had the highest Hb concentration at the first prenatal visit. Hb concentration in both groups further decreased until the second trimester but increased in the third trimester. Despite a similar trend of Hb concentration, GDM women showed significantly higher Hb concentration at the first prenatal visit (GDM = 11·91 g/dl; non-GDM = 11·74 g/dl, P < 0·05) compared with non-GDM women. There were non-significant differences in Hb concentration at the first trimester (GDM = 11·70 g/dl; non-GDM = 11·59 g/dl, P > 0·05) and third trimester (GDM = 11·24 g/dl; non-GDM = 11·16 g/dl, P > 0·05) between GDM and non-GDM women.

Table 1. Characteristics of women with gestational diabetes mellitus (GDM) and non-GDM (Number and percentages; mean and standard deviations, *n* 1951)

	GDM (*n* 255)†		Non-GDM (*n* 1696)		
	Mean or *n*	SD or %	Mean or *n*	SD or %	*P*-value
Age (years)	30·23	4·67	28·91	4·38	0·001**
< 35	205	80·4	1518	89·5	
≥ 35	50	19·6	178	10·5	
Ethnicity					
Malay	204	80·0	1432	84·4	0·07
Non-Malay	51	20·0	264	15·6	
Education (years)					
Lower-secondary	156	61·2	1010	59·6	0·62
Others	99	38·8	686	40·4	
Occupation					
Housewife	100	39·2	661	39·0	0·94
Others	155	60·8	1035	61·0	
Parity	1·54	1·42	1·41	1·29	0·13
Height (m)	1·56	0·06	1·56	0·06	0·21
BMI at first prenatal visit (kg/m^2)	25·63	5·14	24·63	5·53	0·01*
Underweight (< 18·5)	19	7·5	188	11·1	
Normal (18·5–24·99)	105	41·2	791	46·6	
Overweight/obese (≥ 25·00)	131	51·3	717	42·3	
Hb (g/dl)					
Hb 1	11·91	1·20	11·74	1·14	0·03*
Hb 2	11·70	1·02	11·59	1·02	0·12
Hb 3	10·80	0·96	10·83	0·92	0·56
Hb 4	11·24	0·99	11·16	0·96	0·24
Gestational weeks at Hb performed (weeks)					
Hb 1	9·09	1·91	9·01	1·94	0·69
Hb 2	13·17	1·41	13·11	1·43	0·65
Hb 3	27·07	1·56	27·03	1·58	0·61
Hb 4	36·53	2·18	37·05	2·00	0·08
Hb change (g/dl)					
Hb change 1	0·21	0·06	0·15	0·02	0·30
Hb change 2	1·11	0·07	0·91	0·02	0·01*
Hb change 3	0·90	0·06	0·76	0·02	0·07

MOH, Ministry of Health; FPG, fasting plasma glucose; 2hPG, 2-h plasma glucose.
* $P < 0·05$.
† GDM was classified according to MOH criteria, either of both FPG ≥ 5·6 mmol/lor 2hPG ≥ 7·8 mmol/l[22].
Hb 1, Hb at first prenatal visit (< 12th week of gestation); Hb 2, Hb at first trimester (12–14th weeks of gestation); Hb 3, Hb at second trimester (23–27th weeks of gestation); Hb 4, Hb at third trimester (34–38th week of gestation); Hb change 1, Hb 1–Hb 2; Hb change 2, Hb 1–Hb 3; Hb change 3, Hb 2–Hb 3.

