

# Hematological Profile Changes Among Oral Contraceptive Users: A Narrative Review

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**Abstract:** Hematological profiles are measurable indices of blood that can be used to identify and monitor some pathological and physiological abnormalities. Oral contraceptives are one of the factors which may exert an influence on hematological laboratory test results and have a critical importance. Therefore, the main goal of this review was to evaluate the hematologic profile alterations brought on by the use of oral contraceptives. Accordingly, even though there were studies that showed no significant difference, most of the oral contraceptive users had higher hemoglobin, platelet, and erythrocyte counts than non-users. Other erythrocyte metrics, such as mean corpuscular volume, mean corpuscular hemoglobin, mean corpuscular hemoglobin concentration and red cell dispersion width, did not significantly change. Moreover, leukocyte count and leukocyte differential count had no significant change among the oral contraceptive users in comparison to non-users. Oral contraceptive users typically have shorter prothrombin times, activated partial thromboplastin times, thrombin times, and greater levels of fibrinogen and D-dimer compared to non-users. However, this review is a narrative review and did not show the pooled effect of oral contraceptives on these hematological parameters. Therefore, it is recommended to do systematic and meta-analysis to determine the pooled effect of oral contraceptives.

**Keywords:** contraceptives, hematological parameters, hematopoiesis, hemostasis, oral contraceptives, thromboembolism

## Introduction

### Background

Hematological profiles are measurable indices of blood that can be used to identify and monitor some pathological and physiological abnormalities. Different illness situations that influence hematopoietic physiology and immunological responses can have an impact on these profiles,<sup>1,2</sup> and they are frequently utilized in clinical settings in the medical field.<sup>3,4</sup> These include parameters routinely given by complete blood count that gives a clue about erythrocyte count (EC), Mean corpuscular volume (MCV), Mean corpuscular hemoglobin concentration (MCHC), Mean corpuscular hemoglobin (MCH), Erythrocyte volume fraction (EVF), Hemoglobin (Hb) concentration and Red cell dispersion width (RDW).<sup>5</sup>

Hematological markers that have levels outside of normal ranges can be used to diagnose disorders like cancer, immunological diseases, and cardiovascular disease.<sup>6</sup> For example, RDW, RBC parameter that measures the variability in the size of erythrocytes circulating in the blood circulation, is usually used for the differential diagnosis of hematological disorders<sup>7</sup> including iron deficiency anemia (anemia that results when there is deficiency of iron for the production of erythrocytes), megaloblastic anemia, and thalassemia<sup>8,9</sup> and a variety of other diseases, such as heart failure,<sup>5</sup> atrial fibrillation,<sup>10</sup> lung cancer<sup>11</sup> or disorders characterized by inflammation.<sup>12</sup> Hematocrit, more commonly known as the EVF, is a determinant of whole blood viscosity, the viscosity of which will affect peripheral resistance to blood flow, which will affect blood pressure.<sup>13</sup> Red cell destruction due to RBCs' reduction in deformability and an increase in cell size, high and low Hb levels are associated with cardiovascular risk.<sup>14</sup>

The second most frequent cell type, platelets are small anucleated cell fragments that are essential for maintaining vascular integrity and controlling hemostasis. In addition to their primary role in hemostasis, platelets are crucial in the defense against viral infections.<sup>15</sup> The most important parameters related to platelet count include plateletcrit, Mean platelet volume (MPV)

which is the measure of average size of platelets, and Platelet distribution width (PDW).<sup>4</sup> The morphology of platelets changes as a result of their activation, and an increase in platelet swelling results in a rise in MPV and PDW.<sup>16</sup> A more precise index of activation platelet is the distribution width of platelets, which represents the reactivity of the thrombocytes.<sup>17</sup> In circumstances like hypertension, activation of thrombocytes is a risk factor for thrombotic disorders.<sup>18</sup>

White blood cells (WBC) are immune system cells that protect the body against external substances and infectious diseases. Similar to how RBCs and thrombocytes are created, they are all created in the bone marrow microenvironment from hematopoietic stem cells (HSC). These cells, called WBCs, can be seen all over the body, especially in the lymphatic and blood systems.<sup>18</sup> Changes in WBC may indicate different disorders, including infection, inflammation, and hematological cancer.<sup>6</sup>

