Pro Index | Journal of Science in Medicine and Life

Volume: 3 Issue: 4 Year: 2025
ISSN: 2992-9202 | http://journals.proindex.uz

The Correlation between Liver Enzymes, Red Cell Distribution Width and Mean Platelet Volume in Gestational Diabetes

Sarah Najim Abd
M.B.Ch.B

Dr. Ahmed Rifat Shakr
M.B.Ch.B, F.I.B.O.G., Consultant in Obstetrics and Gynecology, Al-Elwiya Maternity Teaching Hospital

Abstract: **Background:** Gestational diabetes mellitus is defined as any degree of glucose intolerance with onset or first recognition during pregnancy. It is the most common metabolic complication of pregnancy; in the Middle East, it represents 27.6% of all pregnant women. Evidence of inflammatory dysregulation (i.e., an imbalance between pro- and anti-inflammatory mediators) can be observed as early as the first trimester among pregnant women who later develop gestational diabetes mellitus. The serum levels of the liver function test parameters are generally reduced during normal pregnancy compared to the non-pregnant state, owing to the expansion of the extracellular fluid compartment, except for alkaline phosphatase, which is increased in the third trimester due to increasing placental production. Increased red cell distribution width values reflect greater variability in RBC size, which is associated with advanced fibrosis in non-alcoholic fatty liver disease. The increased production of platelets is accompanied by a reduction in their mean volume, which happened mainly in inflammatory conditions.

Aim of the study: To assess the correlation between Liver enzymes, red cell distribution width, and mean platelet volume in gestational diabetes.

Patients and methods: A case-control study was conducted in Al-Elwiya Maternity Teaching Hospital Department of Obstetrics and Gynecology, over a period extending from the 1st of June 2021 to the 1st of June 2022. Data obtained from the obstetrical consulting clinic were patients attained for antenatal care visits. One hundred term pregnant women with gestational diabetes were enrolled in the study as a case group. Other one-hundred-term pregnant women without gestational diabetes as a control group.

Results: The mean maternal and gestational ages, gravidity, parity, and miscarriage were not different between the two groups. The mean body mass index was higher in case group than control Regarding investigations, the fasting blood glucose, glycosylated hemoglobin, liver enzymes, and red cell distribution width, were significantly higher in case group in comparison to the control, mean platelet volume was significantly lower in case group than control, while total serum bilirubin, white blood cells, and hemoglobin were not different. The mean platelet volume ≤ 8.35 fL is associated with 87% sensitivity and 81% specificity.

Conclusion: Cases of gestational diabetes had higher body mass index, liver enzymes, and red cell distribution width, with low mean platelet volume level. mean platelet volume level ≤8.35 fL had 87% sensitivity and 81% specificity for marking gestational diabetes at time of delivery.

Chapter one:

Introduction

INTRODUCTION:

Background:

Gestational diabetes mellitus (GDM) is defined as any degree of glucose intolerance with onset or first recognition during pregnancy [1]. GDM is the most common metabolic complication of pregnancy, affecting up to 14% of all pregnancies. Its prevalence depends on the diagnostic criteria used [2].

The incidence of GDM is increasing globally due to the increasing prevalence of obesity, sedentary lifestyles, and advancing maternal age. Adoption of the new, stricter diagnostic criteria proposed by the International Association of the Diabetes and Pregnancy Study Groups (IADPSG) has also contributed to its rising incidence[1].

Untreated GDM is associated with adverse outcomes for both mother and fetus during pregnancy and childbirth, including pre-eclampsia, cesarean delivery, birth trauma, macrosomia, and neonatal hypoglycemia and hyperbilirubinemia. GDM is also associated with severe long-term consequences, as women who develop GDM are at high subsequent risk of developing type 2 diabetes mellitus (DMT2), metabolic syndrome, and cardiovascular disease later in life[3].

Prevalence

The prevalence of GDM at 2021 according to IADPSG's criteria, universal OGTT strategy and 25–30 years of age, globally is 14.0 %, while in Middle East is 27.6% of all pregnant women and this represent the highest prevalence worldwide[4]. In the Middle East and North Africa region which had on average the highest prevalence of GDM, the prevalence estimates ranged from 8.4 % in Iran to 24.5 % in United Arab Emirates, whereas Qatar, and Bahrain had intermediate estimates (i.e., 16.3, and 12.9%, respectively). In Southeast Asia, Malaysia had the highest prevalence of 18.3 %, followed by India (13.6 %), Bangladesh (9.7%), and Sri Lanka (8.1%). In South and Central America, data on GDM prevalence were only available in two countries (16.6 and 5.7 % in Cuba and Brazil, respectively) (Figure 1)[5]. Likewise, only two countries in Africa had qualified and available data on prevalence of GDM (i.e., 8.2 % in Nigeria and 9.5 % in Tanzania), which used the WHO and IADPSG criteria. In Iraq the reported GDM prevalence was 7% [6].

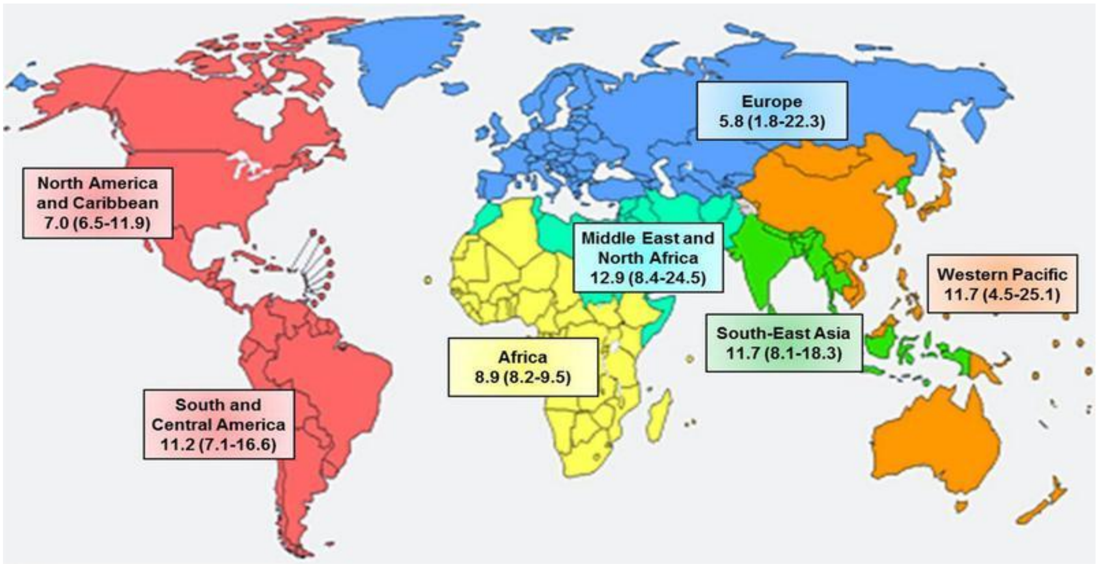


Figure 1: Median (interquartile range) prevalence (%) of GDM by WHO region[5]

Risk Factors for GDM

- ✓ Vitamin D deficiency:

- ✓ Metabolic Syndrome and Nutritional Diet
- ✓ Polycystic Ovary Syndrome (PCOS)
- ✓ Pre-Eclampsia
- ✓ Ethnicity: Hispanics, women from the Indian subcontinent and the Middle East, and women low socioeconomic status are at an increased risk for gestational diabetes[7].
- ✓ Maternal Age: The incidence GDM was especially high in women who were primiparas and were older than 30 years [8].
- ✓ Gravidity and Parity: Potential mechanisms include the influence of multiple pregnancies on postpartum weight retention and development of obesity[9].
- ✓ Genetics and Family History of Hyperglycemia
- ✓ Overweight, Obesity [10].

