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Effect of Combined Oral Contraceptive Pills on Clotting Factor VII Activity Percentage

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ORIGINAL STUDY

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Abstract

Background: Combined hormonal pills that are used for contraception are widely used around the world as a straightforward, secure, and reversible approach to contraception. Over time, many side effects of these contraceptive pills have been discovered, including prothrombotic effects, one of which is the effect on clotting factor VII.

Objectives: To evaluate the impact of combined hormonal contraceptives on FVII active state percentage and, consequently, the prothrombotic risk associated with these medications.

Materials and Methods: It is a case-control study involving 50 users of COC of different types and compared with other 50 non-user controls after obtaining their verbal consent. The study was conducted at Al-Zahraa Teaching Hospital in Al-Najaf. The tests were conducted in the laboratories of Babylon Medical College using the FVII and performed by the manual method.

Results: The study and control groups' ages were in the range of (18-45) years. the second generation, which is a combination of levonorgestrel/ethinyl estradiol, is the most commonly used type with 56% percent. The second one is the third generation, which is a combination of gestodene/ethinyl estradiol with 32% and the third one is the fourth generation, which is the combination of drospirenone/ethinyl estradiol with 12%.

Conclusion: Combined oral contraceptive pills increase FVII activity significantly more than users, and this increment was highest in third-generation contraceptives.

Keywords: Combined oral contraceptives, Factor VII, Estrogen, Progesterone

1. Introduction

In contemporary times, there has been a consistent rise in the preference for smaller families and well-spaced births in both developed and developing nations. The Development Goals advocate for universal access to contraceptive services, enabling women and couples to achieve their desired number of births at their preferred intervals [1, 2] Initial oral contraceptive pills were granted approval by the FDA in 1960. Over 300 million women globally have utilized the pill within 2 years after its introduction, recognizing it as a straightforward, safe, and effective method for attaining reproductive autonomy [3]. Combined oral contraceptive pills consist of both estrogen and progesterone. These pills interfere with ovulation by inhibiting gonadotropin release, exerting their effects on both the pituitary gland and the hypothalamic center [4].

Initially, the estrogenic content of combined oral contraceptives (COCs) was believed to be primarily responsible for their prothrombotic effects. Reducing the ethinyl estrogen (EE) dose from 50 mcg or more in the original COC formulations to the current doses of 20–35 mcg has decreased the incidence and relative risk of venous thromboembolism (VTE). However, in 1995, it was recognized that the progestin content of COC pills also modulates the thrombotic risk associated with COC use [5].

Estrogen influences the transcriptional process of the genes of different proteinic products, involving clotting FVII. This increases the level of those

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coagulation factors in the plasma due to enhanced transcription of factors' genes. Despite the complexity and incomplete understanding of the precise mechanism, Estrogen traverses the cell membrane of various specific target tissues—many of which are influenced by estrogen—and, on entering the cytoplasm, binds to nuclear receptors, including estrogen receptors [6].

Following formation, the estrogen/nuclear receptor complex undergoes translocation into the nucleus, where it recognizes and engages with specific sites termed hormone response elements, herein referred to as "estrogen response elements." This interaction triggers the initiation of gene transcription by facilitating RNA polymerase II to transcribe the corresponding DNA segment into mRNA. The resultant proteins synthesized through this process encompass clotting factors and other previously delineated proteins [7].

The estrogen/nuclear receptor complex also capable of repressing gene transcription, potentially explaining the observed reductions in factor V concentrations. The extent of estrogen's influence on gene transcription is intricate and not solely confined to nuclear receptor binding to DNA. Estrogen, when bound to nuclear receptors (estrogen receptors), additionally regulates gene expression through protein-protein interactions with other transcription factors [8].

This modulation of gene expression can induce either upregulation or downregulation of gene activity. Moreover, estrogen receptors exert influence on intracellular signaling cascades, notably including the MAPK and IP3 kinase pathways, which can exert additional regulatory effects on overall gene expression patterns. As highlighted earlier, heightened doses of estrogen correlate with an augmented propensity for venous thrombus formation. This heightened susceptibility can be ascribed to an intensified level of nuclear receptor engagement and the subsequent induction of gene transcription about clotting factors [9].