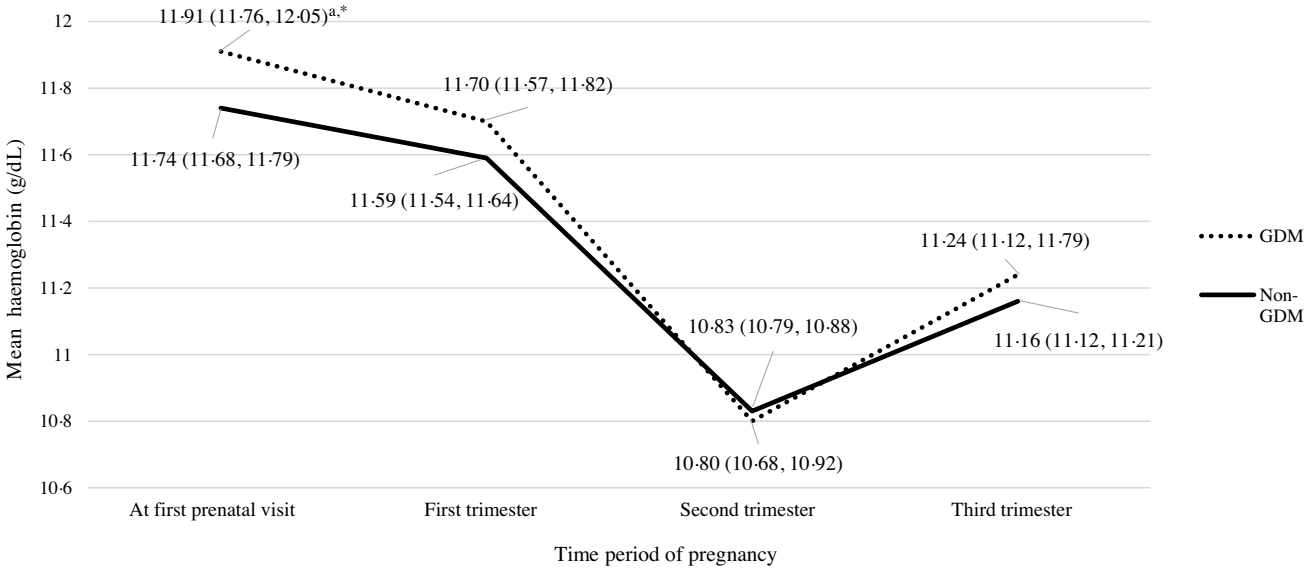

Fig. 2. Mean of Hb concentration at each trimester among women with gestational diabetes mellitus (GDM) and non-GDM groups. At first, prenatal visit (< 12th weeks of gestation); first trimester (12–14th weeks of gestation); second trimester (28–32nd weeks of gestation); third trimester (37–40th weeks of gestation). a*Significant association between GDM and non-GDM in the first prenatal visit, $P < 0·05$.

Table 2. Association between Hb as a continuous variable and the risk of gestational diabetes mellitus (GDM) (Odd ratio and 95 % confidence intervals)

Hb (g/dl)	Crude OR	95 % CI	*P*-value	AOR	95 % CI	*P*-value
Hb 1	1·14	1·01, 1·29	0·03*	1·14†	1·01, 1·28	0·03*
Hb 2	1·11	0·97, 1·26	0·12	1·11†	0·97, 1·26	0·14
Hb 3	0·96	0·83, 1·10	0·56	0·93†	0·80, 1·07	0·31
Hb change 1	1·02	0·85, 1·23	0·85	1·08‡	0·93, 1·26	0·33
Hb change 2	1·25	1·07, 1·47	0·001**	1·25‡	1·09, 1·43	0·001**
Hb change 3	1·17	0·98, 1·39	0·07	1·20‡	0·98, 1·45	0·07
Interaction term§						
Age × Hb 1	1·10	1·00, 1·17	0·001**			
Age × Hb change 2	1·10	1·10, 1·13	0·001**			
Ethnicity‖ × Hb 1	1·03	1·01, 1·06	0·03*			
Ethnicity‖ × Hb change 2	1·46	1·19, 1·80	0·001**			
BMI at first prenatal visit × Hb 1	1·10	1·00, 1·14	0·02*			
BMI at first prenatal visit × Hb change 2	1·10	1·01, 1·15	0·001**			

AOR, adjusted odds ratio; OGTT, oral glucose tolerance test.
Non-GDM group as reference group.
Hb 1, Hb at first prenatal visit (< 12th week of gestation); Hb 2, Hb at first trimester (12–14th weeks of gestation); Hb 3, Hb at second trimester (23–27th weeks of gestation). Hb change 1, Hb 1–Hb 2; Hb change 2, Hb 1–Hb 3; Hb change 3, Hb 2–Hb 3.
* $P < 0·05$,
** $P < 0·001$.
† Adjusted for age, BMI first prenatal visit and gestational weeks at OGTT performed.
‡ Adjusted for age, BMI at first prenatal visit, gestational weeks at OGTT performed and Hb at first prenatal visit.
§ Interaction analyses were performed for age, ethnicity, parity, height and BMI at first prenatal visit. Only significant factor showed in the table.
‖ Ethnicity (Malay *v.* non-Malay).

Associations between Hb concentration and the risk of gestational diabetes mellitus

Table 2 presents the unadjusted OR and AOR and 95 % CI for associations between Hb concentration and the risk of GDM. Hb 1 and Hb change 2 were significantly associated with the risk of GDM. Women with higher Hb at first prenatal visit (AOR = 1·14, 95 % CI 1·01, 1·29) and Hb change 2 (AOR = 1·25, 95 % CI 1·05, 1·49) were significantly at higher risk for GDM compared non-GDM women. Significant interaction effects were found between age, ethnicity and BMI at first prenatal visit with Hb concentration to the risk of GDM. Table 3 further shows the AOR and 95 % CI for associations between Hb concentration and the risk of GDM as stratified by age, ethnicity and BMI at first prenatal visit. The significant associations between Hb 1 and Hb change 2 with the risk of GDM were found among non-Malays, overweight/obese and women aged 35 years and above.