Pathophysiology of inflammation in development of gestational diabetes

Evidence of inflammatory dysregulation (i.e., an imbalance between pro- and anti-inflammatory mediators) can be observed as early as the first trimester among pregnant women who later develop GDM[11].

Toll like receptors (TLRs) are expressed in numerous cell types that are relevant in the pathogenesis of GDM, including adipose cells. They are also abundantly expressed in the placenta, where they are localized on both the syncytiotrophoblast facing the maternal blood and on the perivascular cells in direct contact with fetal blood. Further, TLR activation and downstream cytokine production may lead to the development of diabetes in experimental animal models[12].

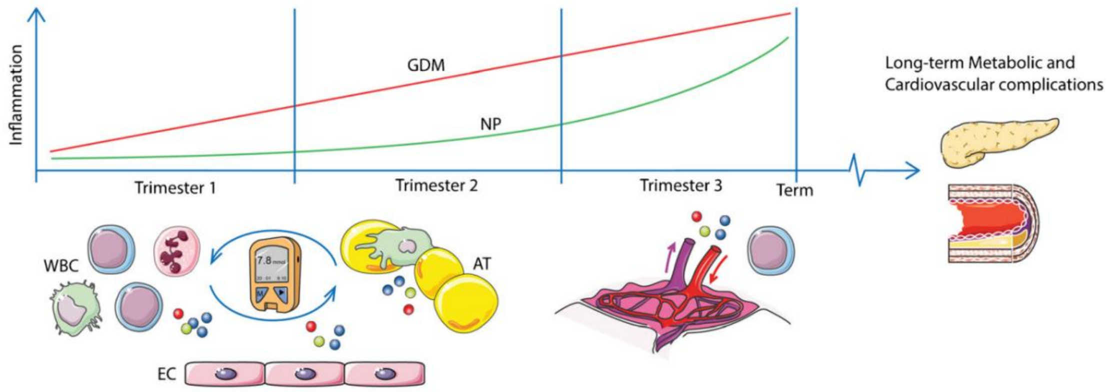


Figure 2: Pregnancy is accompanied by a systemic inflammatory state[13].

*Adipose tissue: AT, Leukocytes: WBC, Endothelial cells: EC, and normal pregnancy: NP

In GDM, hyperglycemia and increased adipose tissue mass may enhance inflammatory responses from leukocytes and endothelial cells, increasing systemic inflammation. Towards the end of pregnancy, the placenta may contribute more to systemic inflammation[13]. The activation of inflammatory pathways in GDM may increase the risk of long-term complications such as T2DM, CVD and serious liver disease[14].

Screening for GDM:

Whom to screen?

American Diabetes Association (ADA) states that low risk women, those with age less than 25 years, not a member of ethnic group, BMI 25kg/m^2 or less, no previous history of abnormal glucose tolerance or adverse obstetrics outcomes and no known history of diabetes in first degree relatives, in these women there is no need to screen and less likely to benefit from any screening[15]. In risk based screening GDM was found in 1.45% of women as against universal screening which showed 2.7% in the same population showing that risk based screening has missed half of the GDM[16].

Based on these facts there is a need for universal screening especially in South east Asians countries more so in Indian women as they have high prevalence of Type II DM and genetic predisposition(16).

When to screen?

Screening for GDM is usually done at 24-28 weeks of gestation because insulin resistance increases during the second trimester and glucose levels rise in women who do not have the ability to produce enough insulin to adopt this resistance(16).

Placental hormones mediate insulin resistance which increases GDM as the pregnancy advances so testing too early may not be helpful in some patients. Similarly, performing tests too late in third trimester limits the time in which metabolic interventions can take place. Because of these reasons, it is advised to perform the tests at 24-28 weeks of gestation. The recommendations given by IADPSG which was endorsed by American diabetes association (ADA) based on Hyperglycemia and Adverse Pregnancy Outcome (HAPO) study is to do on the first prenatal visit, fasting plasma glucose, HbA1C or random plasma glucose in all women. If results are not diagnostic of overt DM and fasting plasma glucose ≥ 92 mg/dl diagnosis of GDM is made. If fasting glucose is < 92mg/dl at the first antenatal visit a 2-hour 75g OGTT should be repeated at 24-28 weeks(17).

How to screen?

In 1960, O' Sullivan et al., proposed that screening, diagnosis and treatment of hyperglycemia in women who are not a known diabetes mellitus (DM) improve outcomes. They proposed diagnostic criteria for GDM based on 3-hour 100g glucose oral glucose tolerance test (OGTT) and then they validated these criteria for the development of future DM in the mother. There is no consensus regarding screening and diagnostic methods for GDM. Screening and diagnostic methods can be universal or risk based one step or two step procedure. Risk factors for GDM include obese women, BMI above 30 kg/m^2, previous macrosomic baby weighting 4.5 kg or above, previous GDM, family history of DM (first degree relative with DM), ethnic family origin with a high prevalence of DM, clinical conditions associated with insulin resistance like PCOS, acanthosis nigricans, history of hypertension or hypercholesterolaemia(18).

World Health Organization (WHO) in 1999 defined and classified criteria for the diagnosis of GDM. These include:

1. GDM is a carbohydrate intolerance resulting in Hyperglycemia of variable severity with the onset or first recognition during pregnancy.
2. In first and early second trimester fasting and postprandial glucose concentrations are normally lower than in normal non-pregnant women. Elevated fasting or postprandial plasma glucose levels at this time in pregnancy may well reflect the presence of DM which has antedated the pregnancy.
3. Testing for GDM usually done between 24-28 weeks of gestation.
4. To determine if GDM is present, a standard OGTT should be performed with 75g anhydrous glucose in 250-300ml of water after overnight fasting of 8-14 hours. Plasma glucose is measured, fasting and after two hours, pregnant women who meet the criteria for DM or Impaired Glucose Tolerance (IGT) are classified as having GDM. Then these women should have 75g OGTT at 6 weeks or more after delivery(19).

Maternal and Fetal Complications

Women with GDM have a higher risk of developing preeclampsia (9.8% in those with a fasting glucose less than 115 mg/dL and 18% in those with a fasting glucose greater than or equal to 115 mg/dL), and undergoing a cesarean delivery (25% of women with GDM who require medication and 17% of women with diet-controlled GDM underwent cesarean delivery versus 9.5% of controls)(20).

Furthermore, women with GDM have an increased risk of developing diabetes (predominantly type 2 diabetes) later in life. It is estimated that up to 70% of women with GDM will develop diabetes within 22–28 years after pregnancy. The progression to diabetes also is influenced by race, ethnicity, and obesity. For example, 60% of Latin American women with GDM may develop type 2 diabetes within 5 years of their index pregnancy. The offspring of women with GDM are at increased risk of macrosomia, neonatal hypoglycemia, hyperbilirubinemia, shoulder dystocia, and birth trauma. There also is an increased risk of stillbirth, although how much this is related to glycemic control is debated. The results of the hyperglycemia and adverse pregnancy outcome study (HAPO), an international, multicenter study, demonstrated a continuous relationship between maternal glucose levels on each of the 75-g, 2-hour oral glucose tolerance test (OGTT) and cesarean delivery, birth weight greater than the 90th percentile, clinical neonatal hypoglycemia, and fetal hyperinsulinemia. Other studies have demonstrated that fetal exposure to maternal diabetes contributes to childhood and adult-onset obesity and diabetes in offspring, which is independent of risks associated with obesity and genetic predisposition[(20)].