Most progestin-mediated effects primarily arise from engagements with the progesterone receptor (PR), although they can additionally interface with the androgen receptor (AR), the estrogen receptor (ER), the glucocorticoid receptor (GR), or the mineralocorticoid receptor (MR). The agonistic or antagonistic character of a progestin molecule hinges on the equilibrium established between receptor coactivators and corepressors recruited by the progestin. This equilibrium subsequently dictates whether receptor transactivation is stimulated or suppressed [10]. This effect is influenced by the androgenic properties of the progestin. Preparations containing LNG (levonorgestrel) have been demonstrated to counteract the ethinyl estradiol (EE)-induced increase in F VII activity [11].

The thrombotic potential of (OCPs) has been understood not solely as dependent on the estrogen dosage, but rather on the cumulative estrogenic effect of the formulation. This cumulative effect increases with higher estrogen doses but diminishes with increased anti-estrogenic properties of the progestogen component. Third-generation progestogens, as well as drospirenone and cyproterone acetate, demonstrate weaker anti-estrogenic characteristics compared to levonorgestrel. Consequently, individuals using these combinations may face an elevated risk of thrombosis when compared to those using second-generation OCPs. This observation potentially explains the differences in thrombotic risk observed among users of various OCP formulations [12].

FVII is a vitamin K-dependent protein crucial for initiating tissue factor (TF)-induced coagulation. The majority of circulating FVIII exists in the plasma as an inactive form or zymogen. Upon encountering TF, native Factor VII is transformed into its activated two-chain form, Factor VIIa. This transformation can be catalyzed by various coagulation proteases, including FXa, FIXa, FXIIa, thrombin, and Factor VIIa itself. The complexes formed between TF and Factor VIIa efficiently cleave FIX and FX into their active forms, potentially resulting in thrombin generation and the formation of fibrin clots. Thus, when cell-surface TF is exposed to plasma, low levels of Factor VIIa may serve as a "priming" mechanism, preparing the clotting cascade for subsequent activation [13, 14].

2. Materials and methods

It is a case-control study conducted at the AL-Zahraa Teaching Hospital in Al-Najaf. The sample size was 100 women, 50 of them were using combined oral contraceptives of different types and were regarded as cases, and the other 50 were not users of these drugs, so regarded as controls. The study was performed from October 2023 to March 2024 and the laboratory work was done at the University of Babylon Medical College.

The combined oral contraceptives were classified according to the type of progesterone into second-generation (levonorgestrel/ethinylestradiol) combination, third-generation (gestodene/ethinyl estradiol), and fourth-generation (drospirenone/ethinylestradiol) formulation.

The investigation was done by manual methods using an FVII kit from Stago company/France and the results were calculated manually using log-log paper. Statistical analysis was done using ANOVA with a P. value significant at 0.05 or less.

Table 1. Descriptive statistics and differences in age and FVII activity between control and study groups.

Indicators	Stat.	Control N = 50	Group I N = 28	Group II N = 16	Group III N = 6	Chi^2	P value (Sig.)
Age/Years							
18–27	Freq.	19	7	4	1	3.2	0.78 (NS)
	%	38.0%	25.0%	25.0%	16.7%		
28–37	Freq.	20	15	7	3		
	%	40.0%	53.6%	43.8%	50.0%		
38–45	Freq.	11	6	5	2		
	%	22.0%	21.4%	31.3%	33.3%		
	%	100.0%	100.0%	62.5%	83.3%		
> 500	Freq.	0	0	6	1		
	%	0.0%	0.0%	37.5%	16.7%		
FVIIa (%)							
≤ 100	Freq.	50	28	5	4	57.81	0.000 (HS)
	%	100.0%	100.0%	31.3%	66.7%		
> 100	Freq.	0	0	11	2		
	%	0.0%	0.0%	68.8%	33.3%		

NS: Non-significant at P value > 0.05: High Significant correlation at p-value < 0.01.

Table 2. Descriptive statistics and differences in the duration of COCP between control and other study groups.

Indicators	Stat.	Group I N = 28	Group II N = 16	Group III N = 6	Chi ^{2}	P value (Sig.)
Duration of COCP/Years						
< 1	Freq.	10	7	2	0.75	0.94 (NS)
	%	35.7%	43.8%	33.3%		
1–3	Freq.	8	3	2		
	%	28.6%	18.8%	33.3%		
> 3	Freq.	10	6	2		
	%	35.7%	37.5%	33.3%		

NS: Non-significant at P value > 0.05.

