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Association between Combined Hormonal Contraception Use and Deep Vein Thrombosis in Dyslipidemic Patients

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ABSTRACT

Background: *The risk of Deep Vein Thrombosis (DVT) and Combined Hormonal Contraception (CHC) use is well established in the literature in women of childbearing age. CHC has an estrogen component with a pro-thrombotic effect and progestin which can alter the lipid profile. There is controversy regarding the safety of CHC use in patients with dyslipidemia in terms of DVT. Thus, the association between CHC use and DVT risk in women with dyslipidemia needs to be reviewed.* ***Objectives:*** *This study aimed to assess the risk of DVT in women with dyslipidemia who were exposed to combined hormonal contraception compared to non-exposed women; to identify which CHC type carries the most DVT risk and to determine the association between CHC and lipid profile.* ***Methods:*** *Using a matched case-control study, we screened all women aged 18-79 years diagnosed with DVT in King Khalid University Hospital between 2017 and 2019 and abnormalities in their lipid profiles. We recruited 70 DVT cases and 210 controls from the family medicine outpatient clinic. Cases were matched to controls for age group, and all participants had dyslipidemia. The main outcome is a deep vein thrombosis event.* ***Result:*** *Combined hormone contraception use among dyslipidemic patients was significantly associated with a more than two-fold (OR=2.591, p<0.011, 95% CI: 1.244-5.396) increase in the risk of DVT.* ***Conclusion:*** *A theoretical concern is present for the use of CHCs in women with known dyslipidemia, and further studies are essential to confirm these findings.*

Keywords: Deep vein thrombosis, Dyslipidemia, Combined hormonal contraception, Oral contraceptives, Venous thromboembolism

Abbreviations: CHC: Combined Hormonal Contraception, COC: Combined Oral Contraception, OC: Oral Contraception, DVT: Deep Vein Thrombosis, VTE: Venous Thromboembolism, PE: Pulmonary Embolism, TCH: Total Cholesterol, LDL: Low Density Lipoprotein, HDL: High Density Lipoprotein, TG: Triglycerides,

DM: Diabetes Mellitus, HTN: Hypertension, DRSP: Drospirenone/ethinyl estradiol, SHIS: Saudi Health Interview Survey, OR: Odds Ratio, RR: Risk Ratio, KSUMC : King Saud University Medical City, KKUH: King Khalid University Hospital, eSIHI: Electronic System for Integrated Health Information

INTRODUCTION

Dyslipidemia is a recognized cause of morbidity worldwide. In the United States, 12.4% of women had increased total cholesterol ≥ 240 mg/dL (≥ 6.2 mmol/dL) per the National Health and Nutrition Examination Survey in 2016 [1]. In the Chinese National Nutrition and Health Survey in 2002, there was a marked elevation in dyslipidemia prevalence up to 18.6% [2]. Locally, the Saudi Health Interview Survey (SHIS) in 2013 reported the prevalence of hypercholesterolemia as 7.3% in women [3]. In contrast, a recent systematic review in 2016 reported a higher prevalence of 24.5% of Saudi women having dyslipidemia [4]. Combined hormonal contraception has an estrogen component with a prothrombotic effect, and progestin alters the lipid profile. Progestin may increase LDL cholesterol and decrease HDL cholesterol [5,6]. Due to these findings, we hypothesize that dyslipidemic patients using combined hormonal contraception would have a higher chance of experiencing deep vein thrombosis events [7,8]. Deep vein thrombosis risk with combined hormonal contraception use is well defined in the literature among women of childbearing age. A case-control study in 2009 reported a four-fold increased risk of venous thromboembolism in all CHC users [9].

Among all types of contraception, the risk for VTE with transdermal patches was two-fold greater than with other types per a case-control study [10]. In contrast, Jick, et al. reported an odds ratio of 0.9 for VTE in transdermal patch users [11]. In a cohort study of 573,680 women using combined hormonal contraceptives, the Drospirenone (3.0 mg)/ Ethinyl estradiol (30 mcg) (DRSP) tablet was related to venous thromboembolism more than the lower estrogen dose CHCs [12]. Moreover, there was no statistically significant association between the transdermal patch or vaginal ring and venous thromboembolism in the Sidney S, et al. study [12]. Many other studies agree with the notable VTE risk with Drospirenone-Containing Pills (DRSPs), with a modest risk for vaginal rings [13-16]. As explained by the literature, the first year of hormonal contraception use carries the maximum risk of VTE. Martinelli, et al. performed a case-control study in 2016 and found a venous thromboembolism odds ratio of 9.0 (95% CI 6.9-12.2) in Oral Contraception (OC) users for one year or less compared to longer durations, they concluded that the threat of VTE in OC users decreases over time [17]. Another population-based case-control study performed in the Netherlands supports this finding. They showed that DVT risk was highest in the initial 6-12 months of CHC use, with a three-fold increase in the first 6 months and a two-fold increase in the first year compared to prolonged use [18]. Dyslipidemia appears to have a role in venous endothelial dysfunction through the pro-thrombotic and endothelium-deteriorating properties of lipid particles [19].

