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Meta-Analysis

First Trimester Hematological Indices in Gestational Diabetes Mellitus: A Meta-Analysis

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Abstract

Context: The association between blood parameters and gestational diabetes (GDM) is of renewed interest. Some blood cell parameters are assumed to be associated with GDM.

Objective: This meta-analysis was performed to assess the association of hematological indices in the first trimester of pregnancy and later development of GDM.

Methods: A comprehensive database search, including PubMed, Web of Science, Epistemonikos, Scopus, Scientific Information Database, and Magiran, was conducted to identify potential peer-reviewed publications. The PECO framework was applied to evaluate the eligibility of all included studies. Standardized mean differences (95% CI), were calculated. Additionally, pooled odds ratios, summary estimates of sensitivity and specificity, positive and negative likelihood ratios, and diagnostic odds ratios (DOR) were determined.

Results: The meta-analysis encompassed 33 studies involving a total of 247 107 pregnant women. Compared to control groups, GDM groups exhibited statistically significantly higher hemoglobin levels (standard mean difference: 0.50, 95% CI: 0.39-0.62), red blood cell (RBC) (0.23, 0.15-0.32), and hematocrit (0.44, 0.34-0.55). The pooled adjusted estimate (aOR:1.02, 1.006-1.03) indicated that the hemoglobin levels were significantly associated with an increased risk of GDM. GDM groups had significantly higher platelet count (0.280, 0.16-0.39) and white blood cells (WBC) counts, as well as (0.482, 0.377-0.58), lymphocytes (0.12, 0.025-0.22), neutrophils (0.541:0.404-0.679), and neutrophil-lymphocyte ratio (0.31, 0.20-0.43). In distinguishing women with GDM from the control group, the DOR was found to be 3.21 for the hemoglobin and 2.94 for the mean platelet volume.

Conclusion: Higher levels of RBC, platelet, and WBC counts during the first trimester of pregnancy were observed in women who subsequently developed GDM compared to control groups.

Key Words: blood parameters, meta-analysis, gestational diabetes (GDM), hemoglobin, platelet, white blood cells (WBC)

Abbreviations: DOR, diagnostic odds ratio; GDM, gestational diabetes; Hb, hemoglobin; Hct, hematocrit; LR+, positive likelihood ratio; LR−, negative likelihood ratio; LYM, lymphocyte ratio; MCH, mean corpuscular hemoglobin; MCHC, mean corpuscular hemoglobin concentration; MCV, mean corpuscular volume; MONO, monocytes; MPV, mean platelet volume; NEUT, neutrophil; NLR, neutrophil to lymphocyte ratio; OGTT, oral glucose tolerance test; OR, odds ratio; PDW, platelet distribution width; PLR, platelet to lymphocyte ratio; PLT, platelet; RBC, red blood cell; ROS, reactive oxygen species; SMD, standard mean difference; WBC, white blood cell.

Gestational diabetes mellitus (GDM) is an adverse pregnancy outcome that affects about 17 million pregnancies worldwide [1]. The estimated global prevalence is almost 10% [2]. GDM is defined as newly developing hyperglycemia during pregnancy [3]. Factors such as advanced maternal age, family history of diabetes, obesity, prepregnancy low physical activity, history of macrosomia in previous pregnancy, and history of GDM in previous pregnancy are well established predisposing risk factors for GDM [4-8]. Placental hormones (including progesterone and estrogen), chronic inflammation, and genetic and epigenetic alterations may be the main drivers of developing GDM [9]. GDM carries adverse short-term and long-term health outcomes for both mother and her child [5, 10-12].

There is variation in GDM diagnosis criteria, and in different countries various criteria have been adopted [13]. The most recommended method of diagnosing GDM is to use an oral glucose tolerance test (OGTT) between 24 and 28 gestational weeks, as recommended by most guidelines [13]. However, diagnosis and

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management of GDM before 20 weeks not only can prevent diabetes-related complications but also may have significant economic benefits [14, 15]. Different biomarkers, including adiponectin, adipocyte fatty acid binding protein, betatrophin, C-reactive protein, cystatin-C, and delta-neutrophil index are the most frequently studied biomarkers that can differentiate GDM status from normoglycemic status [16]. Furthermore, additional biomarkers, including inflammatory markers, fatty acids, amino acid profile, hormones involved in energy homeostasis, and various blood parameters are recognized as predictors of GDM [17]. However, not all biomarkers are suitable for early detection of GDM [17]; moreover, the early identification of GDM remains a challenge and is an area of ongoing research among scientists [18].

The relationship between hematological parameters and GDM has garnered renewed interest in recent research. Numerous studies have documented hematological alterations in women diagnosed with GDM when compared to healthy pregnant women. Research indicates that various blood parameters, including hemoglobin, hematocrit, red blood cell (RBC) indices, platelet count, white blood cells, lymphocytes, neutrophils, and monocytes exhibit significant variations in women with GDM [19]. For instance, elevated white blood cell counts and altered hemoglobin concentrations have been implicated as potential biomarkers for GDM, suggesting a link between inflammatory responses, glucose metabolism during pregnancy, and microvascular complications of diabetes mellitus [20].

Blood count assessment is a cost-effective, practical, and readily accessible diagnostic tool [21]. This systematic review and meta-analysis aimed to synthesize the current evidence regarding the association between various blood parameters and GDM.

