REVIEW ARTICLE

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The Utility of Platelets Indices and Other Blood Parameters in Gynecological Diseases

Wassan Nori,[1,*] Alaa Ibrahim Ali,[1] and Roaa Mokram Hamed[2]

[1] *Department of Obstetrics and Gynecology, College of Medicine, Mustansiriyah University, Baghdad, Iraq.*
[2] *The National Center of Hematology, Mustansiriyah University, Baghdad, Iraq.*

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ABSTRACT

Platelets are circulating cells known for their contribution to hemostasis, coagulation, protecting the blood vessels integrity, and wound healing. In the last decade, increasing evidence has linked platelets to activities beyond that. Platelets have been implicated in many physiological and pathological conditions involving immunity, inflammation, and even malignant tumors. Their role has been evaluated both as prognostic and diagnostic markers. Interestingly, platelets communicate with each other through a range of cytokines and interleukins secreted by their intracellular granules once activated or triggered. The understanding of this sophisticated mechanism of secretion and the genetic guidance of granule biosynthesis remained unclear. Complete blood count and its parameters are informative and affordable diagnostic tests as they highlighted platelet counts, plateletcrit, platelet indices; mean platelet volume, and platelet distribution width. Recently, increasing evidence suggests that implementing these parameters is a useful biomarker in the field of gynecology. Their role in obstetrics has been discussed in many studies, especially in hypertensive diseases, diabetes, abnormal fetal growth pattern, and early pregnancy loss. This review outlines the role of platelets and their indices in Gynecological disease.

Keywords: Platelets; Mean platelet volume; Platelets distribution width; Platelet counts; Gynecological diseases.

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INTRODUCTION

Platelets are small, non-nucleated discoid cells that circulate as resting fragments in the blood. Their mean life span is 8−9 days [1]. Platelet formation is a well-orchestrated cellular process called megakaryocytopoiesis and thrombopoiesis. The series begins with the hematopoietic stem cell as they proliferate, differentiate into progenitors, and mature into megakaryocytes producing functional platelets [2, 3].

Platelets exhibit multifaceted roles that exceed thrombosis/hemostasis. Recent reports have linked platelet indices to neoplastic transformation since the latter involves a chronic inflammatory process, which affects platelet parameters [4–6]. It is becoming increasingly clear that platelets have an integral role in regulating immunity and orchestrating inflammatory reactions. Platelet role may be protective or contribute to adverse inflammatory and thrombotic activities based on physiological or pathological conditions [7, 8]. Platelets are natural sources of growth factors such as platelet-derived growth factor (PDGF), vascular endothelial growth factor (VEGF), and insulin-like growth factor 1 (IGF-1) all show a key role in inflammation, angiogenesis, repair, and regeneration of the tissue [9, 10]. Many morphological alterations accompany the process of platelet activation in the environment of inflammation. Activated platelets seem larger, transform into spherical shapes, and form pseudopodia. As a result, activated platelets with enhanced pseudopodia numbers and sizes will have different indices [10, 11]. This was the basis of using mean platelet volume (MPV), platelet distribution width (PDW) a parameter of routine blood examination as diagnostic or prognostic factors in many infectious diseases [6]. Platelet distribution width (PDW) reflects the variation in platelet size distribution in a range of 8.3% to 56.6% [8, 12].

Thus, PDW can be utilized as a sign of some inflammatory diseases as their level changes under specific conditions compared to healthy individuals as in dengue fever [13, 14].

*Corresponding author: E-mail: dr.wassan76@uomustansiriyah.edu.iq
Phone number: +9647831889043

The mean platelet volume (MPV) is a precise measurement of platelet dimension, estimated by a hematological analyzer based on volume distribution in a range of 7.5−12.0 fL [15]. Under physiological conditions, MPV is negatively correlated to platelet count, which is necessary to establish hemostasis and preserve constant platelet mass. In other words, a reduction in MPV is associated with increased platelet production. As for pathologic conditions, this physiological balance is disturbed as in viral and bacterial infections [16, 17]. Interpreting the changes in platelet indices is not an easy task keeping in mind the complexity of the mechanisms involved. This review will discuss platelet indices' role from a diagnostic and prognostic view in several gynecological problems.