Liver function test:

During pregnancy, abnormal maternal liver function is sometimes encountered. In most cases, the cause is attributed to one of the specific obstetric complications associated with liver injury, namely, pre-eclampsia; haemolysis, elevated liver enzymes and low platelets (HELLP) syndrome, acute fatty liver of pregnancy (AFLP), intrahepatic cholestasis of pregnancy (ICP) and hyperemesis gravidarum. The first four conditions mostly present in the last trimester, while the last condition usually presents in the first and occasionally the early second trimester. Perhaps for this reason, maternal liver function test (LFT), which consists of the measurement of serum levels of albumen and globulin, alkaline phosphatase (ALP), aspartate aminotransferase (AST), alanine aminotransferase (ALT), and total bilirubin, and where indicated, the additional assay of gamma glutamyltransferase (GGT) and bile acids, is not requested or routinely performed during antenatal care unless indicated by clinical features suggestive of some form of liver injury or disorder[(21)].

Interpretation of liver function test in pregnancy

The serum levels of the LFT parameters are generally reduced during normal pregnancy compared to the non-pregnant state, owing to the expansion of extracellular fluid compartment except for ALP which is increased in the third trimester due to increasing placental production. As ALT is more specific to the liver than AST, ALT is the usual marker used in assessing hepatocellular damage. Yet the reference range of ALT and other parameters used in most hospital laboratories is based on non-pregnant individuals, including males and females, so that the reference upper limit of normal (ULN) shown in most laboratory reports is not applicable to pregnant women. In one study, the ULN of ALT provided by the laboratory was 40 IU/L, whereas among pregnant women, the ULN was found to be 32 IU/L in all three trimesters. However, another study found no difference in ALT level except for a slightly higher level in the second trimester than in age-matched non-pregnant controls (up to 34 IU/L versus 19 IU/L). In the absence of an established local laboratory reference range for pregnancy, the reported reference range of 6-32 IU/L for ALT in all three trimesters; 32-100, 43-135, and 133-418 IU/L for ALP; and 4-16, 3-13, and 3-14 mmol/L for bilirubin for the first, second, and third trimesters could provide a useful reference[(22)].

Abnormal LFT and GDM

In pregnant women, gamma-glutamyl transferase (GGT) levels at the time of the oral glucose tolerance test (OGTT) correlated positively with the 2-h glucose level, and high GGT was confirmed to increase the risk for gestational diabetes mellitus (GDM)[(23)]. Indeed, even pregravid GGT level in the highest quartile, as compared to that in the lowest quartile, increased the risk of GDM in the subsequent pregnancy[(24)]. There was a significant interaction between GGT with homeostasis model assessment for insulin resistance (HOMA-IR) and with fasting glucose[(25)].

As GGT is also a marker of liver fat accumulation present before pregnancy, the underlying mechanisms for the association between high GGT level with GDM probably is a reflection of underlying NAFLD and chronic hepatic inflammation and fibrosis[22].

Another liver enzyme that could predict subsequent GDM is ALT. In a case control study, the ALT level of 19 IU/L in serum samples collected at 8-18 weeks' gestation was associated with increased GDM by 4.56-fold in women with pre-pregnancy body mass index (BMI) < 30 kg/m^2 and each unit increase in log-transformed ALT was associated with threefold increased odds of GDM, a finding that was limited only to non-obese women[26]. A secondary analysis on the controls of this study also found that non-GDM women giving birth to large-for-gestational-age (LGA) babies had higher mean ALT levels (28 versus 16 IU/L) and ALT >90th percentile (26 IU/L) was associated with a fourfold increased odd for LGA babies (OR 4.03), an association that remained consistent (4.21-fold increase) when the analysis was confined to non-GDM women[27]. One of the main pathogeneses of non-alcoholic fatty liver disease (NAFLD) was found to be inflammation[28].

Hematological markers of inflammations:

Many markers for inflammatory process was identified, but recently a simple complete blood count parameters were found to be markers for inflammation: Red blood cell distribution width (RDW), and mean platelet volume (MPV).

Red blood cells distribution width:

Red cell distribution width is a standard parameter of the complete blood count and indicates variability in red blood cell (RBC) size (i.e., anisocytosis)[29]; RDW is calculated as the proportional variation in mean corpuscular volume (MCV) (normal range: 11% to 16%) [30].

Increased RDW values reflect greater variability in RBC size, which generally indicates dysfunctional erythropoiesis, shortened RBC lifespan, or premature release of reticulocytes. Traditionally, RDW has been used in diagnosing of iron deficiency anemia, particularly when serum ferritin does not accurately indicate total iron stores. RDW is also elevated in other nutritional anemias such as folate or vitamin B12 deficiency. Recently, there has been increasing awareness of a positive association between RDW and risk of both morbidity and mortality in several disease states, principally in critically ill adults. various medical conditions, such as sepsis, acute myocardial infarction, heart failure, autoimmune diseases, liver diseases, and various malignancies. Some studies found that elevated RDW was independently associated with advanced fibrosis in NAFLD, RDW was higher in the severe inflammation group in non-alcoholic steatohepatitis and can be used as an indicator in non-alcoholic steatohepatitis patients with high sensitivity and specificity. The RDW represents an easily obtainable and inexpensive prognostic marker in various patient populations[31].

Of note, mounting evidence suggests that in the course of critical illness, RBCs acquire metabolic and structural injuries that impair oxygen (O2) delivery and influence outcome. Such acquired RBC dysfunction is reported to result in: increased adhesion to endothelium, decreased deformability, decreased hemoglobin (Hb) content, increased O2 affinity, constrained energy metabolism and impaired antioxidant capacity as well as abnormal nitric oxide processing (and vascular signaling). Each of these pathologies may adversely influence tissue O2 delivery, by either impairing blood flow or O2 release itself. [32]

It was suggested that increased RDW may be associated with an increased risk of all-cause mortality in patients with DM. It was reported that a 1% increment in RDW increased mortality risk by 14% regardless of hemoglobin concentration[33]. In the third National Health and Nutrition Examination Survey study, higher RDW values were found to be associated with an increased risk of developing nephropathy in patients with DM. In another prospective study, patients with diabetic foot osteomyelitis had higher RDW values by the end of 1 year compared to a control group[34].

Mean platelet volume:

The mean platelet volume (MPV) is a precise measurement of their dimension, calculated by hematological analyzers on the basis of volume distribution during routine blood morphology test. MPV ranges between 9 and 13.0 fl, whereas the percentage of large platelets should amount to 0.2-5.0% of the whole platelet population [(35)].

In physiological conditions, MPV is inversely proportional to the platelet count, which is associated with hemostasis maintenance and preservation of constant platelet mass. This means that the increased production of platelets is accompanied by a reduction in their mean volume. In various pathologies, this physiological proportion is disturbed. Markedly enhanced or abnormal thrombocytopoiesis, increased wear or the effect of activating factors on blood platelets may lead to changes in the proportions between MPV and PLT [(36)].

Therefore, possible application of these parameters to the diagnosis of certain diseases has been suggested. Moreover, MPV correlates with platelet activity and is thus considered a marker of platelet activity[(36)].