Coagulation tests encompassing Prothrombin time, Activated partial thromboplastin time (APTT), and fibrinogen are frequently used to evaluate coagulopathy and to guide hemostatic interventions.<sup>19,20</sup> Additional tests can be performed to quantify the levels of particular coagulation factors, screen for inhibitors of particular coagulation factors, and evaluate the thrombin clotting time.<sup>20</sup> Thrombin, activated factor XIII and plasmin work in sequence to create a D-dimer antigen, which is another coagulation parameter and a distinctive hallmark of fibrin breakdown. Its testing has primarily been used in clinical settings to rule out venous thromboembolism (VTE).<sup>21</sup>

The rise in fibrinolytic activity balances out the heightened coagulation activity, maintaining hemostatic equilibrium. However, thrombus formation can happen when there is local vascular endothelium damage or when other thromboembolism risk factors, such smoking and advanced age, combine. The little variations in coagulation factor levels among women using different oral contraceptive (OC) formulations may be significant in these circumstances.<sup>22</sup>

The laboratory results of hematological tests may be impacted by various conditions. Age, activity, bed rest, food ingestion, alcohol ingestion, menstrual cycle, obesity, posture, pregnancy, race, gender, smoking, and OC utilization are among factors that may influence laboratory results.<sup>23</sup> The present review was designed to give a brief account of the studies carried out to elucidate the changes in hematological profiles linked to the usage of OCs.

## Mechanism of Action of Oral Contraceptives on Hematopoiesis

Estrogen administration significantly increases the division and proliferation of HSCs and thus explains the higher blood counts in women during the reproductive years.<sup>24,25</sup> High amounts of the estrogen receptor (ER) are expressed by HSCs, and estrogen/ER $\alpha$  signaling promotes self-renewal of HSC, HSC expansion and erythropoiesis.<sup>25</sup>

The use of hormonal contraceptives, which is generally associated with lighter menstrual periods, is associated with better indicators of iron status indicators.<sup>26–29</sup> Poorer iron status indicators (low levels of serum ferritin and Hb) have been linked to menstrual blood loss.<sup>27,30,31</sup> Serum iron levels have been shown to be higher among OC users.<sup>29,32</sup> The endometrium shrinks as a result of progestogenic tablets' endometrial atrophy, and their usage results in scanty withdrawal bleeding that is less than in a typical cycle. This is the first factor that is assumed to be the cause of elevated blood iron content.<sup>33</sup>

Additionally, OCs improve gut absorption of iron<sup>34</sup> and were known to increase biomarkers of tissue iron stores (serum ferritin) thus lowering the risk of developing anemia.<sup>26,35,36</sup> The OC pill increases serum ferritin, therefore improves the body's iron status.<sup>37,38</sup> Oral contraceptives enhanced inflammatory-driven increases in ferritin while decreasing the frequency and volume of menstrual bleeding.<sup>39</sup> As a result, the usage of OCs may be linked to an improvement in Hb status, enhancing the health of low-socioeconomic-class women.<sup>40</sup>

Oral contraceptive decreases intestinal re-absorption of folate and vitamin B-12 which resulted in significantly decreased serum levels of these vitamins in women taking OC pills, even when controlling for intake through diet, and may end up in megaloblastic anemia.<sup>41–44</sup>

## Mechanism of Action of Oral Contraceptives on Hemostasis System

With enhanced procoagulant effects, decreased anticoagulant effects, and equivocal effects on fibrinolysis, oral contraceptives have a net prothrombotic impact (with increases in the activity of the antifibrinolytic system).<sup>45</sup> The biologic, unifying mechanism underlying the thrombotic effects of OC pills is still unclear, despite the fact that individual alterations in procoagulants and anticoagulants with OC pill usage are widely characterized.<sup>46</sup>

## Procoagulant Effects

Oral contraceptives increase adenosine diphosphate, which causes fibrinogen binding and platelet aggregation.<sup>47</sup> They also cause a noticeable and long-lasting increase in the synthesis of cell membrane lipids.<sup>48</sup> An increased synthesis can have a significant influence on hemostatic physiology since platelet membrane lipids are crucial pro-coagulant factors in hemostasis.<sup>49</sup> There have also been reports of increased endothelial replication of endothelial cells and increased endothelial synthesis of the Von Willebrand factor (VWF).<sup>50</sup> This may also explain why platelets stick to vascular endothelium more readily and why thrombosis is more likely to occur.