ADNEXAL TORSION

Adnexal torsion (AT) refers to a Gynecological emergency with fatal complications like pelvic thrombophlebitis and peritonitis. AT involves twisting the ovary or fallopian tube around its vascular axis, leading to the interruption of blood flow and thereby ischemic changes [18, 19]. Ultrasound and Doppler findings can be of value in managing AT; still, they are not conclusive, the proportion of patients diagnosed before surgery ranges between 1/5 and 3/5 of cases [20–22]. Therefore, a reliable method for preoperative diagnosis of AT is needed. A growing body of evidence suggests that complete blood count (CBC) and its parameters can be used as a marker for diseases associated with ischemia such as acute mesenteric syndrome, acute heart attack, and ischemic stroke [23, 24].

Tas et al., in a retrospective study, analyzed the relation of platelet indices in the diagnosis of AT [25]. The author compared 73 (24.5%) patients with AT and 223(75%) healthy controls assigned for elective Gynecological surgeries. Upon comparing the two groups hematological indices, a meaningful increase in white blood cells (WBC), platelet count, and platelets to lymphocyte ratio (PLR) have been reported. The MPV was significantly low in the AT cases compared to healthy controls. The mean number of lymphocytes, hematocrit levels, mean corpuscular volume (MCV), PDW, and plateletcrit levels showed no significant differences as $P>0.05$. A reduced MPV was independently linked to AT by logistic regression. Receiver operator curve ROC determined 10.35 fL as the criterion value of serum MPV to predict AT with 77.4% sensitivity and 74.2% specificity [25]. Interestingly, Tas et al.'s results contradict Kleli et al. [26] who declared that reduced platelet counts and increased MPV were reported in cases of AT, though these differences were statistically insignificant. Numerous studies reported an association between MPV changes and various inflammatory processes [24, 27].

One can appreciate the contradiction in both authors' results if we return to the basics. Platelets have an essential role in inflammation and tissue healing [23, 24]. Activated platelets triggered by inflammation or ischemia will suffer from several morphological changes: they become larger and take a sphere shape with pseudopodia. These alterations contribute to the increase in their MPV. Especially in the early onset of ischemic disease. An important point in practice [28–30]. Consuming the activated platelets will eventually reduce the MPV value, which explains the controversy in both studies [25, 26]. Thus, platelet counts, MPV, PDW, showed to be of diagnostic and prognostic value in ischaemic alignments [23, 31, 32].

In another study, Khan et al. [33] attributed the discrepancies in using platelets to methodological differences, different commercial CBC methods. Moreover, a long-time-interval between the event of torsion and hospital referral admission for many patients is another point to consider. Time lag will lead to consumption of large, hyperactive platelets at sites manifested as a reduction in the MPV in ongoing ischemic processes [34].

ECTOPIC PREGNANCY

Ectopic pregnancy (EP) results from a faulty tubal transport of the fertilized ovum combined with alterations in the microenvironment of a tubal lumen causing early implantation outside the endometrial cavity [35]. Tubal EP is one of the leading causes of maternal mortality, accounting for 0.4 per 1000 estimated ectopic pregnancies per year in the United Kingdom [36]. The diagnosis of EP can be confusing [37, 38]. There is a variation in the clinical picture: 33% of cases can be asymptomatic, some urgently presented as the acute abdomen or even in a collapsed state due to hypovolemic shock. Nine percent of ruptured cases remain silent until the time of presentation. To diagnose EP, we rely on the triad of the missed period, an ultrasound report indicating an empty uterus, and serial serum beta-human chorionic gonadotropins (β-HCG) values [27, 39, 40].

Ulkumen et al. [41] conducted a retrospective study comparing three sub-groups to estimate the role of platelet indices in cases of ruptured (39 cases ruptured/153 total cases of ectopic), unruptured (114 un-ruptured ectopic/153 total cases of ectopic) ectopic pregnancies versus healthy pregnant women. Their results showed a trend of reduced MPV in the EP, particularly in ruptured-subgroup versus healthy control. PDW was increased in the EP, particularly in the ruptured sub-group, in comparison to healthy control. Neither MPV nor PDW showed meaningful differences between the groups as P values were =0.62 and 0.45, respectively. Only Platelets count was significantly low(228.49 /mm3) in ruptured EP in comparison to non-ruptured sub-group(234.17 /mm3) and healthy control (P=0.005) [41].

Turgut et al. [42] in a prospective study enrolled tubal EP patients subdivided into two subgroups composed of 72/138 ruptured and 66/138 non-ruptured cases. Turgut et al. compared them to 72 healthy controls declaring that MPV was significantly larger in patients than controls (P=0.007) whether they were ruptured or not which contradicts the results reported by Ulkumen et al. The latter found no statistical differences between the two subgroups as P value was 0.89. Leukocytosis was significantly higher in the tubal EP group with tubal rupture when compared to the non-ruptured tubal EP and the control groups P=0.022 and P<0.001 respectively. Earlier studies attributed reduced MPV levels to low-grade inflammatory disorders, whereas elevated MPV values were accredited for high-grade inflammatory processes [32].