Blood platelets are not a homogenous population. Those with increased MPV (>15 fl) are often younger and characterized by higher reactivity than those with normal MPV. Their generation is associated with marked activation of megakaryocytes by cytokines, which increases the ploidy of these cells and enhances the release of larger platelets [(37)].

It is also suggested that large thrombocytes show a greater content of cell granules, display higher expression of adhesion molecules, and undergo faster activation, which results in platelet hyperactivity and increased risk of clot formation. Elevated MPV correlates with increased platelet aggregation, enhanced synthesis, and release of thromboxane TXA2 and β-thromboglobulin[(38)] .

In healthy individuals, the increased platelet count, via feedback, leads to considerable inhibition of Thrombopoietin synthesis by the liver and in consequence causes platelet release by megakaryocytes, which is to maintain constant platelet mass. However, in patients with ongoing inflammation, the increasing concentration of proinflammatory cytokines mainly IL-6 can lead to platelet release. This is associated with the stimulation of thrombopoietin generation by IL-6 and with a direct effect of this cytokine on megakaryocytes. IL-6 causes an increase in the ploidy of megakaryocytic nuclei and an increase in cytoplasm volume, which in consequence leads to the production of a large number of blood platelets[(38)].

The course of an inflammatory condition is also associated with increased percentage of large platelets, probably due to intracellular synthesis of procoagulatory and proinflammatory factors, degranulation of granules, and initiation of the platelet pool stored in the spleen. Simultaneously, these cells rapidly migrate to the site of inflammation where they undergo activation and wear. This seems to explain the drop in MPV in patients with ongoing inflammation[(36)].

Many studies investigated the role of Increased MPV and found that it is Associated with a higher risk of acute cardiac incidents[(39)] associated with a risk of acute stroke [(148)], In tuberculosis associated with intensity of inflammation [(149)], Marker of the Crohn's disease activity[(40)], Associated with retinopathy and nephropathy[(41)], Potential marker of liver cancer in patients with chronic liver diseases and many other diseases[(42)].

As explained in above section GDM can be a cause and effect of liver disease in pregnancy also one of the main pathogenesis of GDM is inflammation same can be applied to liver disease as both autoimmune heapititis, and NAFLD[(22)].

As new markers of inflammation were recently investigated, mean platelet volume (MPV) and red blood cell distribution width (RDW) were found related to many inflammatory disorder and provided a predictive tool for many medical illnesses, they may be a marker for the both GDM and liver enzyme abnormality suggesting common pathway in the pathogenesis, for these reasons we intended to estimate the relationship among these investigations in diabetic patients.

AIM OF THE STUDY:

To assess the correlation between Liver enzymes, Red cell distribution width and mean platelet volume in gestational diabetes.

Chapter two:

Patients & methods

PATIENTS AND METHODS:

Study design:

A case control study was conducted in Al-Elwiya Maternity Teaching Hospital Department of Obstetrics and Gynecology, over period extended from 1st of June 2021 to 1st of June 2022.

Patients:

Data obtained from obstetrical consulting clinic, were patients attained for antenatal care visit.

One hundred term pregnant women with gestational diabetes were enrolled in the study as case group.

Another one hundred term pregnant women without gestational diabetes as control group.

Inclusion criteria:

- ✓ Term single viable fetus.
- ✓ Diabetic pregnant women (gestational diabetes).
- ✓ Not in labor.

Exclusion criteria:

- ✓ Fetal congenital abnormality or fetal death.
- ✓ Women in labor.
- ✓ Chronic medical comorbidities other than GDM.
- ✓ Obstetrical complications such as: Preeclampsia, Preterm labor, Abnormal placentation (Previa, accrete, and abruption placentae), etc…
- ✓ Twin pregnancy.

Data collection:

All of the patients were assessed by obtaining history and examination with recording a pre forma which included the demographic factors with the history of GDM control, type of medication, with previous history of macrosomia, diabetes, obstetrical complications also family history of diabetes. Also detailed history and physical examination practiced for the detection of any of exclusion criteria.

Blood sample withdrawn from all participant for measurement of random blood sugar, HbA1C, CBC, LFT.

Laboratory analysis:

Five milliliters (ml) of venous blood withdrawn from participants and divided into two tube, the first one EDTA containing tube with adding one ml of blood for measuring of PDW and MPV. The remaining blood transferred into the second tube without EDTA for measuring fasting blood sugar, liver function test (ALP, S. GOT, S. SGPT and TSB).

Ethical considerations

The proposal of the study was fully discussed and approved by the scientific and ethical committee of Iraqi Board of Obstetrics and Gynecology.

The agreement of scientific committee in AL-Elwiya Maternity Teaching Hospital was taken before start of the study.

A verbal consent was taken from each patient after full explanation of aim of the study and ensures that collected data will be used for research purposes only and will be anonymous.

Statistical analysis:

The collected data were introduced into Microsoft excel worksheet 16 and loaded into IBM – SPSS V26 to be used in statistical analysis. Descriptive statistics were presented using tables (No. and frequency, means & standard deviations), Chi square used to estimate the level of significance for categorical data while Mann-Whitney U test was used to find out significance of difference between continuous variables because of abnormal distribution of collected data which is essential assumption for t test. P-value less than 0.05 was considered as cut-off point for discrimination of significance.

Chapter three:

Results

RESULTS:

The study included 200 participants divided equally into two groups case, and control. The mean maternal and gestational ages were not different between the two groups. The gravidity, parity, and miscarriage were not different between the two groups. The mean BMI was higher in case group than control (p value 0.033), as shown in Table 1.

Table 1: Distribution of demographical data.

Variables	Case		Control		P value
	Mean	SD	Mean	SD	
Age	30.88	5.55	32.53	5.6	0.083
Gravida	6.55	2.43	5.9	2.71	0.076
Parity	4.7	2.48	4.04	2.62	0.069
Miscarriage	0.85	0.82	0.86	0.83	0.932
BMI	30.56	3.71	29.44	3.68	**0.033**
Gestational age	38.46	0.65	38.55	0.72	0.319

Regarding investigations, the FBS, HbA1c, liver enzymes, and RDW, were significantly higher in case group in comparison to control, MPV was significantly lower in case group than control, while TSB, WBC, and Hb were not different, as shown in Table 2.

Table 2: Distribution of investigation

Variables	Case		Control		P value
	Mean	SD	Mean	SD	
FBS	158.05	15.99	97.01	7.43	**<0.0001**
HbA1c	9.72	1.59	6.8	0.7	**<0.0001**
AST	56.44	19.59	47.06	12.09	**<0.0001**
ALT	70.49	18.23	51.65	14.08	**<0.0001**
ALP	132.5	44.73	110.12	38.74	**<0.0001**
TSB	0.54	0.29	0.52	0.3	0.55
WBC	9.37	2.15	9.44	2.09	0.79
HB	10.68	0.95	10.64	1.02	0.763
RDW	18.3	2.58	16.3	2.16	**<0.0001**
MPV	7.64	0.67	9.86	1.16	**<0.0001**

Regarding the correlation of the investigations with blood glucose level, we found that liver enzymes and RDW had significant positive correlation with both FBS and HbA1c. While MPV had significant negative correlation with BMI, FBS, and HbA1c. On the other hand, no significant correlation found with TSB, WBC, and hemoglobin, as shown in Table 3.

Table 3: correlation of the variables with blood sugar, and BMI.

