

Determination of D-Dimer Levels Among Healthy Women Using Oral Contraceptives: A Cross-Sectional Study Comparative Analysis

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The oral contraceptive pills (OCPs) have been commonly used to regulate hormones and control conception in females. The use of OCPs causes marked changes in the coagulation pathway making them prone to venous thromboembolism (VTE). The D-dimer level has been found to be an important biomarker of fibrin turnover and a tool to interpret the possibility of VTE. This cross-sectional comparative study aims at assessing the effect of the OCPs on D-dimer levels and comparing them with the existing global evidence. The study was cross sectional in design; it was carried out in Khartoum, Sudan. It involved 200 women; 100 women in the case group were taking oral combined OCPs while the other 100 women who made up the control group were not using the OCPs. D-dimers concentration levels were measured using Ichroma™ II fluorescence immunoassay. The mean level of D-dimer was significantly elevated in the case group (418 ± 104.3 ng/mL) compared to the control group (223 ± 39.2 ng/mL; $P < 0.001$). In the case group, 62% of participants had a higher than clinical value of D-dimer (400 ng/mL), while only 5% of control group subjects showed a higher value. No significant relationship was detected between the level of D-dimer and age ($P > 0.05$), but the level showed a positive correlation with OCP period of use ($P < 0.05$). Women on OCP who are healthy show a state of continuous and physiological rise in their D-dimer concentration. This shows a condition of increased fibrin turnover. These findings suggest that OCP use may influence baseline D-dimer concentrations and could potentially affect the interpretation of D-dimer results in clinical practice. These findings should therefore be considered hypothesis-generating and warrant further prospective studies involving women with suspected VTE to determine whether OCP-specific reference ranges or diagnostic thresholds may be clinically useful.

Keywords: Clinical laboratory analysis; D-dimer; Hemostasis; Oral contraceptives; Venous thromboembolism; Procoagulant state.

Since its appearance in the late 1960s, hormonal contraception has become a major step forward in reproductive health, offering efficient family planning and management of numerous gynaecological problems, such as PCOS,

endometriosis, and primary dysmenorrhea.^{1,2} Of those, COCPs are the most commonly prescribed drugs among women of reproductive age and comprise synthetic estrogen usually ethinyl estradiol and a progestogen. However, despite all the evident

advantages that are associated with the use of this medicine (prevention of unintended pregnancy, alleviation of various symptoms of menopause, the relation of COCP use to the increased risk of developing venous thromboembolism is still a serious problem in clinical practice. The risk of venous thromboembolism consisting of DVT and pulmonary embolism is believed to be 2 to 6 times higher among users of the oral contraceptives compared to non-users. Various factors can influence the increased risk of developing VTE, among which are progestogen generation (progestogens of the third and the fourth generations, such as desogestrel, gestodene, and drospirenone, have been associated with a greater risk of developing VTE compared to levonorgestrel of the second generation), the dose of ethinyl estradiol, and individual risk factors (obesity, age, smoking). Although the risk is small for young women.³⁻⁵

The physiological mechanism for the increased vulnerability of the patients to thrombosis involves changes in the system that result from the disruption of hemostatic equilibrium due to its tilt towards procoagulant status. The synthesis of the majority of coagulation factors, such as Factor I (Fibrinogen), Factor II (Prothrombin), Factor VII, Factor VIII, Factor IX, and Factor X, is increased in the liver due to the effect of artificial estrogens on it. At the same time, oral contraceptives reduce the levels of anticoagulant factors in the blood, namely Protein S and Antithrombin III, and lead to the development of acquired resistance to activated protein C (APC).⁶ D-dimer is a soluble molecule formed as a result of the lysis of cross-linked fibrin by plasmin. It is considered to be a highly sensitive biomarker of the activation of both coagulation and fibrinolysis systems. Being a biomarker of fibrin turnover and not a specific diagnostic test for VTE, the assay is considered to be a basic instrument for the exclusion of DVT and PE among patients with low to moderate pre-test probability. Due to high negative predictive value, a D-dimer level lower than a clinical threshold can be regarded as an indicator of safe exclusion of DVT or PE in patients without any need for additional imaging procedures.^{7,8}