Estrogen is linked to a variety of prothrombotic pathways that modify coagulation proteins and tip the hemostatic scales in favor of a prothrombotic state. Increased levels of factors II, VII, VIII, X, and fibrinogen, reduced levels of protein S and Antithrombin (AT), and activated protein C resistance are some of these changes. The PT and APTT may become shorter as a result of these modifications.<sup>51</sup>

Prothrombin, factor VII, factor VIII, factor X, fibrinogen, and prothrombin fragment 1+2 levels rise while factor V levels fall during the use of OCs, according to a recent randomized, crossover research. It is now understood that prothrombin<sup>52</sup> and factor VIII<sup>53</sup> concentrations which are somewhat elevated are linked to a more risk of venous thrombosis. Since factor V may exhibit anticoagulant activity because of its ability to act as a cofactor in the inactivation of activated factor VIII that is mediated by activated protein C; a reduction in the level of factor V may contribute to the thrombotic side effects of OCs.<sup>54</sup>

## Fibrinolytic Effects

The usage of OCs is indicated to increase fibrinolytic activity through changes in fibrinolytic variables such as plasminogen, tissue plasminogen activator (T-PA), Plasminogen activator inhibitor type 1 (PAI-1), and plasmin-anti-plasmin complexes.<sup>55,56</sup> Tissue plasminogen activator levels are raised and PAI-1 levels are decreased by COCs, which has an impact on fibrinolysis. Higher levels of Thrombin activatable fibrinolysis inhibitor (TAFI) in women taking COCs appear to counterbalance these effects, though.<sup>56</sup>

Because of the lack of evidence linking alterations in the fibrinolytic system to an elevated risk of venous thrombosis, it is unknown if alterations in fibrinolytic activity during OC usage has therapeutic consequences. The TAFI, which when activated prevents fibrinolysis by removing from fibrin the lysine residues necessary for the binding and activation of plasminogen, is one antifibrinolytic mechanism.<sup>57</sup> Venous thrombosis is at increased risk due to elevated TAFI levels.<sup>58</sup>

The total clot-lysis time was shown to be unaffected by OC usage in an assay for clot lyses that measured the activity of both the fibrinolytic system and the TAFI dependent antifibrinolytic pathway. This data implies that the increased fibrinolytic potential caused by the use of OCs is offset by the TAFI system's enhanced down-regulation of fibrinolysis. Increased TAFI levels and improved thrombin (the activator of TAFI) synthesis are most likely responsible for the increased TAFI-dependent inhibition of fibrinolysis.<sup>39</sup>

## Change in Blood Cells and Blood Cell Parameters Among Oral Contraceptive Users

### Red Blood Cell Parameters

To make sure the tissues receive a proper amount of oxygen, the red cell volume must be maintained. Erythropoietin primarily regulates the process that links red cell synthesis with tissue oxygen supply. The creation of Hb, a specialized protein necessary for delivering oxygen within the red cell, is a prerequisite for the formation of functioning RBCs. As the erythroid precursor cells develop, this protein is produced more and more. Iron atoms from heme molecules are introduced into globin to form it.<sup>59</sup> Recycled iron from the Hb of dying erythrocytes is used to maintain the Hb level, and when necessary, iron from the reticuloendothelial storage is also used. The main protein that stores iron is called ferritin, and the concentration of ferritin in the blood is a reliable predictor of the quantity of stored iron. In plasma, the carrier molecule transferrin is linked to iron.<sup>59</sup>

RBC count<sup>60</sup> and Hb concentration rise as a result of OCs.<sup>30,61</sup> The decrease in menstrual blood loss, which is known to be frequent among OC users, may be to blame for the rise in RBC count.<sup>26,30,34,36,62–64</sup> Menstrual blood loss has been

linked to worse iron status markers.<sup>27,30,31</sup> Likewise, the use of hormonal contraceptives is linked to better markers of iron status and is frequently related with lighter menstrual cycles.<sup>26–29</sup> According to reports, OC users had higher serum iron levels.<sup>29,32</sup> Progestogenic medications promote endometrial shrinkage and generate scanty withdrawal bleeding that is less than in a typical cycle, which is the first reason hypothesized to be the cause of elevated serum iron content.<sup>33</sup>