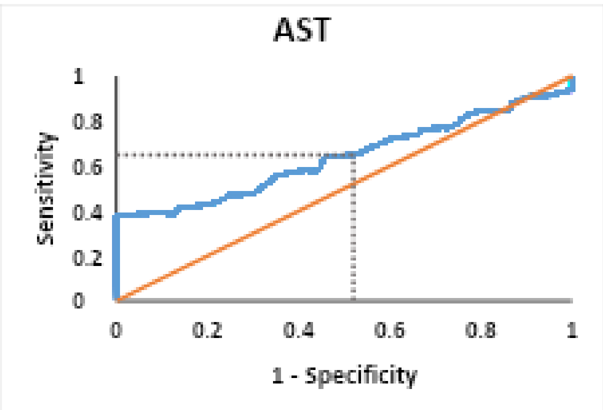
Variables	Correlations coefficient		
	BMI	FBS	HbA1c
AST	0.126	**0.268***	**0.165***
ALT	0.041	**0.433***	**0.381***
ALP	0.045	**0.222***	**0.237***
TSB	0.072	0.08	0.055
WBC	-0.003	-0.008	-0.033
HB	0.016	0.027	0.033
RDW	0.129	**0.332***	**0.345***
MPV	**-0.209***	**-0.687***	**-0.581***

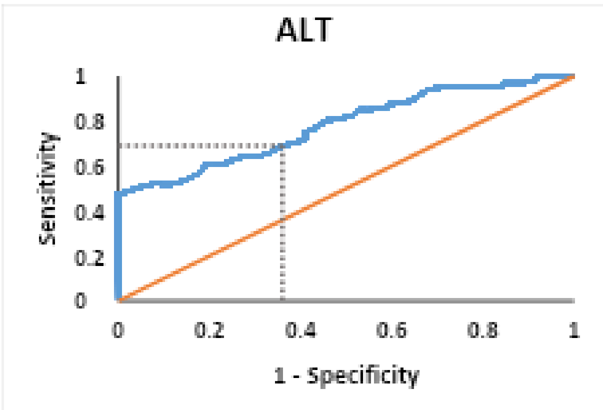
*Significant correlation

After application of ROC curve analysis (Figure 3), we found that only MPV had acceptable selectivity and specificity in prediction of gestational diabetes, as shown in Table 4.

Table 4: Predictive ability of investigations.

Variables	AUC	95% CI	CP	SN (%)	SP (%)	PPV (%)	NPV (%)	ACC (%)	OR	95% CI
AST	0.641	0.562-0.719	≥46.5	65	57.8	55.6	48	56.5	1.71	0.97-3.02
ALT	0.78	0.717-0.844	≥61.5	69	64	65.7	67..4	66.5	3.95	2.19-7.12
ALP	0.632	0.556-0.709	≥109.5	65	51	57	59.3	58	1.93	1.09-3.41
TSB	0.525	0.445-0.605	≥0.45	62	44	52.5	53.7	53	1.28	0.72-2.25
RDW	0.719	0.649-0.788	≥17.25	67	60	62.6	64.5	63.5	3.05	1.71-5.42
MPV	0.952	0.928-0.977	≤8.35	87	81	82.1	86.2	84	28.53	13.24-61.47





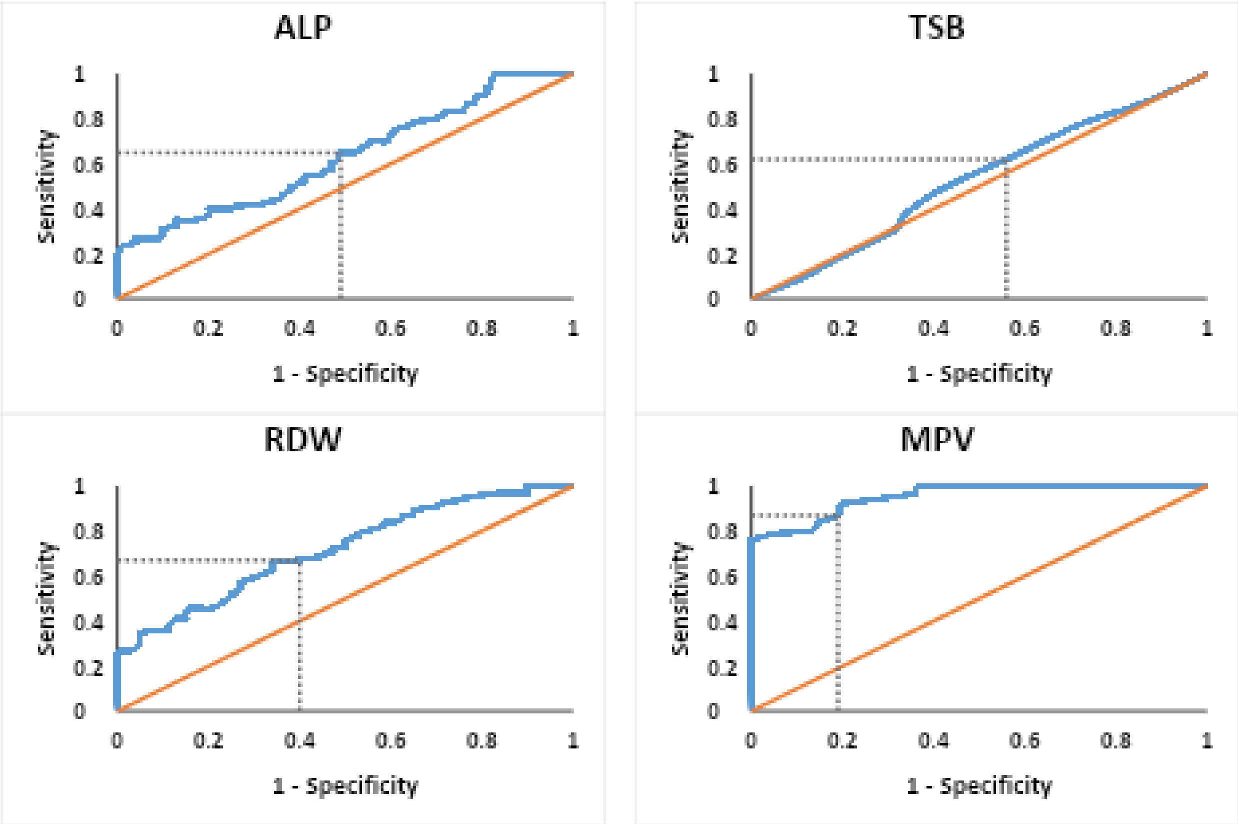


Figure 3: ROC curve analysis.

Chapter four:

Discussion

DISCUSSION

Gestational diabetes mellitus has long been associated with obstetric and neonatal complications primarily relating to higher infant birthweight and is increasingly recognized as a risk factor for future maternal and offspring cardiometabolic disease. The prevalence of GDM continues to rise internationally due to epidemiological factors including the increase in background rates of obesity in women of reproductive age and rising maternal age[(43)].

The current study aimed to investigate the role of liver enzymes, and some blood parameters in diagnosing GDM.

The study included 200 participants, case and control groups. The maternal age was not different between the two groups, this was intentionally selected to eliminate selection bias. To note that advancing maternal age associated with increasing risk of gestational diabetes as stated by Li et al[(44)] and Dong et al[(45)].

The mean gravidity and parity were not different between the two groups, Schwartz et al[(46)] (n=788) found that multiparous women have higher risk of GDM and after applying multivariate analysis they found that short interpregnancy interval (that occur in multiparous women than primiparity) was the true predictor of GDM rather than parity.

The rate of previous miscarriage was not different between the two groups. To note that previous study that tended to examine the effect of gestational diabetes on the rate of miscarriage found that GDM increase rate of miscarriage as estimated by Magnus et al[(47)].