Although these changes in the hemostasis have been studied globally, the issue of local data among the Sudanese people needs further research,

as environmental and genetic factors along with the use of a certain method of contraception might have an effect on the results. The question about whether or not adjusted thresholds of D-dimers for OC users need further evidence to be provided. As a rationale the D-dimer is an important biomarker used in clinical practice as part of the diagnostic evaluation of suspected VTE. However, factors that increase baseline D-dimer concentrations may influence the interpretation of this test. Although increased D-dimer levels have been reported among OCP users, there is a need for further evaluation of D-dimer concentrations in healthy women using OCPs compared with non-users. The purpose of this study is to assess the effect of the OCPs on D-dimer levels and comparing them with the existing global evidence. Such comparative analysis will prove the need for reconsidering the cutoff point for women taking oral contraception.

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MATERIALS AND METHODS

Study Design and Setting

A cross-sectional comparative study conducted in Sudan between February and June 2024. Including participants from various community clinics and health centres.

Participant Selection

A total of 200 women of reproductive age (18–45 years) were enrolled. The participants were divided into two groups:

- Case Group (n=100): Healthy women who had been using combined oral contraceptive pills for at least three consecutive months.
- Control Group (n=100): Healthy women who were not using any form of hormonal contraception and had no history of hormonal use in the past six months.

Inclusion Criteria

Healthy female participants from medical records had a normal BMI and no known health problems or medical history that could affect D-dimer levels. They had regular menstrual cycles, were not using hormonal contraception, and had not used hormonal contraceptives during the previous six months. Their D-dimer levels were within the normal range, and all participants provided informed consent.

Exclusion Criteria

Pregnant or postpartum (last six months), past experience of VTE or cardiovascular diseases, smokers, recent surgical procedure (last three months), presence of thrombophilia, on anticoagulants or other medication that interferes with hemostasis, and any systemic diseases.

Data Collection

A structured questionnaire was used to collect demographic information, including age, duration of OCP use, and medical history.

Laboratory Analysis

Venous blood samples (3 mL) were obtained from each subject in sodium citrate (3.2%) containing vials. The blood samples were subjected to centrifugation at 3000 rpm for 15 minutes for the preparation of platelet-poor plasma. Samples were analyzed immediately after collection. Any remaining samples were stored under refrigerated conditions for 24 hrs until analysis. D-dimer levels were assayed by using Ichroma™ II D-Dimer test (Boditech Med Inc., South Korea) (Cat. No. FPRR021). It is a fluorescence immunoassay (FIA) which is used to quantify D-dimer in human blood, according to the manufacturer's instructions. The assay was calibrated according to the manufacturer's recommendations, and appropriate quality-control procedures were followed. The assay range is from 50 ng/mL to 10,000 ng/mL. According to manufacturer instructions, clinical cutoff value for the exclusion of VTE is 400 ng/mL.

Statistical Analysis

Data were analyzed using the Statistical Package for Social Sciences (SPSS) version 26.0. Quantitative variables were expressed as mean $\pm$ standard deviation (SD). Differences between the case and control groups were assessed using the independent samples t-test. The correlation between D-dimer levels and age or duration of

OC use was evaluated using Pearson's correlation coefficient. A P-value of less than 0.05 was considered statistically significant.

RESULTS

Demographic Characteristics

The demographic profiles of the two groups were well-matched to minimize confounding variables. The mean age of the case group was 28.6 ± 5.4 years, while the control group had a mean age of 27.9 ± 4.8 years ($P = 0.34$). The mean BMI was 23.8 ± 3.2 kg/m² for cases and 23.4 ± 2.9 kg/m² for controls ($P = 0.45$). (Table 1, 2)

Comparison of D-Dimer

The primary outcome of the study revealed a significant difference in hemostatic markers between OC users and non-users. The mean D-dimer concentration in the case group was 418 ± 104.3 ng/mL, which was significantly higher than the 223 ± 39.2 ng/mL observed in the control group ($P < 0.001$) (Table 3).