3. Results

Ifferences in age and FVIIa between control and other study groups:
According to Table 1, there is little difference (P > 0.05) in age subgroup distribution between control and other study groups. This table also shows a significant difference (P < 0.01) in FVIIa distribution in study groups compared to control groups.

Descriptive statistics of the duration of COCP between control and other study groups.
According to Table 2, there is a mild difference (P > 0.05) in the distribution of women's subgroups classified according to the duration of COCP between patients and control groups.

Activity of FVIIa among the control and other study groups:
According to Table 3, there is an important elevation (P > 0.05) in the FVIIa activity in group II (third generation of COCP) compared to other study and control groups (Fig. 1).

Level of activity FVIIa among control and other study groups within each age subgroup:
According to Table 4, regarding the age subgroup (18–27) years, (28–37), and (38–45), there is a high significant increase (P > 0.05) in the FVIIa activity in group II (third generation of COCP) compared to other study and control groups.

Table 3. Descriptive statistics and differences in the activity of FVIIa among control and other study groups.

Indicators	Study Groups	Mean	SD	F Test	P value (Sig.)
FVIIa (%)	Control	89.8	6.42	36.00	0.000 (HS)
	Group I	85.9	5.14		
	Group II	102.3	2.65		
	Group III	99.5	3.21		
F Test (P value)		15.57 (0.000)		16.69 (0.000)	

High Significant correlation at p-value < 0.01.

Activity of FVIIa among control and other study groups within each COCP duration subgroup:
According to Table 5, regarding the COCP duration subgroup (≤1) years, (1–3) years, and (>3) years, there is an important elevation (P > 0.05) in FVIIa activity in group II (third generation of COCP) compared to other study and control groups.

The Pearson Correlation Coefficient (r) between studied variables:
Table 6 shows a significantly positive relation (P < 0.05) of FVIIa (r = 0.743) with COCP duration (r = 0.356) as in Fig. 2; a significantly positive relation (P < 0.05) of FVIIa with age (r = 0.554) as in Fig. 3.

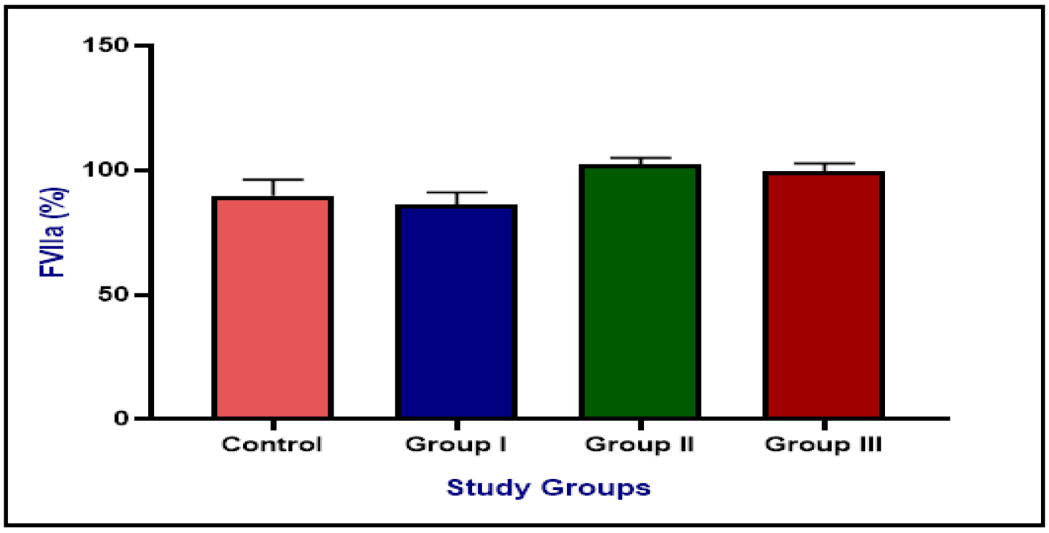

Fig. 1. Differences in the activity of FVIIa among study groups.

Table 4. Descriptive statistics and differences in FVIIa activity between control and other study groups within each age subgroup.

		Age Subgroups					
		18–27		28–37		38–45	
Indicators	Study Groups	M	SD	M	SD	M	SD
FVIIa (%)	Control	90.0	6.16	87.2	6.49	94.0	4.52
	Group I	79.3	1.89	86.4	2.44	92.5	2.74
	Group II	99.0	1.15	102.0	1.15	105.2	1.30
	Group III	96.5	2.12	99.0	1.41	103.0	1.41
F Test (P value)		15.57 (0.000)		22.7 (0.000)		16.69 (0.000)	

Table 5. Descriptive statistics and differences in age, and FVIIa between patients and control groups within each COCP Duration subgroup.