Table 4 identifies the value of Hb that was associated with the risk of GDM. Women in the highest quartile (Q4) of Hb (> 12·5 g/dl) at first prenatal visit (AOR = 1·57, 95 % CI 1·08, 2·30) had significantly higher risk of GDM compared with women in the lowest quartile of Hb.

Discussion

Similar to previous studies[8,10,24], this study supports that a higher early pregnancy Hb concentration was significantly associated with an increased risk of GDM. Body Fe is regulated and dependent on nutritional needs and availability[25]. Although the underlying mechanism of how early Fe status acts as a risk factor for maternal hyperglycaemia is still unclear, the association might be due to the deterioration of endocrine functions by excess Fe that could increase β-cell oxidative stress, thus causing insulin resistance and impaired glucose metabolism[13,26].

The present study showed that the Hb concentration of pregnant women tended to decline from early pregnancy to second trimester. This finding was not surprising as Fe demands increase dramatically throughout pregnancy, with a peak during second trimester in order to support placental and fetal growth[27,28]. This study also found that Hb change from the first prenatal visit to second trimester (Hb change 2) was associated with risk of GDM. Further analyses were performed to determine the associations between Hb change 2 and the risk of GDM among women with higher (Hb > 12·0 g/dl) and lower baseline Hb concentrations (Hb ≤ 12·0 g/dl) (online Supplementary Table 1). For women with higher baseline Hb concentrations, those with decreased Hb concentrations at the second trimester had significantly higher risk for GDM (AOR = 1·27, 95 % CI 1·02, 1·78). Meanwhile, for women with lower baseline Hb concentrations (Hb ≤ 12·0 g/dl), those with increased Hb concentrations at the second trimester were at lower risk for GDM (AOR = 0·89, 95 % CI 0·60, 0·94). The finding that women with higher Hb concentrations at early pregnancy and lower Hb concentrations thereafter were at higher risk for GDM could mean that they were already experiencing oxidative stress, and its consequent damage to pancreatic β-cells that impairs insulin synthesis and secretion. Whether Fe intake from foods or supplements and in the form of heme or non-heme Fe during early pregnancy and into mid-pregnancy contribute to Fe-replete women to be at risk of GDM warrants further investigation.

Similar to the association between excess Fe and T2DM[17,29], elevated Fe, measured as Hb concentration, has been shown to be associated with increased risk of GDM. Previous studies reported that pregnant women with Hb concentrations above 12·5 g/dl had increased risk of developing GDM than those with

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Table 3. Adjusted odds ratios (AOR) and 95 % CI for Hb and risk of gestational diabetes mellitus (GDM) as stratified by age, ethnicity and BMI at first prenatal visit (Odd ratio and 95 % confidence intervals)

	Age (years)†				Ethnicity‡				BMI at first prenatal visit§							
	< 35 (*n* 1723)		≥ 35 (*n* 228)		Malay (*n* 1636)		Non-Malay (*n* 315)		UW (*n* 207)		NW (*n* 896)		OW/OB (*n* 848)	
	AOR	95 % CI	AOR	95 % CI	AOR	95 % CI	AOR	95 % CI	AOR	95 % CI	AOR	95 % CI	AOR	95 % CI
Hb 1	0·96*	0·94, 0·98	1·06**	1·03, 1·10	0·98	0·95, 1·01	1·04*	1·01, 1·07	0·96	0·92, 1·10	0·98	0·97, 1·10	1·05**	1·01, 1·10
Hb change 2	1·11	0·96, 1·26	1·65**	1·34, 2·21	1·09	0·95, 1·25	1·49**	1·21, 1·84	1·08	0·82, 1·44	1·05	0·92, 1·24	1·36**	1·16, 1·60

OGTT, oral glucose tolerance test.
UW, underweight (BMI < 18·49 kg/m^2); NW, normal weight (BMI 18.50–24·99 kg/m^2); OV/OB, overweight/obese (BMI ≥ 25·00 kg/m^2).
The lowest tertile as reference group. Hb 1, Hb at first prenatal visit (< 12th week of gestation); Hb 2, Hb at first trimester (12–14th weeks of gestation); Hb change 2, Hb 1–Hb 3. BMI at first prenatal visit.
* $P < 0·05$.
** $P < 0·001$.
† Adjusted for BMI at first prenatal visit and gestational weeks at OGTT performed.
‡ Adjusted for age, BMI at first prenatal visit and gestational weeks at OGTT performed.
§ Adjusted for age and gestational weeks at OGTT performed.