Methods

The systematic review and meta-analysis followed the last version of the guidelines of the Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) statements and Meta-analysis Of Observational Studies in Epidemiology (MOOSE) [22, 23]. Advanced searching of databases (PubMed, Web of Science, Epistemonikos, Scopus, Scientific Information Database [SID], and Magiran) was performed for potential peer-reviewed publications from database inception to May 2024. There was restriction to English and Persian language and an absence of any time restriction.

The search was conducted using combination of searching terms related to the gestational diabetes mellitus and blood parameters (Supplementary Table S1) [24].

In addition, references from pertinent studies were thoroughly examined to identify any additional research that may be relevant to the topic at hand. All output of searches in databases were included in Endnote X7, and after removing duplicates, title-abstract screening of the remaining records was proceeded. Then the full text of eligible articles was assessed.

Eligibility Criteria

The study assessed the various blood parameters among women diagnosed with GDM in comparison to those without the condition. The PECO framework was used to assess the eligibility of all included studies:

- Population: pregnant women
- Exposure: Blood parameters in first trimester of pregnancy
- Comparison: pregnant women without GDM
- Outcome: Mean (SD)/odds ratio and 95% CI/sensitivity and specificity of blood parameters associated with development of GDM

To be included in our study: (i) studies had cross-sectional, case-control, prospective, or retrospective cohort designs; (ii) studies had a control group; and (iii) studies had to report at least one of the blood parameters in the first trimester of pregnancy.

Data Extraction

In the next step, selected studies were included in the data extraction process. The extracted variables included: first author, years, country, GDM diagnosis criteria, sample size, mean (SD)/odds ratio and 95% CI/sensitivity and specificity of blood parameters that are associated with development of GDM.

Methodological Quality Assessment

We used the Newcastle-Ottawa scale to assess the quality of studies [25]. Selection, comparability, and outcome/exposure in all studies were assessed and rated for cross-sectional, case-control, and cohort studies separately. The final score has 3 grades: high quality (7-9), fair quality (4-6), and low quality (0-3). Any disagreement was resolved through discussion with a third reviewer.

Data Analysis

The analysis was carried out with MedCalc® version 22.032 and Stata Version 13 (Stata Corporation). We also used an updated version of Meta-DiSc 2.0 for meta-analysis of diagnostic test accuracy data [26]. For continuous data, the standardized mean differences (SMDs) and their corresponding 95% CIs were calculated. For the purpose of pooling odds ratios (ORs), the OR was converted to effect size by using their natural logarithms. These logarithmic numbers and their corresponding 95% CI were used to calculate the standard errors (SEs).

The assessment of publication bias was made using Egger's and Begg's statistics. To assess heterogeneity, the I^2 index was utilized. Mild heterogeneity is indicated by I^2 values below 25%, moderate heterogeneity is indicated by I^2 values between 25% and 50%, and significant heterogeneity is indicated by I^2 values above 50%. A random-effects model was used in heterogeneous studies when the I^2 was >50%. In absence of heterogeneity, a fixed-effect model was applied. In order to identify potential sources of heterogeneity, sensitivity analysis was performed by omitting each study one time. If one study is found to be a significant contributor to heterogeneity, it was excluded from the analysis and the overall findings were recalculated. For studies with reported data on diagnostic accuracy, summary estimates of sensitivity, specificity, positive and negative likelihood ratios (LR+ and LR−), and diagnostic odds ratio (DOR) with their 95% CI were assessed.

Results

Study Selection

Initially, 8537 articles were discovered through a search of electronic databases (PubMed, Web of Science, Epistemonikos, Scopus, SID, and Magiran) and manual search of references. Subsequently, 5182 were removed through a thorough scanning