Additionally, OCs have a tendency to boost gastrointestinal absorption of iron<sup>34</sup> and they are known to raise tissue iron reserves' biomarkers, which decreases the likelihood of developing anemia.<sup>26,35,36</sup> Higher ferritin levels in OC users are a positive biomarker impact. Reduced menstrual bleeding frequency and volume, as well as increases in ferritin brought on by inflammation, are two reasons why there may be increased levels of ferritin.<sup>39</sup>

However, several investigations revealed no discernible alteration in RBC count, EVF,<sup>60,65,66</sup> and Hb values.<sup>46,60,66</sup> Ended, there was also a contradictive study that showed a decrement in RBC count among OC users compared to non-users.<sup>63</sup> However, the change in other RBC characteristics such MCV, MCH, MCHC, and RDW was not significantly impacted by the change in RBC count.<sup>60</sup> Also a study by<sup>66</sup> showed no difference in MCV, MCH, and MCHC between the groups who were using OCs and those who were not using (Table 1).

**Table 1** Changes in Red Blood Cell Parameters Among Oral Contraceptive Users

Parameter	OC Used	Result		Conclusion	Author
		Users	Non-Users		
RBC × 10 <sup>12</sup> /L	COC	4.35 ± 0.48	4.14 ± 0.42	Increase	[61]
	Progestin only	–	–	Decrease	[63]
	COC	4.4 ± 0.51	4.6 ± 0.39	No difference	[69]
EVF (%)	COC	37.64 ± 2.46	36.52 ± 3.56	No difference	[60]
	COC	34.42	36.40	No difference	[65]
	COC	35.8 ± 3.27	37.3 ± 3.18	No difference	[69]
Hb (g/dl)	Not indicated	–	–	Increase	[30]
	COC	–	–	Increase	[61]
	COC	12.45	12.67	No difference	[46]
	COC	12.32 ± 0.81	11.93 ± 1.20	No difference	[60]
	COC	11.9 ± 1.14	12.1 ± 1.24	No difference	[69]
MCV	COC	87.04 ± 5.92	88.03 ± 4.56	No difference	[60]
	COC	81.4 ± 8.67	81.0 ± 7.73	No difference	[69]
MCH (pg)	COC	28.73 ± 2.16	28.47 ± 1.76	No difference	[60]
	COC	27.2 ± 3.32	26.7 ± 2.96	No difference	[69]
MCHC (g/dl)	COC	32.71 ± 0.90	32.55 ± 0.93	No difference	[60]
	COC	33.3 ± 0.93	32.9 ± 1.13	No difference	[69]
RDW (%)	COC	13.05 ± 1.35	12.89 ± 1.61	No difference	[60]

**Note:** The conclusions are derived from the respective authors listed.

**Abbreviations:** g/dl, gram per deciliter; pg, pico gram.

## Platelet Parameters

Circulating platelets, coagulation factors, the endothelium of the blood vessel wall, naturally occurring anticoagulants (such as protein C, protein S, and AT), and fibrinolysis (clot digestion) all interact to regulate hemostasis.<sup>59</sup> The platelet count assesses if there are enough platelets to achieve early hemostasis. There is a typical range of 150,000 to 450,000 platelets.<sup>67</sup>

Use of OCs raises platelet count.<sup>65,67</sup> The increase in the number of platelets may be explained by the fact that estrogen administration significantly increases the division and proliferation of HSCs in women during the reproductive years.<sup>24,25</sup> Additionally, PLT count<sup>46,60,66,68,69</sup> and MPV<sup>66</sup> among OC users were observed to have remained stable. The lack of substantial alterations might be attributable to the use of smaller sample sizes or the short duration of OC usage, which might not have produced differences in these parameters (Table 2).

## White Blood Cell Parameters

White blood cells, also referred to as leukocytes, are the body's defense against infection. Depending on the presence or lack of granules in the cell cytoplasm, they can be generically categorized as granulocytes or agranulocytes. Neutrophils (polymorphs), eosinophils, and basophils are examples of granulocytes. Monocytes and lymphocytes are examples of circulating agranulocytes. By phagocytosing pathogens, neutrophils and monocytes have a crucial part in the defense against acute bacterial infections. Lymphocytes help phagocytes by generating a regulated immune response.<sup>59</sup>

Regarding their count, there was no difference between OC users and non-users in WBC.<sup>46,60,65,66</sup> Additionally, there was no discernible difference between users and non-users in the WBC differential count, which includes LYM, MON, NEU, EOS, and BAS percentages<sup>60</sup> (Table 3).