Ulkumen [41] attributed this contradiction to Turgut et al. study to multiple factors; one is hemorrhage which contributes to activated platelet, those showed altered MPV and PDW. Moreover, as a physiological pregnancy phenomenon, dilutional thrombocytopenia depended on the gestational age and was accredited to increase MPV and PDW levels during the pregnancy [6, 7]. Multiple studies have discussed the importance of platelets and platelet-derived factors in thrombosis, immunity, and inflammatory reaction [10, 11]. Certain inflammatory cytokines are elevated in EP at the implanta-

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tion site and circulatory system [27]. Consequent platelet activation will contribute to their increased number and associated morphological alterations. Platelets will develop pseudopodia and turn spherical, which will lead to alteration in PDW and MPV values [10]. The trend of reduced MPV and increased PDW in ruptured EP implies a potential high-grade inflammatory pathology. The reduction in platelet counts in ruptured EP cases reflects platelets' utilization at the inflammation site [41, 42]. However, further research is required to explain the utility of platelet indices as a prognostic marker.

MOLAR PREGNANCY

Molar pregnancy is a member of gestational trophoblastic disease (GTD) which is a heterogeneous disease group that shared an abnormal growth of trophoblastic tissue [43]. Luckily its malignant sequelae are uncommon diseases, one of which is invasive mole; a malignant variant of trophoblastic origin. It affects 15% of complete molar pregnancy cases with an ability to invade the myometrium and causing local hemorrhagic necrosis besides its ability to cause distant metastasis [43, 44]. The diagnosis of molar pregnancy depends on ultrasound imaging of a classical snowstorm appearance,-HCG titer, and definitive diagnosis will depend upon histopathological examination. Molar pregnancy is usually treated by suction curettage and /or chemotherapy according to the malignant potential of GTD followed by a period of follow-up [45, 46].

Zhang et al. [47] conducted a retrospective analysis on 102 invasive hydatidiform cases versus a healthy control. The authors concluded that a red blood cell distribution width RDW, absolute lymphocytes count, and platelets to lymphocytes ratio PLR were significantly increased in the invasive mole cases compared to healthy control as $P < 0.05$. The hemoglobin concentration, mean corpuscular volume, and platelets to lymphocytes ratio (PLR) were significantly decreased in the invasive mole cases versus the healthy controls ($P < 0.05$). However, the age, total WBC, MPV, PDW, and absolute neutrophil cells between invasive hydatidiform mole versus control groups were not statistically different. Further statistical analyses showed a negative correlation between RDW and neutrophilia to lymphocyte ratio NLR ($r = -0.24$; $P = 0.02$), RDW, and absolute neutrophil counts ($r = -0.22$; $P = 0.03$). A positive relationship between RDW and PDW ($r = 0.23$; $P = 0.02$) and RDW was linked with the clinical staging of invasive mole ($r = 0.35$; $P = 0.0001$)[47]. The reason for RDW and platelets increase in patients diagnosed with invasive mole is not fully clear. However, a possible explanation includes: inflammatory circumstances can increase RDW and platelet counts, increasing the heterogeneity of peripheral red blood cell RBC volume and platelets as a part of the primary immune response.

Consequently, this alteration will suppress the bone marrow hematopoietic action [48, 49]. The reduction in RBC surviving time, impaired iron absorption, and decreased RBC deformability are possible co-factors that depress erythropoietin response [47]. Another possible cause is the increase in the production of cytokines in patients with malignant tumor; which is part of the chronic inflammatory process keeping in mind that most of this cytokine possess receptors on the surface of the RBC furthermore many cytokines are stored in RBCs which acts as a reservoir for them. It is prudent to say that RBCs are accredited in inflammations alongside the gas exchange function [48–50]. Hunziker et al. [51] discussed that RBC life span is affected by the inflammatory reactions as it tends to rise in these reactions. On the other hand, the increase and positive correlation between RBC and PDW can be understood if we reviewed its uses in medicine [52]. PDW is mostly used in the setting of thrombocytosis as an indicator of a reactive process as in invasive mole cases and other Gynecological malignancies [53].