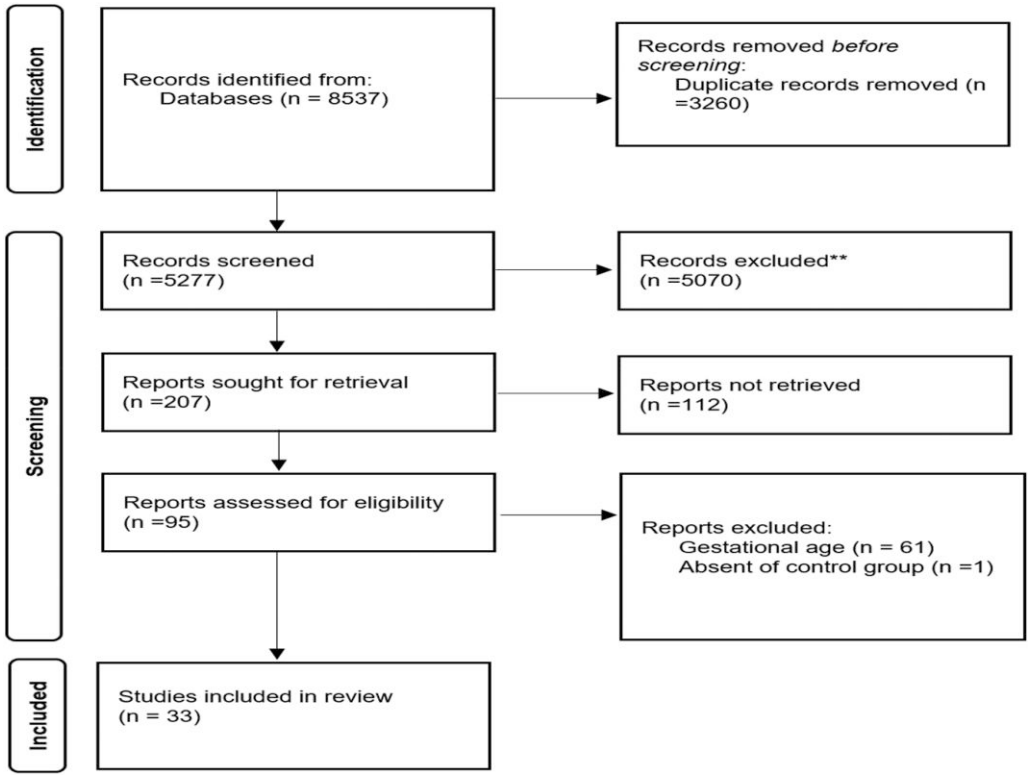

Figure 1. Study selection diagram.

of titles and abstracts. Moreover, the full text of 95 articles was assessed for determination of eligibility. Ultimately, 33 articles fulfilled the predefined inclusion criteria and were included in the final analysis. Figure 1 presents a comprehensive flow chart illustrating the study selection process (Fig. 1).

Characteristics of the Included Studies

A total of 247 107 pregnant women, including 61 503 diagnosed with GDM and 185 604 without GDM, participated in the included studies. About half of the included studies (47.4%) used The International Association of Diabetes and Pregnancy Study Groups criteria. Almost a quarter of them used Carpenter and Coustan criteria (26.3%), and the rest of studies used other criteria, including from the World Health Organization (5.3%), The American Diabetes Association (5.3%), Ministry of Health Malaysia (7.3%), National Finnish Current Care guidelines (2.6%), Guidelines for Diagnosis and Treatment of Diabetes in Pregnancy (2014) in China (2.6%), and ICD10 (2.6%). More than three-quarters of the included articles were conducted in Asia (29 studies), followed by Africa (2 studies), and Europe (2 studies). Details of included studies are described in Supplementary Tables S2-S6 [24]. Of 33 included studies 23 had cohort design, and 9 of them were case-control studies, and 1 cross-sectional. According to the Newcastle-Ottawa scale, more than two-thirds of the included studies were high quality, as demonstrated in Supplementary Fig. S1 [24].

Pooled Results

Erythrogram and GDM

Of the 33 studies, 26 studies reported mean (SD) of hemoglobin in their studies. Standardized mean differences (SMDs) with 95% CIs were calculated for this parameter. In all calculations, a random-effect statistical model was employed to estimate the pooled SMD. Compared with control groups, GDM groups demonstrated significantly higher hemoglobin (Hb) levels (SMD: 0.508; 95% CI: 0.390 to 0.627), RBC (SMD: 0.237; 95% CI: 0.150 to 0.325), and hematocrit (Hct) (SMD: 0.449; 95% CI: 0.343 to 0.555). The mean corpuscular volume (MCV), mean corpuscular hemoglobin (MCH), and mean corpuscular hemoglobin concentration (MCHC) levels were not significantly different between women with GDM and those without GDM (Fig. 2A–2G). There was heterogeneity in the studies, with I^2 values ranging from 26.17% to 99.85% (Table 1).

In this meta-analysis, the pooled crude OR of Hb was calculated to be 1.037 (95% CI: 1.017-1.057, $I^2 = 78.9\%$, [$P = .001$]); the pooled adjusted estimate yielded an OR of 1.021 (95% CI: 1.006-1.036; $I^2 = 70.6\%$), indicating that Hb levels are significantly associated with an increased risk of GDM.

Platelets measurements and GDM

Women diagnosed with GDM had significantly higher platelet (PLT) counts compared to the control groups (SMD: 0.280; 95% CI: 0.162 to 0.397; $P < .001$; I^2: 94.96%; Fig. 3A). However, mean corpuscular hemoglobin concentration (MPV) (SMD: 0.0825; 95% CI: 0.319 to 0.484; $P = .403$; I^2: 96.18%; Fig. 3B) and platelet distribution width (PDW) (SMD: 0.185; 95% CI: −0.169 to 0.539; $P = .306$; I^2: 92.38%; Fig. 3C) levels were not significantly different between these 2 groups. In all calculations, a random-effect statistical model was employed to estimate the SMD pooled (Table 1).