A case-control study by Kawasaki, et al. was the earliest to demonstrate a link between dyslipidemia and DVT. They described a higher DVT risk with elevated total cholesterol levels (Odds Ratio (OR) 5.1, 95% CI 2.0-13.0) [20]. Furthermore, elevated triglyceride levels were associated with a two-fold increased risk for DVT risk per the Doggen, et al. case-control study on 477 women with DVT and 1986 controls [21]. On the other hand, a large case-control study with 2234 cases and 2873 controls was conducted by Morelli VM, et al. in 6 anticoagulation clinics in the Netherlands. They identified no correlation between abnormal laboratory lipid results and thrombosis events [22]. A meta-analysis of a randomized controlled trial and 9 observational studies in 2010 evaluated 971,307 patients to examine the role of statins in deep vein thrombosis prevention. A significant 41% DVT risk reduction was observed (Odds Ratio (OR) 0.59, 95% CI 0.43-0.82) among statin users [23]. In patients with medical conditions, such as dyslipidemia, the risks and recommendations for using CHC have been inconsistent over time [24,25]. For instance, in 2006, the American College of Obstetricians and Gynecologists recommended that only controlled dyslipidemic patients use CHC. In uncontrolled patients with LDL levels above 190 mg/dL (4.9 mmol/L), CHC is contraindicated [24]. Additionally, for patients older than 35 with LDL above 160 mg/dL (4.1 mmol/L), alternative options, such as progestin-only contraceptives, should be considered. In contrast, in 2015, the World Health Organization agreed with using CHC in females with dyslipidemia once they are cleared from cardiovascular risk factors [25]. A systematic review in 2015 included three main studies [26]. A case-control study reported an elevated risk for MI among Combined Oral Contraception (COC) users with dyslipidemia (Odds Ratio (OR) 24, 95% CI 5.6-108) compared to nonusers without dyslipidemia (Odds Ratio (OR) 2, 95% CI 1.4-2.8) [27]. A retrospective cohort study suggested a higher risk for stroke and venous thromboembolism among COC users with dyslipidemia than among COC users without dyslipidemia (Risk Ratio (RR) 1.39, 95% CI 1.04-1.85) [16]. In contrast, a prospective cohort study demonstrated no worsening of the lipid profile among CHC users with dyslipidemia compared to nonusers with dyslipidemia [28]. They concluded that CHC use in women with dyslipidemia may increase the risk of myocardial infarction, cerebrovascular accident, and venous thromboembolism. Nevertheless, the available data were few and obtained from observational studies with low-quality evidence.

Objective

Our primary objective in this study: to assess the risk for deep vein thrombosis in women with dyslipidemia who were exposed to combined hormonal contraception compared to nonexposed women. Our secondary objectives: to identify which type of hormonal contraception carries the most risk for deep vein thrombosis. Also, to determine the association between combined hormonal contraception and lipid profile.

Rationale

The recommendations and eligibility for using combined hormone contraception in patients with dyslipidemia have varied over time, with many conflicting statements in the literature [24,25]. There are a limited number of articles discussing the association between CHC use and DVT risk in dyslipidemic patients. Most are observational studies with low-quality evidence [26]. Moreover, no similar local studies in Saudi Arabia were found in our search, reflect-

ing a knowledge gap. This underlines the necessity for additional studies to demonstrate the true associations between combined hormonal contraception use and DVT risk among dyslipidemic patients with better-quality evidence.

METHODS

Research Design and Setting

This matched case-control study was implemented in King Saud University Medical City (KSUMC) in King Khalid University Hospital (KKUH) in Riyadh, Saudi Arabia between May 2019 and November 2020.

Subjects and Sampling

Cases were identified from the KKUH vascular lab registry for deep vein thrombosis and were diagnosed through Doppler ultrasound. All women aged 18-79 years diagnosed with DVT in King Khalid University Hospital between 2017 and 2019 were screened for the presence of abnormal lipid profile. The National Cholesterol Education Program (NCEP) Guidelines for diagnosing dyslipidemia were followed in the inclusion criteria. Levels of total cholesterol ≥ 5.2 mmol/L, LDL ≥ 3.37 mmol/L, HDL <1.03 mmol/L, or triglycerides ≥ 1.7 mmol/L are defined as abnormal lipid profiles [29].

A total of 319 patients were identified, and their files were reviewed in the electronic System for Integrated Health Information (eSIHI). The phone consultation was performed, verbal informed consent was obtained and confidentiality of the details of the participants was ensured. We found that out of the 319 identified patients, 41 patients died, 90 patients had missing lipid profile labs, and 4 refused to participate. Additionally, 104 were eliminated for having one or more of the exclusion criteria: anti-phospholipid syndrome, Factor V Leiden mutation, Protein S, C deficiency, antithrombin deficiency, active malignancy, undergoing chemotherapy, and taking tamoxifen. Therefore, the remaining participants entered into the study comprised 70 cases. Out of 319 DVT cases, we recruited 70 cases with both DVT and dyslipidemia. Cases were matched for the age group with 210 controls with dyslipidemia from the family medicine outpatient clinic. A case-control ratio of 1:3 was used; henceforth, 210 control subjects were selected through simple random sampling from the family medicine outpatient clinic. Matching was performed for age: each case was matched to control in the same five-year age group.