## Changes in Coagulation Profiles Among Oral Contraceptive Users

Platelets collect on the blood vessel endothelium as a result of vascular injury, and a group of coagulation factors designated by their roman numbers are activated. Von Willebrand factor serves as a carrier of factor VIII and promotes platelet interaction with the exposed endothelium. The final step in the coagulation pathway's activation is thrombin's conversion of fibrinogen into a fibrin gel. A sophisticated network of activating and feedback processes makes sure that proteases are formed to both activate and degrade the coagulation factors, avoiding the development of large-scale clots.<sup>59</sup>

The fibrinolytic system, which is made up of the proenzyme plasminogen and its related activators and inhibitors, regulates the removal of fibrin. The tissue protease, T-PA, which is triggered concurrently with the initiation of the coagulation process, is the primary activator of plasminogen. The fibrinolytic system's final step is plasmin, which breaks

**Table 2** Changes in Platelet Parameters Among Oral Contraceptive Users

Parameter	OC Used	Result		Conclusion	Author
		Users	Non-Users		
Platelet $\times 10^9/L$	COC	270.59	249.75	Increase	[65]
	COC	–	–	Increase	[67]
	COC	289.86	283.38	No difference	[46]
	COC	206.28 $\pm$ 39.08	196.65 $\pm$ 35.12	No difference	[60]
	COC	–	–	No difference	[66]
	COC	–	–	No difference	[68]
	COC	258 $\pm$ 100	294 $\pm$ 69	No difference	[69]
MPV	COC	–	–	No difference	[66]

**Note:** The conclusions are derived from the respective authors listed.

**Abbreviation:** L, liter.

**Table 3** Changes in White Blood Cell Parameters Among Oral Contraceptive Users

Parameter	OC Used	Result		Conclusion	Author
		Users	Non-Users		
WBC $\times 10^9$ /L	COC	5.07	4.93	No difference	[65]
	COC	–	–	No difference	[66]
	COC	6.49	6.99	No difference	[46]
	COC	6.07 $\pm$ 1.29	6.19 $\pm$ 1.33	No difference	[60]
LYM%	COC	32.69 $\pm$ 3.83	32.81 $\pm$ 4.11	No difference	[60]
MON%	COC	8.04 $\pm$ 1.63	8.30 $\pm$ 1.82	No difference	[60]
NEU%	COC	56.12 $\pm$ 3.70	55.67 $\pm$ 4.14	No difference	[60]
EOS%	COC	2.35 $\pm$ 1.10	2.16 $\pm$ 0.83	No difference	[60]
BAS%	COC	0.91 $\pm$ 0.25	1.00 $\pm$ 0.34	No difference	[60]

**Note:** The conclusions are derived from the respective authors listed.

**Abbreviation:** L, liter.

down fibrin and fibrinogen into degradation products (FDPs) such fibrinopeptide A and D-dimer. Plasminogen activator inhibitor-1 is a potent inhibitor of T-PA and is mostly generated by endothelial cells.<sup>59</sup>

The liver produces proteins C and S, which are physiological anticoagulants that depend on vitamin K. Through the neutralization of active coagulation factors V and VIII, they work as one of the primary regulators of hemostasis. Congenital or acquired protein C or S deficiency are both possible.<sup>70</sup> A glycoprotein called antithrombin predominantly inhibits thrombin while also inhibiting a number of activated coagulation proteins.<sup>71</sup>

Several investigations were made to clarify the effects of OCs on blood coagulation<sup>72,73</sup> and it is important to emphasize here the changes to the coagulation profile brought on by using these drugs.

## Fibrinogen

Fibrinogen level increases among users of OCs.<sup>46,65,67,74,75</sup> The increase may be because of the effect of the estrogen hormone. The hormone has been reported to increase the level of various coagulation proteins including fibrinogen.<sup>51</sup> On the contrary, fibrinogen level in OC pill users was found to be similar to non-users among Chinese women.<sup>76,77</sup>

## Activated Partial Thromboplastin Time

A test called activated partial thromboplastin time is used to check for anomalies in the intrinsic and general clotting systems as well as to track how well circulating heparin is preventing clotting. It assesses the activity of factors from the intrinsic and common pathways, including factors I, II, V, VIII, IX, X, and XI.<sup>78</sup>