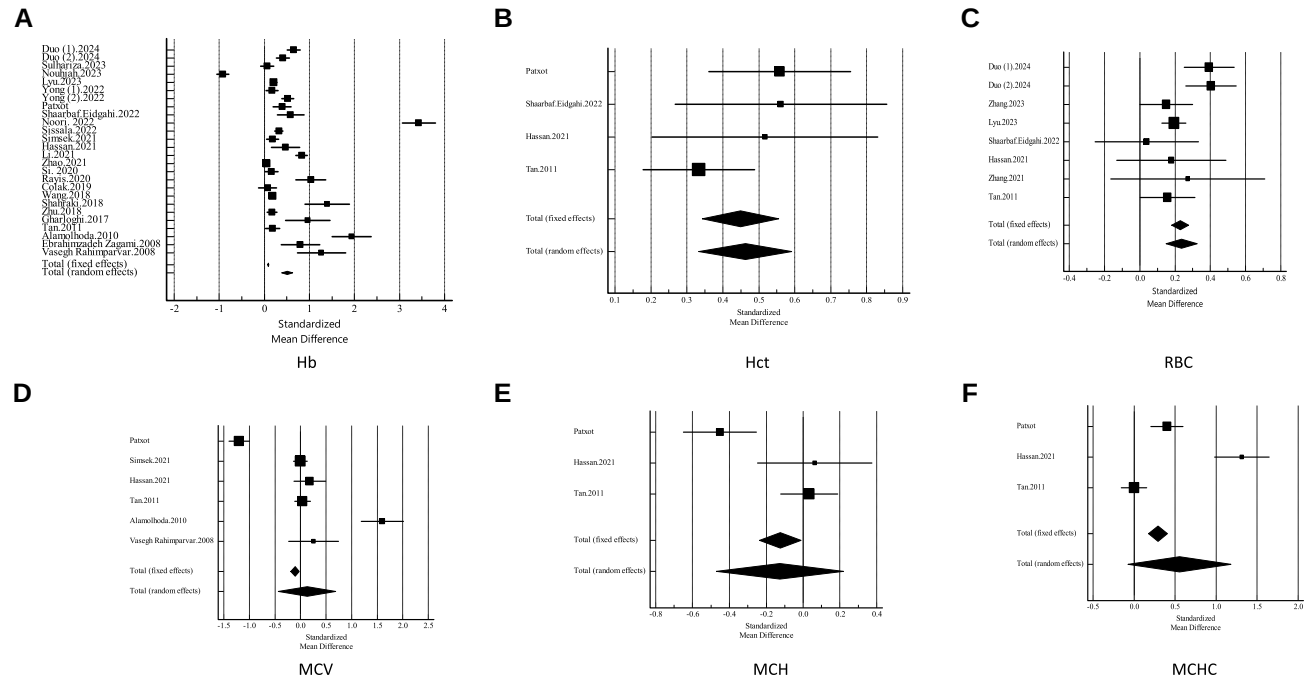

Figure 2. Forest plot of A, hemoglobin (Hb); B, hematocrit (Hct); C, red blood cells (RBC); D, mean corpuscular volume (MCV); E, mean corpuscular hemoglobin (MCH); and F, mean corpuscular hemoglobin concentration (MCHC).

Table 1. Pooled standard mean differences of hematological parameters, heterogeneity, and publication bias results

Variable	Study	N1	N2	Total	SMD	95% CI	*P*	Test for heterogeneity		Publication bias	
								I^2 (inconsistency)	*P* value	Egger test	Begg test
Hb	26	59 877	176 736	236 613	0.508	0.390 to 0.627	<.001	97.75%	$P < .0001$	$P = .0017$	$P = .2090$
Hb sensitivity	24	59 342	176 016	235 358	0.439	0.346 to 0.532	<.001	95.91%	$P < .0001$	$P < .0001$	$P = .3459$
Hct	4	387	3820	4207	0.449	0.343 to 0.555	<.001	26.17%	$P = .2547$	$P = .2920$	$P = 1.0000$
MCV	6	802	3914	4716	0.128	−0.432 to 0.689	.653	97.42%	$P < .0001$	$P = .5586$	$P = .8510$
MCH	3	338	3269	3607	−0.125	−0.470 to 0.219	.476	87.52%	$P = .0003$	$P = .9620$	$P = .6015$
MCHC	3	338	3269	3607	0.555	−0.0724 to 1.183	.083	96.15%	$P < .0001$	$P = .0614$	$P = .1172$
RBC	8	2094	8887	10 981	0.237	0.150 to 0.325	<.001	55.45%	$P = .0279$	$P = .9000$	$P = .6207$
PLT	18	53 807	156 766	210 573	0.280	0.162 to 0.397	<.001	94.96%	$P < .0001$	$P = .2366$	$P = .6769$
PDW	4	741	1850	2591	0.185	−0.169 to 0.539	.306	92.38%	$P < .0001$	$P = .9033$	$P = 1.0000$
MPV	6	1047	3760	4807	0.0825	−0.319 to 0.484	.403	96.18%	$P < .0001$	$P = .8498$	$P = .8510$
WBC	16	53 125	153 893	207 018	0.482	0.377 to 0.587	<.001	91.99%	$P < .0001$	$P = .8478$	$P = .9283$
LYM	11	3137	14 463	17 600	0.127	0.0257 to 0.228	.014	79.20%	$P < .0001$	$P = .7378$	$P = .9379$
MONO	5	1208	7810	9018	−0.0498	−0.257 to 0.157	.637	88.45%	$P < .0001$	$P = .5496$	$P = .5496$
NEUT	14	3369	15 085	18 454	0.541	0.404 to 0.679	<.001	89.52%	$P < .0001$	$P = .3026$	$P = .7016$
NLR	9	2852	13 571	16 423	0.319	0.202 to 0.436	<.001	82.65%	$P < .0001$	$P = .6136$	$P = 1.0000$
PLR	2	499	651	1150	−0.375	−0.681 to 0.0694	.016	76.92%	$P = .0374$	$P < .0001$	$P = .3173$

Abbreviations: Hb, hemoglobin concentration; Hct, hematocrit; LYM, lymphocyte; MCH, mean corpuscular hemoglobin; MCHC, mean corpuscular hemoglobin concentration; MCV, mean corpuscular volume; MONO, monocytes; MPV, mean platelet volume; NEUT, neutrophils; NLR, neutrophil to lymphocyte ratio; PLR, platelet to lymphocyte ratio; PLT, platelet count; RBC, red blood cell; RDW, red cell distribution width; SMD, standard mean difference; WBC, white blood cells.