Table 4. Adjusted odds ratios (AOR) and 95 % CI for risk of gestational diabetes mellitus (GDM) by quartiles of Hb at first prenatal visit

	Hb quartile			
Hb	Q1	Q2	Q3	Q4
Hb 1				
Concentration, g/dl	≤11·1	11·2–11·9	12·0–12·5	>12·5
No. of cases	55	62	63	75
No. of controls	461	466	377	392
AOR†	1·00	1·10	1·38	1·56*
95 % CI		0·77, 1·62	0·93, 1·98	1·08, 2·30

NA, not applicable.
The lowest quartile as reference group. Hb 1, Hb at first prenatal visit (< 12th week of gestation)
* $P < 0·05$.
† Adjusted for age, BMI first prenatal visit and gestational weeks at OGTT performed.

lower Hb concentrations[8,30,31]. Wang *et al.* (2018) further showed that pregnant women with Hb concentrations of 13·0 g/dl and above had increased risk of GDM and the association became more significant when the Hb concentrations exceeded 15·0 g/dl[8]. These finding are supported by the results of a systematic review and meta-analaysis which showed that Hb concentrations between 12·5 and 13·0 g/dl in the first trimester increased the risk of GDM[6]. Additional work is needed to characterise excess Fe during early pregnancy that is associated with risk of GDM. If elevated Hb in early pregnany is confirmed to be a risk factor for GDM, then Hb in the first trimester of pregnancy could serve as a simple screening tool to identify women at risk of developing GDM.

Previous studies consistently reported that maternal age, ethnicity and BMI at first prenatal visit are significantly associated with the risk of GDM[3,8,21,32–40]. The present study found that maternal age, ethnicity and BMI at first prenatal visit had a moderating effect on the association between Hb concentration and risk of GDM. The significant association between early Hb concentration and GDM risk was observed among women aged 35 years old and above, non-Malays and overweight/obese. Normal ageing is associated with the deterioration of endocrine functions such as decreasing β-cell function and insulin sensitivity[41]. Thus, older pregnant women with higher Hb concentration may have further reduced insulin sensitivity that could increase the risk for GDM. In the present study, a higher percentage of non-Malay were overweight/obese (44·7 %) compared with Malays (37·1 %). Increased body fat might increase the development of insulin resistance and further lead to a greater risk of hyperglycaemia[42]. Besides, studies showed that women with high Hb concentrations had higher BMI[43–45], which also suggested that the high Hb concentrations may be a consequence of better nutrient intake as high Hb concentration may reflect higher Fe intake, whether from food or supplements.

The trend of maternal Hb concentration during pregnancy observed in this study is aligned with previous studies that showed Hb starts to decline from the first trimester and reaches the lowest value at the end of the second trimester and then increases in the third trimester of pregnancy[27,46]. This trend may reflect the normal pregnancy physiology in that the total blood volume increases to supply the demand of the new vascular bed and to compensate for blood loss occurring at

delivery[47]. Expansion of plasma volume, rather than actual blood volume expansion to help the blood circulation in the placenta occurs at 6–12 weeks of gestation and further increases and reaches the peak at 24–26 weeks of gestation[48,49]. The increase in plasma volume results in the drop of Hb concentration in the first and second trimester and stabilises thereafter in the third trimester[48].

This study is not without limitations. Data on other indicators of Fe status (e.g. hepcidin, transferrin, soluble transferrin receptor and ferritin) or markers of inflammation (e.g. C-reactive protein) were not available in the antenatal clinic cards of mothers that could support Hb as a risk factor of GDM. These Fe indicators, particularly ferritin, have also been found to be associated with the risk of developing GDM. As the data were retrospective, Fe intake from diet and/or dietary supplement prior and during pregnancy was not assessed. Such information is crucial as Fe status is regulated by dietary Fe and dependent on the type of dietary Fe, such as heme and non-heme. Nevertheless, this study has provided some support to previous research suggesting that Fe status, as measured by Hb, in early pregnancy is associated with the risk of developing GDM.

In conclusion, higher maternal Hb concentration in early pregnancy was significantly associated with higher GDM risk, and this association was significantly higher in women aged 35 years old and above, non-Malays and overweight/obese women. These findings support for a close monitoring of Fe status during pregnancy, particularly among Fe-replete women in early pregnancy. Further investigation is warranted to determine whether Fe from foods or supplements and in the forms of heme or non-heme Fe during early to mid-pregnancy is associated with GDM risk among Fe-replete women.

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Z. M. S. is the project leader of the SECOST study and designed the project with H. Y. Y. H. Y. Y conducted the literature search, data collection, statistical analyses and wrote the first draft of the paper. B. N. M. Y., Z. R., Y. Y. S. T. and J. B. contributed to methodology and resources. Z. M. S. and E. M. van der B. revised the subsequent drafts for important intellectual content and approved the final version of the paper to be published. All authors read and approved the final manuscript.

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Supplementary material

For supplementary material/s referred to in this article, please visit https://doi.org/10.1017/S000711452100502X

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