The mean body mass index was significantly higher in cases of gestational diabetes than control, this illustrate the close relationship between obesity and gestation diabetes (as a cause-and-effect relationship), many previous studies found that obesity increase the rate of GDM, such as Martin et al[(48)], Shin et al[(49)], and Lewandowska et al[(50)].

The mean gestational age was not different between the two groups, that was intentionally selected to eliminate the effect of gestational age on the level of the measured investigations.

The mean fasting blood sugar was significantly higher in cases of GDM than control. Previous studies found that the fasting blood glucose is used during first trimester to predict the future development of gestational diabetes (Cosson et al(51) and Agarwal et al(52)). While in third trimester elevated maternal FBS associated with poor pregnancy outcome as found by Zhao et al(53) and Panyakat et al(54).

The mean HbA1c was significantly higher in GDM cases. The role of HbA1c in diagnosing gestational diabetes is still an area of controversy, but previous studies showed that HbA1c could be good predictor of adverse pregnancy outcome in cases of gestational diabetes as stated by Ye et al(55) and Lemaitre et al(56).

The mean level of aspartate aminotransferase (AST) and alanine aminotransferase (ALT) were significantly higher in cases of GDM than control. The mechanism that associated with increased these liver enzymes with GDM could be attributed to the fact liver is the organ involved in glucose metabolism and storage to achieve glycemic homeostasis by formation of fatty acid or glycogen in case of hyperglycemia and gluconeogenesis in case of hypoglycemia, as stated by Zhang et al(57) as such abnormal liver function test had its deleterious effect on blood glucose regulation. On the other hand, elevated blood glucose could lead to liver damage in the form of hepatic fibrosis or non-alcoholic fatty liver disease as found by Chang et al(58). While Zhao et al(59) in their meta-analysis found that elevated liver enzymes associated with increased risk of GDM. To note tat some studies investigated the role of liver enzymes in first trimester in prediction of GDM and found that due to insulin resistance liver would be more prone to injury giving common pathological process as stated by Powe et al(60). The inflammatory process and fighting oxygen free radicals are also had its role in the pathophysiology of elevated liver enzymes and gestational diabetes as found by Mishra et al(61).

The mean alkaline phosphatase was significantly higher in cases of GDM than control. ALP had many roles and related to the function of many tissues and organs, it is elevated to mild extent during normal pregnancy, also it reflects biliary function (de Vries et al(62)). Xiong et al(63) found that elevated serum ALP in early pregnancy associated with increased risk of gestational diabetes. This elevation may be attributed to the development of fatty liver as ALP is marker for visceral obesity as stated by Ali et al(64). Visceral obesity and fatty livers are both cause and effect diabetes, as stated by Kwak et al(65).

The mean level of total serum bilirubin was not different between the two groups, while Nishimura et al(66) stated that low level of TSB was associated with higher prevalence of gestational diabetes, but with the use of multivariate analysis they found that TSB is not the real cause of this increased prevalence instead insulin resistance and BMI were the predictors of GDM rather than TSB.

The mean white blood cells count was not different between the two groups. Similar result found by Mertoglu et al(67), while Yilmaz et al(68) investigated the role of measuring WBC in first trimester in prediction of future development of GDM and found that high WBC count in first trimester associated with increased risk of GDM. In the current study we measured WBC count at time of delivery and this may be the cause for the difference in this result.

The mean hemoglobin level was not different between the two groups. Similar results found by Mertoglu et al(67), Yilmaz et al(68), Hongling et al(69) and Gorar et al(70).

The mean red cell distribution width was significantly higher in cases of gestational diabetes than control. RDW level describe the variation in red blood cell diameter that affected in cases of anemia and inflammation. The elevated level of RDW found to be associated with many inflammatory conditions such as rheumatoid arthritis (71) or coronary heart disease(72) and many other inflammatory conditions. In diabetes it was found by Yilmaz et al(68) that elevated RDW level in first trimester of pregnancy associated with increased risk of future development of GDM. On the other hand, Tripolino et al(73) found that elevated level of RDW had associated with elevated level of glucose after two hours from OGTT. These associations clarify the relation of inflammatory process and development of gestational diabetes.

The mean platelet volume was significantly lower in cases of GDM than control. Similar result found by Mertoglu et al(67), Yilmaz et al(68), and Hongling et al(69).

The ability of these parameters to be markers of gestational diabetes were examined using ROC curve analysis and found that MPV ≤ 8.35 fL is associated with 87% sensitivity and 81% specificity. This predictive ability of MPV at time of delivery was poorly investigated in other studies.

Chapter five:

Conclusion & Recommendations

CONCLUSION & RECOMMENDATIONS

Conclusion

- ✓ Cases of GDM had higher BMI, liver enzymes, and RDW, with low MPV level.
- ✓ MPV level ≤8.35 fL had 87% sensitivity and 81% specificity for marking GDM at time of delivery.

Recommendations

- ➢ This study may be considered as pilot study for future studies that investigate the role of liver enzymes and blood markers in early pregnancy in prediction of GDM. Also examine the effect of treatment of GDM on these parameters
- ➢ The MPV level could be considered an aid for prediction of maternal hyperglycemia thus better directed care could be given.
- ➢ Medical education to the mothers about the risk of obesity and diabetes on liver health.

References

REFERENCES:

1. MM A. Consensus in gestational diabetes mellitus: looking for the holy grail. *Journal of clinical medicine*. 2018;7(6):123.
2. Koning SH, Hoogenberg K, Lutgers HL, Van den Berg PP, Wolffenbuttel BH. Gestational Diabetes Mellitus: current knowledge and unmet needs. *Journal of diabetes*. 2016;8(6):770-81.
3. Burlina S, Dalfrà M, Lapolla A. Short-and long-term consequences for offspring exposed to maternal diabetes: a review. *The Journal of Maternal-Fetal & Neonatal Medicine*. 2019;32(4):687-94.
4. Wang H, Li N, Chivese T, Werfalli M, Sun H, Yuen L, et al. IDF Diabetes Atlas: Estimation of Global and Regional Gestational Diabetes Mellitus Prevalence for 2021 by International Association of Diabetes in Pregnancy Study Group's Criteria. *Diabetes Research and Clinical Practice*. 2022;183:109050.
5. Zhu Y, Zhang C. Prevalence of gestational diabetes and risk of progression to type 2 diabetes: a global perspective. *Current diabetes reports*. 2016;16(1):1-11.
6. Aziz RA, Fattah CN. Maternal and fetal outcome in gestational diabetic women. *Zanco Journal of Medical Sciences (Zanco J Med Sci)*. 2018;22(3):401-10.
7. Carroll X, Liang X, Zhang W, Liu G, Turner N, S L-W. Socioeconomic, environmental and lifestyle factors associated with gestational diabetes mellitus: a matched case-control study in Beijing, China. *Scientific reports*. 2018;8(1):1-10.