		COCP Duration Subgroups (years)					
		≤ 1		1–3		≥ 3	
Indicators	Study Groups	M	SD	M	SD	M	SD
F Test (P value)		33.14 (0.000)		27.77 (0.000)		49.77 (0.000)	
FVIIa (%)	Group I	81.2	3.06	85.4	1.13	91.5	2.42
	Group II	99.0	1.15	102.0	1.15	105.2	1.30
	Group III	96.5	2.12	99.0	1.41	103.0	1.41
F Test (P value)		77.33 (0.000)		370.6 (0.000)		81.13 (0.000)	

Table 6. Pearson Correlation Coefficient (r) between studied variables.

Markers	Age	COOP Duration
FVIIa	0.554*	0.356**

*Significant correlation at p-value < 0.05.

**High Significant correlation at p-value < 0.01.

4. Discussion

Our study aims to discover the possible effect of COC pills on the hematological system regarding the level of factor VII activity. This parameter is used in this study to assess the prothrombotic risk of these drugs, as recently many researchers have approved that COC pills are associated with venous and arterial thrombosis.

4.1. Factor VII activity distribution

A difference in the distribution of FVII activity observed in the study group was more compared with the control group with significantly different results (P = 0.000). This result was inconsistent with the findings obtained by Junge et al. [15] in Berlin/Germany in 2013, while Roshidah et al. [16] observed a mild difference in Factor VII activity in users compared with the control group in a study on coagulation indices. FVII is the clotting factor that

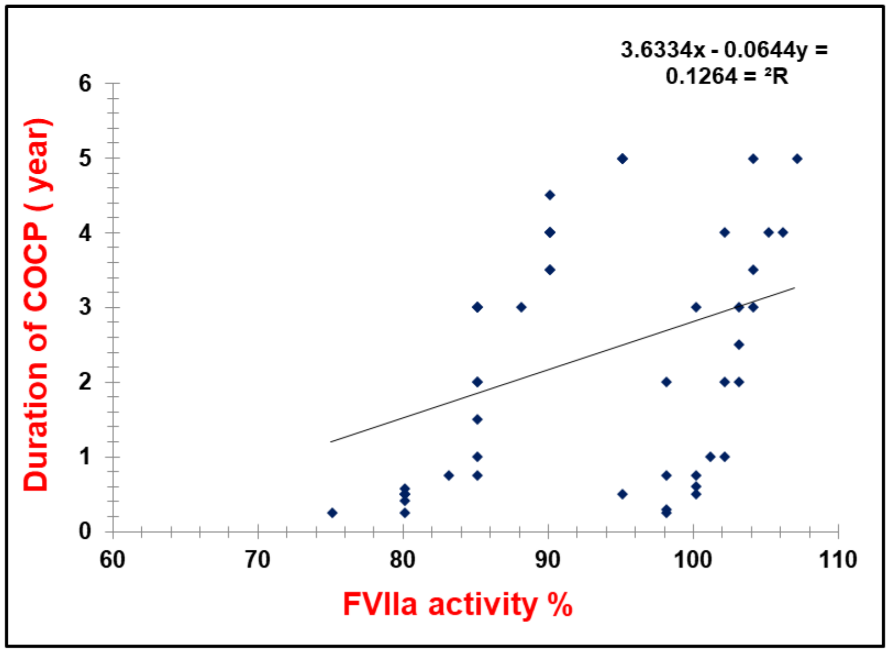

Fig. 2. Scatter plot and regression equation for the correlation between FVIIa activity and duration of COCP.