Shorter APTT has been demonstrated among users of OC.<sup>65,69,73,75,79</sup> Shorter APTTs may occur with the administration of OCs if one or more of the clotting factors, including as prothrombin, factor VIII, factor X, fibrinogen, and prothrombin fragment 1+2, as well as due to decreases in the levels of protein S, AT, and activated protein C resistance.<sup>22,50,80</sup> Few studies, meanwhile, claimed that there was no discernible difference in APTT levels between people who used and did not use OC.<sup>46,67,76</sup>

## Prothrombin Time

The extrinsic and common coagulation pathways are tested in the laboratory using the prothrombin time. It is the amount of time needed for platelet-poor plasma to clot after calcium, phospholipid, and tissue factor have been added. The component that is “extrinsic” to the plasma-based coagulation mechanism is the tissue factor. Patients on warfarin for

anticoagulation may experience isolated prolongations of the PT due to factor VII insufficiency, fibrinogen abnormalities, or both. It is also regarded as the most accurate screening method for coagulopathies caused by malfunction of the liver.<sup>81</sup>

Shortening of the PT<sup>46,65,67,73,75</sup> has been demonstrated in OC users. Increases in the levels of activity of one of the clotting factors including prothrombin, factor VII, factor X, fibrinogen, and prothrombin fragment 1+2 and decreases in the levels of factor V, AT, protein S, and activated protein C resistance during the use of OCs might cause shorter PT.<sup>22,51</sup> However, the PT of OC users resulted in no difference from the non-users according to other studies.<sup>69,76,77,79</sup>

## Thrombin Time

The term “thrombin time” (TT) refers to the amount of time needed for fibrin to polymerize into a solid clot when thrombin is present.<sup>6</sup> It mostly reflects the fibrinogen concentration. However, it also reflects the fibrinopeptides’ cleavability and fibrinogen’s polymerization.<sup>82</sup> When fibrinogen levels are low, fibrinogen is dysfunctional, or thrombin inhibitors such heparin or fibrin-split products are present, the TT is extended but remains normal in individuals with abnormalities in the intrinsic or extrinsic route.<sup>20</sup>

Shortening of the TT has been reported among women that were using OCs.<sup>65,67,75,77</sup> The shortening of TT maybe because of the increase in the concentration of fibrinogen among OC users.<sup>51,80,82</sup>

## D-Dimer

The D-dimer antigen, a characteristic biological indicator of fibrin breakdown, is produced by the sequential activities of the enzymes thrombin, activated factor XIII, and plasmin.<sup>21</sup> Oral pill users were shown to have considerably higher D-dimer levels than non-users.<sup>65,79,83</sup> The enhanced fibrinolytic activity that prevents excessive fibrin deposition inside the vascular channels and its obstructive effects is reflected in the higher plasma D-dimer level. As independently reported by Winkler and Meijers et al, the enhanced fibrinolysis thereby physiologically counteracts the hypercoagulable condition and maintains normal circulation<sup>55,56</sup> (Table 4).

**Table 4** Changes in Coagulation Profile Among Oral Contraceptive Users

Profile	Type of OC Used	Result		Conclusion	Author
		OC Users	Non-Users		
PT in second	COC	11.46	13.79	Decrease	[65]
	COC	-	-	Decrease	[67]
	COC	13.4	13.6	Decrease	[73]
	COC	12.8 ± 1.5	13.7 ± 2.05	Decrease	[75]
	COC	10.35	10.78	Decrease	[46]
	Both	14	13.4	No difference	[77]
	Not indicated	14.8 ± 1.2	14.8 ± 2.1	No difference	[76]
	COC	11.8 ± 2.27	12.4 ± 1.08	No difference	[69]
	Not indicated	14	13.5	No difference	[79]

(Continued)