Total and differential white blood cell count and GDM

Women in GDM groups exhibited significantly higher numbers of white blood cells (WBC) (SMD: 0.482; 95% CI: 0.377 to 0.587; $P < .001$; I^2: 93.42%; Fig. 4A), lymphocyte ratio (LYM) (SMD: 0.127; 95% CI: 0.0257 to 0.228; $P = .014$; I^2: 79.20%; Fig. 4D), neutrophils (NEUT) (SMD: 0.541; 95% CI: 0.404 to 0.679; $P < .001$; I^2: 89.52%; Fig. 4B), and neutrophil to lymphocyte ratio (NLR) (SMD: 0.319; 95% CI: 0.202 to 0.436; $P < .001$; I^2: 82.65%; Fig. 4E) than control groups. Two studies provided data concerning the platelet to lymphocyte ratio (PLR). Women diagnosed with GDM had significantly lower PLR compared to the control groups (SMD: −0.375; 95% CI: −0.681 to 0.0694; $P = .01$; I^2: 76.92%; Fig. 4F). Nevertheless, no

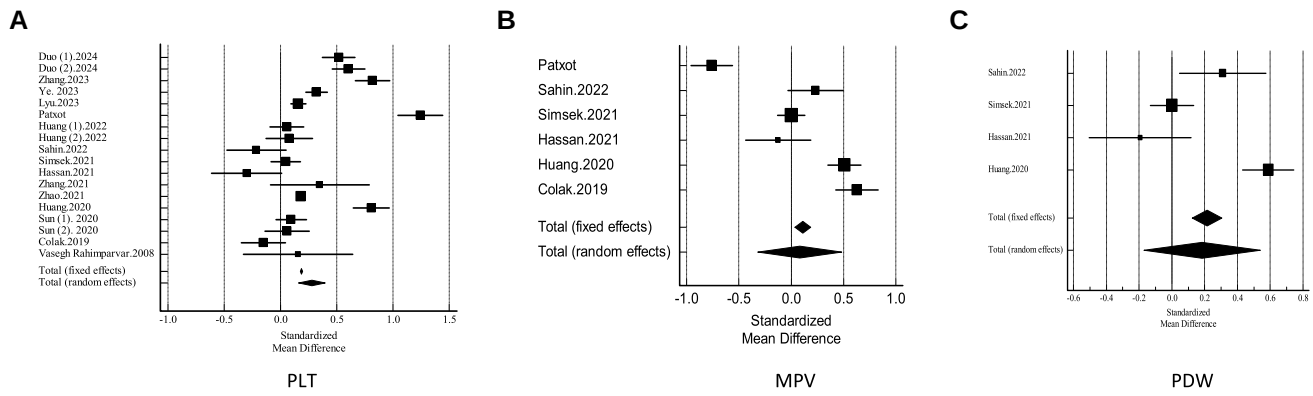

Figure 3. Forest plot of A, platelets (PLT); B, mean corpuscular volume (MPV); and C, platelet distribution width (PDW).