Distribution Relative to Clinical Threshold

The clinical cutoff was 400 ng/mL, the study assessed the prevalence of elevated D-dimer results in healthy individuals using OCP. In the case group, 62% of women had D-dimer levels above the 400 ng/mL threshold despite being asymptomatic and healthy. In contrast, only 5%

Table 1. Age, Duration and no. of pregnancies data

Characteristics	Category	Percentage
Age group	19-29 years	57.5%
	30-40 years	42.5 [^] %
Duration of OCP use	1-3 years	65%
	>3 years	35%
Number of pregnancies	1-3	72.5%
	>3	27.5%

Table 2. Average Age and Body Mass Index between the study group

Characteristics	Case	Control	P. value
Age group	28.6 ± 5.4 years	27.9 ± 4.8 years	0.34
BMI: Body Mass Index	23.8 ± 3.2 kg/m ²	23.4 ± 2.9 kg/m ²	0.45

A P-value of less than 0.05 is considered statistically significant.

Table 3. D-Dimer Results Between the Study Group groups

Comparison	Results/ng/mL	P. Value
Study Group Results	Cases: 418 ± 104.3 ng/mL Control: 223 ± 39.2 ng/mL	< 0.001
Age groups	30-40 years: 413 ng/mL 19-29 years: 410 ng/mL	0.23
Duration of use	1-3 years: 416 ng/mL >3 years: 405 ng/mL	0.012
Age / Duration	$\chi^2 = 16.45$	<0.001

P-value of less than 0.05 is considered statistically significant.

of women in the control group exceeded this threshold.

D. Dimer Correlation with Age, BMI and Duration of Use

Pearson correlation analysis was performed within the case group to identify factors influencing D-dimer levels. No significant correlation was found between D-dimer levels and age ($r = 0.12$, $P = 0.23$), and BMI also shows no statistical significant. However, a statistically significant positive correlation was observed between the duration of OCP use and D-dimer concentration ($r = 0.38$, $P = 0.012$), suggesting that longer exposure to hormonal contraceptives leads to a more pronounced activation of the fibrinolytic system, age was strongly correlated with duration of OCP use (Cramer's $V = 0.64$, $p < 0.001$), suggesting that duration serves as a mediating variable between age and D-dimer levels. Older women (30-40 yrs) are significantly more likely to have used OCPs for longer durations (>3 years) compared to younger women (19-29 yrs), (Table 2, 3).

DISCUSSION

Interpretation of Findings

The presented study results provide strong evidence of a clear association between oral contraceptive usage and a statistically significant increase in D-dimer levels in healthy women. It should be noted that the almost two times higher mean D-dimer level of the case group (OC users) of 418 ng/mL in comparison with the control group (223 ng/mL) is an obvious sign of systemic procoagulant shift. Moreover, this result is especially important due to the fact that 62% of healthy women in the case group had a D-dimer

level above the clinically accepted threshold value (400 ng/mL), while only 5% of the control group women had an elevated D-dimer level.

Increased D-dimer levels in healthy OC users is based on the hemostatic physiology. Specifically, one of the key components of COCPs – ethinyl estradiol – is an effective activator of hepatic protein synthesis and causes a synthesis of numerous coagulation factors, thus providing the availability of extra substrates for thrombin production. Even a relatively low dose of ethinyl estradiol (20-35 µg) leads to the development of the state of unbalanced hemostasis and the fibrin production in the body exceeds the natural potential of anticoagulation.¹¹ This later elevation of D-dimer is indicative of the fibrinolytic system's reaction—an adaptive measure using plasmin to digest the excessive amount of fibrin and avoid any clinical thrombosis. Hence, with regards to oral contraceptives, the elevation of D-dimer could be taken as an indication of “increased fibrin turnover” and not an acute disease process.¹²

Comparative Analysis with Global Literature

The findings obtained in the current study are corroborated by international literature as well. For example, SB et al¹³ carried out a similar study on Nigerians where they found mean D-dimer concentrations of 813.36 ± 212.35 ng/ml in OC users against 257.04 ± 108.33 ng/ml in controls [12]. Although the values obtained by the authors differ from ours because of the different ELISA-based approach used in their research, the magnitude of the increase and statistically significant results are comparable ($P < 0.05$).