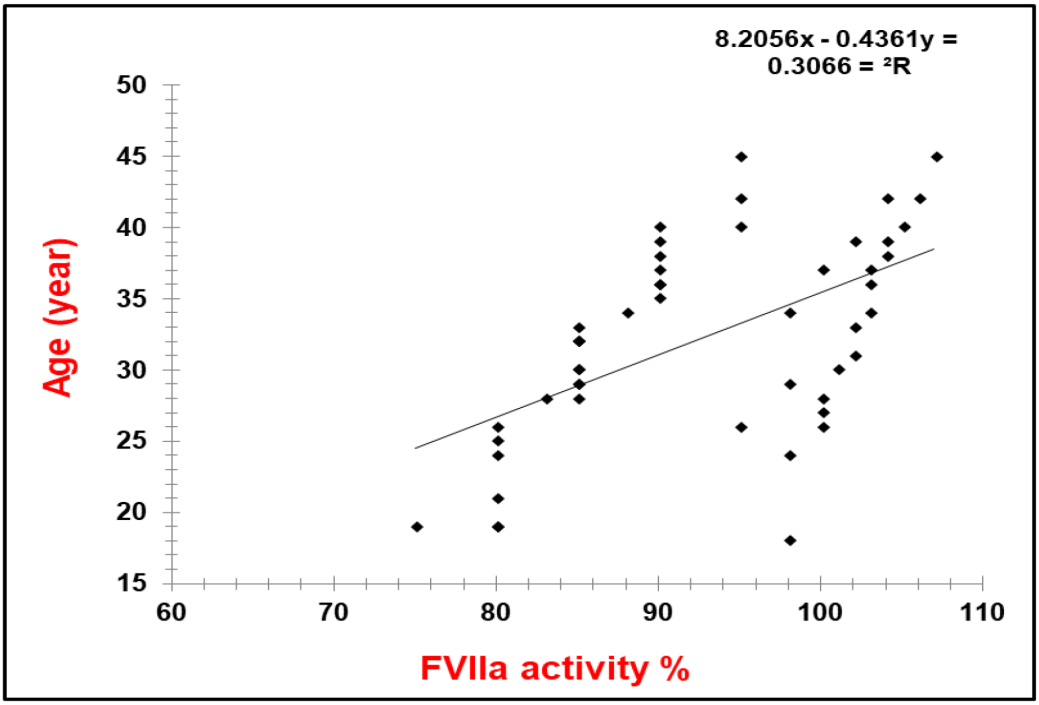

Fig. 3. Scatter plot and regression equation for the correlation between FVIIa activity and age.

is increased in COCP users due to the procoagulant effect of these pills [17].

4.1.1. The difference in FVII activity % between the control and other study groups

group II (third-generation which is gestodene) combined contraceptives have the highest effect on FVII activity in comparison with group I (second-generation which is levonorgestrel-containing preparation) and group III (fourth-generation which is drospirenone) with a statistically significant difference ($p = 0.000$). This result was compatible with Kjaer et al. from Denmark [18] who revealed that both gestodene and levonorgestrel containing combined

contraceptive pills increase FVII activity, but this increase with gestodene preparations is higher than that of levonorgestrel preparation.

Shlinder in Denmark [19] showed that gestodene/ethinyl estradiol oral contraceptive preparation does not cause any effect on hemostatic parameters. In addition, Archer et al. from Germany [20] who reported that FVII activity reduced from baseline as a response to levonorgestrel/ethinyl estradiol COC.

The mean FVII activity in fourth-generation (drospirenone/EE) preparation is higher than that of second-generation (levonorgestrel/EE) preparation. These results were consistent with the study conducted by Kluft et al. in Belgium [21] who approved that the same result had been founded. Regarding the activity percentage of the coagulation FVII activity, Stocco et al. from Brazil [22], showed no significant differences were found between drospirenone/EE and levonorgestrel/EE.

5. Conclusion

1. Using combined oral contraceptive pills increases the level of FVII activity in comparison with controls. The findings suggest that individuals using third-generation combined oral contraceptives exhibited higher FVII activity results compared to those using second and fourth-generation formulations. In comparison, users of fourth-generation contraceptives showed higher results than those utilizing second-generation ones. These results imply that second-generation combined oral contraceptives may be considered the safest option among the formulations studied. The hematologic effect of COC increases with increased duration of use. However, suppose there is a cause of thrombophilia whether inherited or acquired. In that case, this condition will act synergistically with the use of these pills and increase the risk of thrombotic conditions in the first year of using these pills. The effect on coagulation increases synergistically with age.

Ethical approvals

The study was conducted in accordance with the moral guidelines found in the Helsinki Declaration. Before enrolment, the patient's verbal consent were obtained. According to Document No. 145 dated Sptember 22, 2023, an ethical committee at the Al-Najaf Health Directorate, evaluated and approved the study protocol as well as the subject information.

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Conflict of interest

No conflicts of interest exist to declare.

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