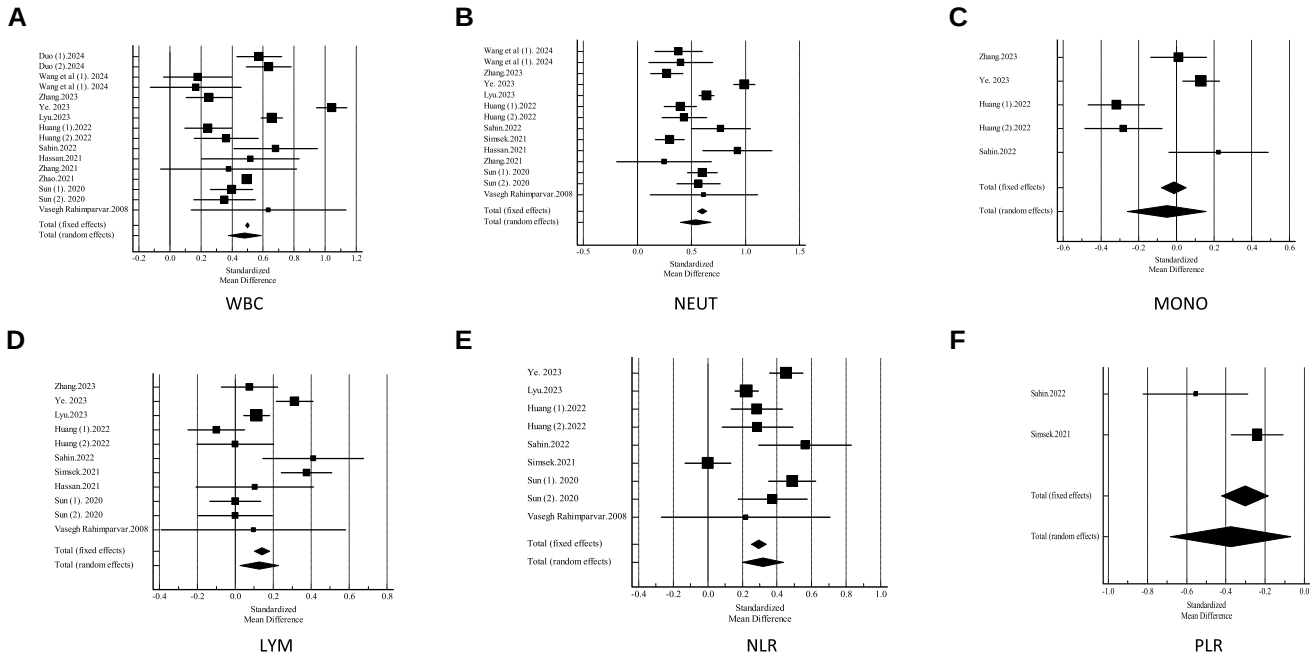

Figure 4. Forest plot of A, white blood cells (WBC); B, neutrophils (NEUT); C, monocytes (MONO); D, lymphocytes (LYM); E, neutrophil to lymphocyte ratio (NLR); and F, platelet to lymphocyte ratio (PLR).

differences were noted between the 2 groups as far as the monocyte (MONO) level was concerned (SMD: −0.0498; 95% CI: −0.257 to 0.157; $P = .637$; I^2: 88.45%; Fig. 4C) (Table 1).

Two studies provided data concerning the odds ratio of the WBC count in relation to GDM, yielding a pooled crude OR of 1.284 (95% CI: 0.912-1.656; I^2: 96.9%). The pooled adjusted estimate yielded an OR of 1.258 (95% CI: 0.954-1.561; I^2: 95.4%), indicating that WBC counts were not significantly associated with an increased risk of GDM.

In all calculations, the random-effect statistical model was employed to estimate the SMD pooled (Table 1).

Accuracy of blood parameters in detecting GDM

In distinguishing women diagnosed with GDM from the controls, the DOR was 3.212 for the Hb value (4 studies, sensitivity = 72%, specificity = 55%) and 2.941 for the MPV (2 studies, sensitivity = 60%, specificity = 66%). Supplementary Fig. S2 [24] shows summary receiver operating characteric (SROC) curve for diagnostic test data related to hemoglobin levels. Supplementary Table S7 [24] shows the pooled sensitivity, specificity, LR+, LR−, and DOR of Hb and MPV.

Exploring Ethnic Differences in Lines of Asian, African, and European Population

As shows in Table 2, in all lines of Asian, African, and European populations, compared with control groups, GDM groups demonstrated significantly higher Hb levels. For other parameters, due to the lack of data, the meta-analysis just was performed in the Asian population.

Table 2 shows pooled SMD of hematological parameters, heterogeneity (along different continent), and publication bias results.

Publication Bias

The Begg test and Egger test were conducted for all studies included in the analysis. Results revealed that with the exception

Table 2. Pooled standard mean differences of hematological parameters, heterogeneity (among different continents), and publication bias results

Variable		Study	N1	N2	Total	SMD	95% CI	*P*	Test for heterogeneity		Publication bias	
									I^2 (inconsistency)	*P* value	Egger test	Begg test
Hb	Asia	22	58 715	173 742	232 457	0.505	0.375 to 0.635	<.001	97.97%	*P* < .0001	*P* = .0078	*P* = .2968
	Africa	2	98	414	512	0.748	0.196 to 1.301	.008	83.35%	*P* = .0142	*P* < .0001	*P* = .3173
	Europe	2	1064	2580	3644	0.339	0.255 to 0.422	<.001	0.00%	*P* = .5176	*P* < .0001	*P* = .3173
hct	Asia	2	231	1907	2138	0.383	0.246 to 0.520	<.001	44.71%	*P* = .1787	*P* < .0001	*P* = .3173
MCV	Asia	4	646	2001	2647	0.441	−0.0401 to 0.922	.072	94.56%	*P* < .0001	*P* = .2509	*P* = .1742
MCH	Asia	3	338	3269	3607	−0.125	−0.470 to 0.219	.476	87.52%	*P* = .0003	*P* = .9620	*P* = .6015
MCHC	Asia	3	338	3269	3607	0.555	−0.0724 to 1.183	.083	96.15%	*P* < .0001	*P* = .0614	*P* = .1172
RBC	Asia	7	2044	8684	10 728	0.241	0.146 to 0.335	<.001	61.56%	*P* = .0160	*P* = .8301	*P* = .8806
PLT	Asia	15	53 651	154 853	208 504	0.252	0.147 to 0.357	<.001	93.22%	*P* < .0001	*P* = .3237	*P* = .5890
PDW	Asia	4	741	1850	2591	0.185	−0.169 to 0.539	.306	92.38%	*P* < .0001	*P* = .9033	*P* = 1.0000
MPV	Asia	6	1047	3760	4807	0.0825	−0.319 to 0.484	.403	96.18%	*P* < .0001	*P* = .8498	*P* = .8510
WBC	Asia	15	53 075	153 690	206 765	0.480	0.371 to 0.588	<.001	92.52%	*P* < .0001	*P* = .8545	*P* = .9605
LYM	Asia	10	3087	14 260	17 347	0.129	0.0221 to 0.235	.018	81.26%	*P* < .0001	*P* = .7639	*P* = .7884
MONO	Asia	5	1208	7810	9018	−0.0498	−0.257 to 0.157	.637	88.45%	*P* < .0001	*P* = .5496	*P* = .6242
NEUT	Asia	13	3319	14 882	18 201	4.315	2.732 to 5.899	<.001	99.82%	*P* < .0001	*P* = .6693	*P* = .0672
NLR	Asia	9	2852	13 571	16 423	0.319	0.202 to 0.436	<.001	82.65%	*P* < .0001	*P* = .6136	*P* = 1.0000
PLR	Asia	2	499	651	1150	−.375	−0.681 to 0.0694	.016	76.92%	*P* = .0374	*P* < .0001	*P* = .3173