ENDOMETRIOSIS

Endometriosis is a common benign chronic disease that affects 6−10% of women in reproductive years [54, 55]. Affected patients are presented with chronic pelvic pain, adhesion band, and infertility [56]. Endometriosis is defined by an ectopic deposit of the endometrium stroma and epithelium outside the endometrial cavity [57, 58] while endometrioma is advanced endometriosis presented as ovarian cysts [59]. Endometriosis is classified into four stages: minimal, mild, moderate, and severe based on the laparoscopic classification, which is the gold standard for its diagnosis [60, 61].

Endometriosis is a disease of multiple theories that suggest a key role of inflammatory and immunological factors in the pathophysiology of endometriosis [62, 63] especially with increased inflammation markers in the serum and peritoneal fluid that imply a chronic inflammatory process [63]. Many kinds of literature used platelet indices in various inflammatory conditions as Crohns disease, SLE, obesity, and vascular diseases [23, 24]. Platelets have a primary hemostasis function. Besides, there is increased recognition of the key roles of platelets in inflammatory reaction [10, 11]. Once platelets are activated, they release their contents of variable cytokine, chemokine, and growth factor [6, 7]. In an inflammatory condition, a positive correlation between thrombopoietin, platelet progenitors, functional activities, and elevated platelets count is obvious.

Many researchers have pursuit a standardized and less invasive test to diagnose and identify the extent of endometriosis. The association between platelet indices as plateletcrit, PDW, and MPV and the white blood cell count and C-reactive protein (CRP), has highlighted the correlation between platelet and inflammatory processes and offers a non-invasive way of diagnosis [64–66].

Avcioğlu et al. [67] have investigated platelets' utility and their indices as a non-invasive predictor of endometriosis's severity in those affected. By correlating them to the laparoscopic assessment based on the revised criteria of the American Society for Reproductive Medicine [60]. The authors enrolled cases of severe endometriosis; they declared that platelet number and plateletcrit levels were meaningfully increased while MPV and PDW values were meaningfully reduced compared to early endometriosis Stages 1-2. Moreover, they correlated platelets and plateletcrit (r: 0.800, P: 0.001) and plateletcrit (r: 0.727, P: 0.002) versus the white blood cell count as an inflammatory marker [67, 68].

Turgut et al. [69] in a similarly designed study discussed a cut-off value for platelet indices in endometriotic patients to the diseases stage and severity. Patients with endometriosis had higher WBC levels, MPV, and lower lymphocyte count and lymphocyte-to-monocyte ratio (LMR) than the control group. The cut-off values were 8fL for MPV at 75.2% and 68.4% sensitivity & specificity respectively. The normal range of platelet volumes is 9.4−12.3 fL [69]. For LMR, the cut-off values were 5.6 with 66.1% and, 50% sensitivity and specificity respectively. Women with stages III or IV endometrio-

sis showed a significant reduction in MPV and lymphocyte to monocyte ratio (LMR) values than women with stages I or II. They recommend that MPV and LMR serve as a good predictor to distinguish endometriotic-affected women from healthy controls [69]. okun et al. [70] have studied the role of platelets in differentiating endometriosis and adenomyosis. They revealed a significant reduction in MPV(8.5fL) in the adenomyosis group in comparison to endometriosis (9 fL, $p<0.05$) and healthy control groups (9 fL, $p<0.01$). Modified platelet activity (MPV/PC) was significantly reduced in adenomyosis patients compared to healthy control. The odds ratio was used to evaluate risk factors correlated to endometriosis. Mean platelet volume was insignificant as a risk factor suggesting it is not a useful diagnostic marker for the differentiating of endometriosis and adenomyosis [70].

Increased platelet count in severe endometriosis supports high-grade inflammatory reaction, which is accredited for endometriosis development. Megakaryocytopoiesis is programmed to deliver needs for activated platelets in physiological and pathological circumstances, with associated alterations in platelet indices [71]. Frequently there is an inverse correlation between platelet number and MPV in physiological and pathological circumstances as a high-grade inflammatory process, reflecting the tendency to secure hemostasis by a constant platelet mass [32, 72]. The increased thrombopoiesis will increase the number of platelets; these newly formed platelets will have reduced MPV values compared to the intensively consumed platelets during inflammation [5, 72, 73].

CONCLUSION

Blood parameters, especially platelets are pivotal cells in hemostasis, coagulation, and repair its primary role has extended beyond where we were ten years ago to include inflammation, immunity, and even metastasis of tumor cells. There are simple and affordable tests. However, targeting the fields of platelets should be tailored according to the situation, they can be an adjuvant test to support provisional diagnosis in cases of lack of more suffocated test. Further clinical research is necessary to study their role in the Gynecological aspects of medical practice.

CONFLICT OF INTEREST

The authors declare that there is no conflict of interest.

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