8. Han Y, Tong M, Jin L, Yu J, Meng W, Ren A. Maternal age at pregnancy and risk for gestational diabetes mellitus among Chinese women with singleton pregnancies. *International Journal of Diabetes in Developing Countries*. 2021;41(1):114-20.
9. Nicholson WK, Asao K, Brancati F, Coresh J, Pankow JS, Powe NR. Parity and risk of type 2 diabetes: the Atherosclerosis Risk in Communities Study. *Diabetes care*. 2006;29(11):2349-54.
10. Svensson H, Wetterling L, Bosaeus M, Odén B, Odén A, Jennische E, et al. Body fat mass and the proportion of very large adipocytes in pregnant women are associated with gestational insulin resistance. *International journal of obesity*. 2016;40(4):646-53.
11. Friis CM, Paasche Roland MC, Godang K, Ueland T, Tanbo T, Bollerslev J, et al. Adiposity-related inflammation: effects of pregnancy. *Obesity*. 2013;21(1):E124-E30.
12. Catalano P, Demouzon S. Maternal obesity and metabolic risk to the offspring: why lifestyle interventions may have not achieved the desired outcomes. *International journal of obesity*. 2015;39(4):642-9.
13. Lekva T, Norwitz ER, Aukrust P, Ueland T. Impact of systemic inflammation on the progression of gestational diabetes mellitus. *Current diabetes reports*. 2016;16(4):1-11.
14. Retnakaran R, Luo J, Shah BR. Gestational diabetes in young women predicts future risk of serious liver disease. *Diabetologia*. 2019;62(2):306-10.
15. Association AD. Standards of medical care in diabetes—2009. *Diabetes care*. 2009;32(Suppl 1):S13.
16. Griffin M, Coffey M, Johnson H, Scanlon P, Foley M, Stronge J, et al. Universal vs. risk factor-based screening for gestational diabetes mellitus: detection rates, gestation at diagnosis and outcome. *Diabetic Medicine*. 2000;17(1):26-32.
17. Diabetes IAo, Panel PSGC. International association of diabetes and pregnancy study groups recommendations on the diagnosis and classification of hyperglycemia in pregnancy. *Diabetes care*. 2010;33(3):676-82.
18. Rani PR, Begum J. Screening and diagnosis of gestational diabetes mellitus, where do we stand. *Journal of clinical and diagnostic research: JCDR*. 2016;10(4):QE01.
19. Saccone G, Khalifeh A, Al-Kouatly HB, Sendek K, V B. Screening for gestational diabetes mellitus: one step versus two step approach. A meta-analysis of randomized trials. *The Journal of Maternal-Fetal & Neonatal Medicine*. 2020;33(9):1616-24.
20. Mellitus GD. ACOG practice bulletin. *ACOG: Washington, DC, USA*. 2018.
21. Westbrook RH, Dusheiko G, Williamson C. Pregnancy and liver disease. *J Hepatol*. 2016;64(4):933-45.
22. Lao TT. Implications of abnormal liver function in pregnancy and non-alcoholic fatty liver disease. *Best Practice & Research Clinical Obstetrics & Gynaecology*. 2020;68:2-11.
23. Kong M, Liu C, Guo Y, Gao Q, Zhong C, Zhou X, et al. Higher level of GGT during mid-pregnancy is associated with increased risk of gestational diabetes mellitus. *Clinical Endocrinology*. 2018;88(5):700-5.
24. Park J-Y, Kim WJ, Chung YH, Kim B, Park Y, Park IY, et al. Association between pregravid liver enzyme levels and gestational diabetes in twin pregnancies: a secondary analysis of national cohort study. *Scientific reports*. 2021;11(1):1-11.
25. Medrano M, Arenaza L, Migueles JH, Rodríguez-Vigil B, Ruiz JR, Labayen I. Associations of physical activity and fitness with hepatic steatosis, liver enzymes, and insulin resistance in children with overweight/obesity. *Pediatric Diabetes*. 2020;21(4):565-74.

26. Yarrington CD, Cantonwine DE, Seely EW, McElrath TF, Zera CA. The association of alanine aminotransferase in early pregnancy with gestational diabetes. *Metabolic Syndrome and Related Disorders*. 2016;14(5):254-8.
27. Yarrington CD, Cantonwine DE, Seely EW, Mcelrath TF, Zera CA. The association of early unexplained elevated alanine aminotransferase with large-for-gestational-age birthweight. *American Journal of Obstetrics and Gynecology*. 2016;215(4):474. e1-. e5.
28. Srinivas AN, Suresh D, Santhekadur PK, Suvarna D, Kumar DP. Extracellular vesicles as inflammatory drivers in NAFLD. *Frontiers in immunology*. 2021;11:3745.
29. Farkas N, Szabó A, Lóránd V, Sarlós DP, Minier T, Prohászka Z, et al. Clinical usefulness of measuring red blood cell distribution width in patients with systemic sclerosis. *Rheumatology (Oxford)*. 2014;53(8):1439-45.
30. Maner BS, Moosavi L. Mean corpuscular volume. *British journal of haematology*. 2019;187(2):7-12.
31. Zhou W-J, Yang J, Zhang G, Hu Z-Q, Jiang Y-M, Yu F. Association between red cell distribution width-to-platelet ratio and hepatic fibrosis in nonalcoholic fatty liver disease: A cross-sectional study. *Medicine*. 2019;98(30):e16565-e.
32. Bateman RM, Sharpe MD, Singer M, Ellis CG. The effect of sepsis on the erythrocyte. *International journal of molecular sciences*. 2017;18(9):1932.
33. Yıldız S, Üçler R, Alay M, Ekici EB. Which hemogram parameter is more cautionary in euthyroid patients with gestational diabetes mellitus. *Eastern journal of medicine*. 2016;21(4):162.
34. Zhou L, Lin S, Zhang F, Ma Y, Fu Z, Gong Y, et al. The correlation between RDW, MPV and weight indices after metabolic surgery in patients with obesity and DM/IGR: Follow-up observation at 12 months. *Diabetes Therapy*. 2020;11:2269-81.
35. Beyan C, Beyan E. Were the measurements standardized sufficiently in published studies about mean platelet volume? *Blood Coagulation & Fibrinolysis*. 2017;28(3):234-6.
36. Noris P, Melazzini F, CL. B. New roles for mean platelet volume measurement in the clinical practic. *Platelets*. 2016;27(7):607-12.
37. Fisher MH, Di Paola J. Genomics and transcriptomics of megakaryocytes and platelets: Implications for health and disease. *Research and practice in thrombosis and haemostasis*. 2018;2(4):630-9.
38. Tiwary SK, Das AK, Khanna S, Das D, Kumar P, Khanna AK. Mean platelet volume: a measure of platelet activity and its relation with other platelet indices in deep vein thrombosis. *Journal of Advanced Scientific Research*. 2020;11(3).
39. He S, Lei W, Li J, Yu K, Yu Y, Zhou L, et al. Relation of platelet parameters with incident cardiovascular disease (the dongfeng-tongji cohort study). *The American journal of cardiology*. 2019;123(2):239-48.
40. Lee SL, Ng CY, Sidhu J, Gew LT, Law KB. Mean Platelet Volume as a Complementary Non-Invasive Biomarker for Disease Activity in Inflammatory Bowel Disease: A Single Centre Study. *Asian Journal of Research and Reports in Gastroenterology*. 2021:1-9.
41. Liu J, Liu X, Li Y, Quan J, Wei S, An S, et al. The association of neutrophil to lymphocyte ratio, mean platelet volume, and platelet distribution width with diabetic retinopathy and nephropathy: a meta-analysis. *Bioscience reports*. 2018;38(3):7-12.
42. Yin J-b, Wang X, Zhang X, Liu L, Wang R-t. Mean platelet volume predicts survival in pancreatic cancer patients with synchronous liver metastases. *Scientific reports*. 2018;8(1):1-6.