Abbreviations: Hb, hemoglobin concentration; Hct, hematocrit; LYM, lymphocytes; MCH, mean corpuscular hemoglobin; MCHC, mean corpuscular hemoglobin concentration; MCV, mean corpuscular volume; MONO, monocytes; MPV, mean platelet volume; NEUT, neutrophils; NLR, neutrophil to lymphocyte ratio; PLR, platelet to lymphocyte ratio; PLT, platelet count; RBC, red blood cell; RDW, red cell distribution width; SMD, standard mean difference; WBC, white blood cells.

of the Egger test for Hb ($P = .0017$), no publication bias was detected in any of the other studies, according to the 2 tests employed. Table 1 shows data on heterogeneity across all calculated models.

Discussion

This meta-analysis aimed to compare the blood parameters in the first trimester of pregnancy among women diagnosed with GDM in their second trimester and those without GDM. The pooled results showed that compared with control groups, GDM groups demonstrated significantly higher Hb, Hct, RBC, PLT, WBC, LYM, NEUT, and NLR levels. Furthermore, Hb levels were significantly associated with increased odds of GDM. No difference was observed between women diagnosed with GDM and controls in terms of MCV, MCH, MCHC, PDW, MPV, MONO levels. Additionally, the results regarding diagnostic accuracy, despite being based on a limited number of studies, confirmed that Hb and MPV had sensitivity and specificity for the diagnosis of GDM.

Although OGTT conducted during the second trimester of pregnancy is considered as the gold standard reference test for diagnosis of GDM, this screening approach has several limitations [27, 28]; this test can be burdensome for patients due to its lengthy duration and dietary restrictions prior to testing [29]. Conversely, the early prediction and detection of GDM can prevent subsequent complications. Recently, researchers have made efforts to introduce biomarkers in the first trimester or even before conception that may serve as predictors for the development of GDM [30]. Despite the identification of numerous biomarkers for early detection of GDM in previous studies, these findings have not yet been effectively translated into clinical practice [30]. Previous studies have documented an association between hematological markers and risk of autoimmune rheumatic diseases [31], type 1 and type 2 diabetes [32], first trimester preeclampsia screening [33], and cardiovascular disease [34]. The development of GDM is primarily influenced by inflammatory markers, which have the potential to serve as predictive biomarkers for the condition [17]. Complete blood count (CBC), a commonly performed first-line investigation during antenatal visits, can be utilized as an assessment tool for inflammation [35].

This meta-analysis revealed that women diagnosed with GDM had significantly higher levels of Hb compared to the control group during their first trimester of pregnancy. This finding was supported by pooled crude and adjusted models. The pooled adjusted analysis demonstrated that for each 1 mg/dL increase in Hb levels during the first trimester of pregnancy, there was a 2% increase in likelihood of developing GDM in the second trimester. The pooled diagnostic accuracy of Hb further strengthened these findings, demonstrating acceptable sensitivity and specificity as a diagnostic marker for GDM. However, due to the limitations of reported data in studies, we were unable to determine the pooled diagnostic cutoff. Other components of the hematogram, including higher levels of RBC and Hct, were also observed in the GDM group compared to the control group. These findings suggest that alterations in hematological parameters may be associated with the pathophysiology of GDM, indicating a potential link between increased RBC and Hct levels and the development of this condition. The relationship between insulin sensitivity, beta-cell dysfunction, and increased levels of hemoglobin and RBCs is complex and involves several interconnected pathophysiological mechanisms. Chronic hyperglycemia and insulin resistance can lead to increased production of erythropoietin, a hormone that stimulates RBC production in the bone marrow. This can occur as a compensatory mechanism to improve oxygen delivery in the

context of metabolic stress [36]. Ren et al (2023) in their study among the Chinese population found that white blood cells can act as predictors of metabolic syndrome [37]. According to a recent study, metabolic syndrome and its components are linked to higher hemoglobin levels [38]. Also, a study demonstrated that high Hct level is a risk factor of diabetes [39]. A recent review by Williams et al has thoroughly examined the pathological alterations of RBCs in patients with diabetes. These alterations encompass a range of hematological changes, including variations in RBC morphology, impaired erythropoiesis, and modifications in hemoglobin function. Such changes are often attributed to the underlying metabolic dysregulation associated with diabetes, which can lead to increased oxidative stress, inflammation, and altered erythropoietin levels [40].