In turn, MA, and AL-Husaynee¹⁴ detected a significant difference between OC users and healthy females in terms of the proportion of patients with D-dimer positivity. Namely, 87.5%

of OC users had a positive result against only 20% of controls. The relatively high frequency of the positive test results in healthy users proves the physiological nature of the effect among people regardless of their ethnic origin.^{13,14,15}

It should be particularly emphasized that there is a positive relationship between the period of usage of OCPs and D-dimer values. This means that the hemostatic system is unable to create a new steady state after starting treatment; on the contrary, continuous hormonal stimulation results in prolonged and possibly accumulating activation of the coagulation and fibrinolytic cascades. This assumption is in line with the research carried out by RNV *et al.*¹⁵ in which they demonstrated that D-dimer was elevated at least for 12 months after usage of third-generation OCs.¹⁵

The Clinical Argument for Adjusted Diagnostic Thresholds

The most significant implication of this research is the challenge it poses to current clinical diagnostic protocols. The significantly higher D-dimer concentrations observed among OCP users suggest that OCP use may influence baseline D-dimer levels and should be considered when interpreting D-dimer results. However, because the present study included asymptomatic healthy women and did not evaluate patients with suspected VTE using a reference diagnostic standard, the effect of OCP use on the diagnostic performance or specificity of D-dimer for VTE cannot be determined from these findings.

Our data show that 62% of healthy OC users would be classified as “positive” under standard criteria. If one of these women presents with non-specific clinical symptoms, a D-dimer test is almost guaranteed to be positive, regardless of the presence of a clot. This results in a significant loss of diagnostic specificity, leading to unnecessary imaging, such as CT pulmonary angiography, exposes young women to significant ionizing radiation and contrast-induced risks. Beside substantial financial burden on healthcare systems. False-positive results cause significant psychological distress for patients and may lead to the unnecessary discontinuation of effective contraception. We argue that the current “one-size-fits-all” approach in clinical laboratory analysis is suboptimal. We propose that the scientific

and clinical communities must move toward a more personalized diagnostic strategy. This could involve: Laboratories should establish and report reference intervals specifically for women on hormonal contraception. Like age-based D-dimer cut-off values. We believe that a higher cut-off value may maintain high sensitivity but improve specificity in this population considerably. Clinicians should be more cautious about using D-dimer testing in women taking OCs with low pre-test probability, since they have a very high chance of having elevated D-dimer levels.^{16,17}

Limitations and Future Directions

A limitation of this study is that an a priori sample-size or power calculation was not performed before data collection. Although 100 participants were included in each group, the sample size was primarily determined by the availability of eligible participants and recruitment feasibility. Future studies should include an a priori power calculation based on the expected effect size and variability. The relatively small sample size of participants may limit the generalizability of the findings. specific day of the menstrual cycle at the time of blood sampling was not recorded. Additionally, the study population lacked diversity in terms of demographic factors such as ethnicity, socioeconomic status, and health conditions, affecting the applicability of the results to broader populations. Furthermore, the study did not specify the types of oral contraceptives used by participants, which is significant as different formulations may have varying effects on hemostatic parameters.

CONCLUSIONS

This study confirms that healthy women using oral contraceptives have significantly higher D-dimer levels compared to non-users, reflecting a chronic state of increased fibrin turnover. These findings suggest that OCP use may influence baseline D-dimer concentrations and could potentially affect the interpretation of D-dimer results in clinical practice. These findings should therefore be considered hypothesis-generating and warrant further prospective studies involving women with suspected VTE to determine whether OCP-specific reference ranges or diagnostic thresholds may be clinically useful.

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Conflict of interest

The authors do not have any conflict of interest.

Data Availability Statement

This statement does not apply to this article.

Ethics Statement

The study protocol was approved by the Research Ethics Committee of Al-Zaiem Al-Azhari University. All participants provided written informed consent. Confidentiality of participant data was strictly maintained.

Informed Consent Statement

Informed consent was obtained from all subjects involved in the study.

Clinical Trial Registration

This research does not involve any clinical trials.

Permission to reproduce material from other sources

Not Applicable

Author Contributions

Dalia Hussein: Conceptualization, Methodology, investigation, software, validation; Wala Eldin Elradi: Data Collection, Writing—original draft preparation, Analysis, software, validation; Ashok Kumar Sah: Formal analysis, Resources, Visualization; Rabab H Elshaikh: Visualization, writing—review and editing, Supervision, project administration.

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