43. Sweeting A, Wong J, Murphy HR, Ross GP. A Clinical Update on Gestational Diabetes Mellitus. *Endocrine Reviews*. 2022;43(5):763-93.
44. Li Y, Ren X, He L, Li J, Zhang S, Chen W. Maternal age and the risk of gestational diabetes mellitus: a systematic review and meta-analysis of over 120 million participants. *Diabetes research and clinical practice*. 2020;162:108044.
45. Dong B, Yu H, Wei Q, Zhi M, Wu C, Zhu X, et al. The effect of pre-pregnancy body mass index and excessive gestational weight gain on the risk of gestational diabetes in advanced maternal age. *Oncotarget*. 2017;8(35):58364.
46. Schwartz N, Green MS, Yefet E, Nachum Z. Modifiable risk factors for gestational diabetes recurrence. *Endocrine*. 2016;54(3):714-22.
47. Magnus MC, Wilcox AJ, Morken N-H, Weinberg CR, Håberg SE. Role of maternal age and pregnancy history in risk of miscarriage: prospective register based study. *bmj*. 2019;364.
48. Martin KE, Grivell RM, Yelland LN, Dodd JM. The influence of maternal BMI and gestational diabetes on pregnancy outcome. *Diabetes research and clinical practice*. 2015;108(3):508-13.
49. Shin D, Song WO. Prepregnancy body mass index is an independent risk factor for gestational hypertension, gestational diabetes, preterm labor, and small-and large-for-gestational-age infants. *The Journal of Maternal-Fetal & Neonatal Medicine*. 2015;28(14):1679-86.
50. Lewandowska M, Więckowska B, Sajdak S. Pre-pregnancy obesity, excessive gestational weight gain, and the risk of pregnancy-induced hypertension and gestational diabetes mellitus. *Journal of clinical medicine*. 2020;9(6):1980.
51. Cosson E, Carbillon L, Valensi P. High fasting plasma glucose during early pregnancy: a review about early gestational diabetes mellitus. *Journal of diabetes research*. 2017;2017.
52. Agarwal MM. Gestational diabetes mellitus: Screening with fasting plasma glucose. *World journal of diabetes*. 2016;7(14):279.
53. Zhao D, Yuan S, Ma Y, An YX, Yang YX, Yang JK. Associations of maternal hyperglycemia in the second and third trimesters of pregnancy with prematurity. *Medicine*. 2020;99(17).
54. Panyakat WS, Phatihattakorn C, Sriwijitkamol A, Sunsaneevithayakul P, Phaophan A, Phichitkanka A. Correlation between third trimester glycemic variability in non-insulin-dependent gestational diabetes mellitus and adverse pregnancy and fetal outcomes. *Journal of diabetes science and technology*. 2018;12(3):622-9.
55. Ye M, Liu Y, Cao X, Yao F, Liu B, Li Y, et al. The utility of HbA1c for screening gestational diabetes mellitus and its relationship with adverse pregnancy outcomes. *Diabetes Research and Clinical Practice*. 2016;114:43-9.
56. Lemaitre M, Ternynck C, Bourry J, Baudoux F, Subtil D, Vambergue A. Association Between HbA1c Levels on Adverse Pregnancy Outcomes During Pregnancy in Patients with Type 1 Diabetes. *The Journal of Clinical Endocrinology & Metabolism*. 2022;107(3):e1117-e25.
57. Zhang X, Yang S, Chen J, Su Z. Unraveling the regulation of hepatic gluconeogenesis. *Frontiers in endocrinology*. 2019;9:802.
58. Chang X, Bian H, Xia M, Zhu X, Sun X, Yang X, et al. Postprandial glucose is correlated with an increasing risk of liver fibrosis in Chinese patients with nonalcoholic fatty liver disease. *Diabetes & Metabolism*. 2022;48(6):101377.
59. Zhao W, Zhang L, Zhang G, Varkaneh HK, Rahmani J, Clark C, et al. The association of plasma levels of liver enzymes and risk of gestational diabetes mellitus: a systematic review and dose–response meta-analysis of observational studies. *Acta Diabetologica*. 2020;57(6):635-44.

60. Powe CE. Early Pregnancy Biochemical Predictors of Gestational Diabetes Mellitus. *Current Diabetes Reports*. 2017;17(2):12.

61. Mishra J, Srivastava SK, Pandey KB. Compromised renal and hepatic functions and unsteady cellular redox state during preeclampsia and gestational diabetes mellitus. *Archives of Medical Research*. 2021;52(6):635-40.

62. de Vries EM, Wang J, Leeflang MM, Boonstra K, Weersma RK, Beuers UH, et al. Alkaline phosphatase at diagnosis of primary sclerosing cholangitis and 1 year later: evaluation of prognostic value. *Liver International*. 2016;36(12):1867-75.

63. Xiong T, Zhong C, Sun G, Zhou X, Chen R, Li Q, et al. Early maternal circulating alkaline phosphatase with subsequent gestational diabetes mellitus and glucose regulation: a prospective cohort study in China. *Endocrine*. 2019;65(2):295-303.

64. Ali AT, Penny CB, Paiker JE, Psaras G, Ikram F, Crowther NJ. The relationship between alkaline phosphatase activity and intracellular lipid accumulation in murine 3T3-L1 cells and human preadipocytes. *Analytical biochemistry*. 2006;354(2):247-54.

65. Kwak MS, Kim D, Chung GE, Kim W, Kim YJ, Yoon JH. Role of physical activity in nonalcoholic fatty liver disease in terms of visceral obesity and insulin resistance. *Liver International*. 2015;35(3):944-52.

66. Nishimura T, Tanaka M, Saisho Y, Miyakoshi K, Tanaka M, Itoh H. Lower serum total bilirubin concentration is associated with higher prevalence of gestational diabetes mellitus in Japanese pregnant women. *Endocrine journal*. 2018;65(12):1199-208.

67. Mertoglu C, Gunay M, Gungor M, Kulhan M, Kulhan NG. A Study of Inflammatory Markers in Gestational Diabetes Mellitus. *Gynecology Obstetrics & Reproductive Medicine*. 2019;25(1):7-11.

68. Yılmaz ZV, Yılmaz E, İçer B, Küçüközkan T. Association of Complete Blood Count Parameters with Gestational Diabetes Mellitus. *Gynecology Obstetrics & Reproductive Medicine*. 2017;23(2):65-9.

69. Yang H, Zhu C, Ma Q, Long Y, Cheng Z. Variations of blood cells in prediction of gestational diabetes mellitus. *Journal of Perinatal Medicine*. 2015;43(1):89-93.

70. Gorar S, Abanonu GB, Uysal A, Erol O, Unal A, Uyar S, et al. Comparison of thyroid function tests and blood count in pregnant women with versus without gestational diabetes mellitus. *Journal of Obstetrics and Gynaecology Research*. 2017;43(5):848-54.

71. He Y, Liu C, Zeng Z, Ye W, Lin J, Ou Q. Red blood cell distribution width: a potential laboratory parameter for monitoring inflammation in rheumatoid arthritis. *Clinical rheumatology*. 2018;37:161-7.

72. Hou P, Xue H-P, Mao X-E, Li Y-N, Wu L-F, Liu Y-B. Inflammation markers are associated with frailty in elderly patients with coronary heart disease. *Aging (Albany NY)*. 2018;10(10):2636.

73. Tripolino C, Irace C, Carallo C, De Franceschi MS, Scavelli FB, Gnasso A. Red blood cell distribution width predicts two-hours plasma glucose levels during OGTT. *Clinical hemorheology and microcirculation*. 2016;62(1):63-9.