In terms of PLT, PDW, MPV, only the PLT counts were significantly higher among those with GDM than among the control group. Furthermore, diagnostic accuracy of 2 studies showed that MPV levels of the first trimester of pregnancy had good sensitivity and specificity in diagnosis of GDM. The relationship between beta-cell dysfunction, hyperglycemia, and increased platelet activity is complex and multifactorial. Several interconnected pathophysiological mechanisms may contribute to this association. One potential pathway involves the role of platelets in directly stimulating insulin secretion from pancreatic beta cells. Platelets release lipid factors such as 20-HETE, which promotes beta-cell function and metabolic fitness, particularly in younger individuals [41]. Platelets have also been found to act as biomarkers in inflammatory response and immune system regulation [42-44]. Altered glycemic levels by activation of protein kinase, and increasing formation of reactive oxygen species (ROS) and nonenzymatic glycation of platelet membrane glycoproteins can affect platelet function [45]. GDM significantly affects platelet activation through mechanisms involving insulin resistance, hyperglycemia, and altered platelet function. Studies have shown that women with GDM exhibit significantly higher MPV compared to healthy pregnant women. An increased MPV is a marker of platelet activation and indicates enhanced platelet production or reactivity. This elevation in MPV correlates with other markers of platelet activation and is associated with an increased risk of vascular complications during pregnancy [46, 47].

Furthermore, in this study we found that the WBC count was significantly higher in the GDM group than control. A meta-analysis also showed that people with metabolic syndrome had higher levels of biomarkers such as total leukocyte count, neutrophil count, lymphocyte count, basophil count, monocyte count, and neutrophil to lymphocyte ratio [48]. The association between increased WBC counts and diabetes, particularly in the context of chronic inflammation and metabolic dysregulation, can be understood through several interrelated pathophysiological mechanisms including chronic inflammation, oxidative stress, and impaired resolution of inflammation [49]. Insulin resistance is often accompanied by a state of chronic low-grade inflammation. Elevated levels of circulating free fatty acids and inflammatory cytokines, such as interleukin-6 and tumor necrosis factor-alpha, contribute to this inflammatory state, leading to the activation of immune cells, including WBCs [50, 51]. Moreover, hyperglycemia is associated with elevated oxidative stress. Among women with GDM, ROS production can activate inflammatory cells and enhance the production of inflammatory mediators. Inflammation, in turn, leads to an increased ROS release, causing a vicious circle to ensue [52]. In a healthy state, inflammation is typically self-limiting, with mechanisms in place to resolve it [53]. However, in diabetes, the resolution of inflammation is impaired, leading to sustained WBC activation and elevated counts. Previous study has reported a positive correlation between obesity and elevated WBC counts, increased platelet numbers, as well as heightened levels of circulating and inflammatory biomarkers [51]. The mechanistic link between obesity and these hematological changes can be attributed to the chronic low-grade inflammation that characterizes the obese state [50]. However, in the present study, we were unable to directly assess or quantify the obesity status of participants.

While the results of the present meta-analysis were robust and statistically significant, several limitations and potential sources of bias should be carefully considered when interpreting the findings. The systematic review and meta-analysis are inherently prone to limitations based on the quality and characteristics of the individual studies included in the analysis. A notable limitation was the substantial heterogeneity observed across the included studies, which was present in both fixed- and random-effects models. To mitigate the impact of this heterogeneity, the random-effects model was utilized in conjunction with SMD as the outcome measure. However, the underlying causes of the significant heterogeneity remain unclear and may be attributed to variations in study structure, target population, statistical methodologies, and sample sizes. Furthermore, the paucity of available data precluded a comprehensive synthesize of evidence regarding the diagnostic accuracy of all hematological markers of interest. Specifically, there were an insufficient number of studies evaluating certain hematological parameters, limiting the ability to draw definitive conclusions regarding their diagnostic utility.

Despite these limitations, the present meta-analysis provides a more consistent and inclusive assessment of the available evidence compared to previous studies. However, the limitations highlighted underscore the need for further high-quality, well-designed studies to corroborate and expand upon the current evidence base.

In conclusion, while the results of this meta-analysis contribute significantly to the understanding of the diagnostic potential of hematological markers, the limitations and potential sources of bias should be carefully considered when interpreting the findings and their clinical implications. Ongoing research and future studies are warranted to address the identified gaps and provide more definitive evidence regarding the diagnostic accuracy and clinical utility of these markers.

Conclusion

Our meta-analysis found that higher erythrogram, platelet, and white blood cell measurements level in the first trimester of pregnancy were observed in women who subsequently experienced GDM compared to control groups. While the results of this meta-analysis contribute significantly to the understanding of the diagnostic potential of hematological markers, the limitations and potential sources of bias should be carefully considered when interpreting the findings and their clinical implications. Ongoing research and future studies are warranted to address the identified gaps and provide more definitive evidence regarding the diagnostic accuracy and clinical utility of these markers.

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Author Contributions

All authors conceived of the study, participated in its design, and helped to draft the manuscript. Likewise, all authors made suggestions and critical reviews to the initial draft and contributed to its improvement until reaching the final manuscript, which was read and approved by all authors.

Disclosures

All authors declare no conflict of interest.

Ethics Approval and Consent to Participate

The study was approved by the ethics committee of the National Institute for Medical Research Development (Ethics code: IR.NIMAD.REC.1403.057)

Data Availability

Some or all datasets generated during and/or analyzed during the current study are not publicly available but are available from the corresponding author on reasonable request.

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