**Table 4** (Continued).

Profile	Type of OC Used	Result		Conclusion	Author
		OC Users	Non-Users		
APTT in second	COC	27.99	32.49	Decrease	[65]
	COC	40.9	41.9	Decrease	[73]
	COC	32.6 ± 1.92	33.7 ± 1.52	Decrease	[75]
	COC	25.9 ± 2.61	28.3 ± 2.76	Decrease	[69]
	Not indicated	31.3	33	Decrease	[79]
	Not indicated	33.1 ± 3.9	34.3 ± 4.9	No difference	[76]
	COC	-	-	No difference	[67]
	COC	29.83	30.46	No difference	[46]
TT in second	COC	17.57	20.45	Decrease	[65]
	COC	-	-	Decrease	[67]
	COC	11.9 ± 1.81	12.6 ± 1.27	Decrease	[75]
	Both	9.1	9.8	Decrease	[77]
Fibrinogen in mg/dl	COC	387.10	276.85	Increase	[65]
	COC	-	-	Increase	[67]
	COC	625	260	Increase	[74]
	COC	347 ± 80.9	305.9 ± 45.99	Increase	[75]
	COC	327.47	296.57	Increase	[46]
	Not indicated	161.4 ± 64.3	161 ± 71	No difference	[76]
	Both	266	249	No difference	[77]
D-dimer in ng/mL	COC	813.36	257.04	Increase	[65]
	Not indicated	1000	Negative	Increase	[79]
	COC	350 ± 0.07	210 ± 0.07	Increase	[83]

**Notes:** Negative D-dimer value is when the D-dimer level is below a predetermined cut-off threshold. The conclusions are derived from the respective authors listed.

## Oral Contraceptive Use Associated Coagulation Disorders

Women on combined OCs have consistently noted changes in blood coagulation that may be the cause of their elevated risk of thromboembolic illness.<sup>73</sup> The balance of hemostasis is impacted by estrogen, and its usage as Combination oral contraceptives<sup>5</sup> are linked to an increased risk of arterial thrombosis<sup>52</sup> and a greater risk of VTE, however the exact risk is uncertain.<sup>84,85</sup>

The risk of VTE may vary across different OCs due to the progestin component.<sup>84</sup> The risk of thrombosis was increased more among users of OCs containing third-generation progestin, drospirenone, and cyproterone acetate than in users of second-generation tablets.<sup>85</sup> It is essential to comprehend that women utilizing COCs run the chance of developing VTE if there is a family history of the condition.<sup>86</sup> The risk of venous thrombosis decreases in COC users with sustained use and reduced estrogen dose. Progestogen-only drugs were not associated with an increased risk of venous thrombosis.<sup>81,87</sup>

## Conclusion

Despite studies that found no difference to be statistically significant, most OC users had higher Hb, PLT, and RBC counts than non-users did. However, other RBC characteristics as MCV, MCH, MCHC, and RDW showed no obvious difference. Moreover, WBC and its differential count had no significant change among the OC users in comparison to non-users.

In contrast to non-users, OC users' coagulation states, measured through tests including PT, APTT, and TT, were shortened, and their levels of fibrinogen and D-dimer tended to rise. An increase in coagulation proteins and a decrease in anticoagulant proteins may be the cause. These might increase the risk of thrombosis among OC users. When pre-exposure variables such as family history of VTE exist, the thrombotic risks might be further increased. Since VTE runs in families, caution should be used while giving these OCs to patients.

Oral contraceptives had a substantial impact on the hematological profile, particularly RBC count, platelet count, Hb, and coagulation states including APTT, PT, TT, fibrinogen, and D-dimer levels, albeit results were not consistent across studies. As a narrative review, our analysis did not demonstrate the pooled impact of OCs on these hematological parameters. Therefore, systematic and meta-analysis are advised to ascertain the combined impact of OCs.

## Abbreviations

APTT, Activated Partial Thromboplastin Time; AT, Antithrombin; COC, Combined Oral Contraceptive; EC, Erythrocyte count; ER $\alpha$ , Estrogen Receptor- $\alpha$ , EVF, Erythrocyte Volume Fraction; Hb, Haemoglobin; HSC, Hematopoietic Stem Cell; MPV, Mean Platelet Volume; MCH, Mean Corpuscular Hemoglobin; MCHC, Mean Corpuscular Hemoglobin Concentration; MCV, Mean Corpuscular Volume; OC, Oral Contraceptive; PAI-1, Plasminogen Activator Inhibitor Type-1; PDW, Platelet Distribution Width; TAFI, Thrombin Activatable Fibrinolysis Inhibitor; PT, Prothrombin Time; TT, Thrombin Time; T-PA, Tissue Plasminogen Activator; RBC, Red Blood Cell; RDW, Red Cell Dispersion Width; VTE, Venous Thromboembolism; VWF, Von Willbrand Factor; WBC, White Blood Cell.

## Disclosure

The authors report no conflicts of interest in this work.

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