Research Instrument

A validated data collection form was developed by the study authors through a literature review and was reviewed by 2 senior consultants. Data collection was performed by the study authors with the help of medical students using an online data collection form, which was completed using KKUH electronic medical records (eSIHI) and phone interviews. The data collection form has 6 sections: demographic information, past medical history, dyslipidemia history, contraception history, DVT history, and recent lipid profile measurement. We asked about demographic information (age, nationality, marital status, educational level, and profession). Past medical history included hypertension, diabetes, hypothyroidism, asthma, ischemic heart disease, stroke, chronic kidney disease, pulmonary embolism, smoking, weight, and height. For dyslipidemia, we assessed the duration of dyslipidemia, statin use, and recent lipid profile measurement, including total cholesterol, HDL, LDL, and triglycerides from the electronic medical record. For contraception, we asked about the history of use, current user or not, type (name and methods), and duration of use. For cases, we asked about DVT history, including event date, provoking factory, use of contraception before the event, and the type of contraception used before the event. A pilot study was performed on 20 members to evaluate the form's practicability and validity.

The exposure of interest in the current study was combined hormonal contraception, including oral contraception pills, transdermal patches, and vaginal rings. Common types of contraception, such as Yasmin (Ethinyl estradiol/drospirenone), Gynera (gestodene/ethinylestradiol), Marvelon (ethinylestradiol/desogestrel), Nordette (levonorgestrel/ethinyl estradiol) and Diane (cyproterone/ethinyl estradiol) were discussed with the patients through phone consultation. The duration of use and status of exposure were also explored. Patients were divided into 3 categories: current user, previous user, and nonuser. Current users were those using combined hormonal contraception in the last three months before the DVT event. Previous users were those who stopped using combined hormonal contraception more than 3 months before the DVT event.

Ethical Considerations

Ethical approval was obtained from the Research Ethics Committee at King Khaled University Hospital (No. E-19-3713) before beginning data collection. Informed consent was obtained from cases and controls, and the purpose of the research was explained to both groups. Confidentiality of study subjects was maintained.

Declaration of Interests

The authors declare that they have no known competing financial interests, personal relationships, or conflicts of interest that could have appeared to influence the work reported in this paper.

Statistical Analysis

Data were analyzed by using Statistical Package for Social Studies (SPSS 22; IBM Corp., New York, NY, USA). Continuous variables are represented as the mean ± standard deviation, and categorical variables are represented as percentages. Venous thromboembolism risk factors were evaluated using univariate and multivariate logistic regression (unconditional logistic regression). A p-value of ≤ 0.05 and 95% confidence intervals were used to report the statistical significance and precision of the results.

RESULTS

Demographic and Clinical Characteristics

The socio-demographic and clinical characteristics of both the case and control groups are presented in Table 1 and Table 2. Overall, there was no significant ($p>0.05$) variation among the participants in terms of nationality, marital status, or job. However, there were statistically significant differences ($p<0.05$) in educational level, medical history of Hypertension (HTN), Diabetes Mellitus (DM), statin use, and CHC use. Percentages of HTN and DM were significantly higher in the controls at 51.90% and 51.90% *vs.* 35.71% and 31.43% for the cases, respectively. Similarly, statin use was significantly higher in the controls at 78.10% compared to 54.29% in cases. For combined hormonal contraceptive use, the percentages of current users and nonusers were higher among cases than controls at 21.43% and 58.57% *vs.* 9.52% and 49.52%, respectively. For previous users, the percentage of controls was almost double that of cases at 40.95% and 20%, respectively.

Table 1 Demographic data of participants in cases and controls groups

		Case (n=70)		Control (n=210)		p-value
		Number	%	Number	%	
Nationality	Saudi	65.00	92.86	199.00	94.76	0.55
	Non-Saudi	5.00	7.14	11.00	5.24	
Marital status	single	8.00	11.43	12.00	5.71	0.41
	Married	52.00	74.29	169.00	80.48	
	Widow	8.00	11.43	21.00	10.00	
	Divorced	2.00	2.86	8.00	3.81	
Education status	Illiterate	10.00	14.29	42.00	20.00	0.024*
	High school or less	43.00	61.43	107.00	50.95	
	Bachelor	13.00	18.57	59.00	28.10	
	Post-graduate	4.00	5.71	2.00	0.95	
Job	Housewife	51.00	72.86	139.00	66.19	0.53
	Employee	12.00	17.14	54.00	25.71	
	Retired	6.00	8.57	15.00	7.14	
	student	1.00	1.43	2.00	0.95	
	No	32.00	45.71	46.0	21.90	
		Mean	SD	Mean	SD	p-value

Body Mass Index	32.96	7.12	31.91	6.48	0.99
Age	53.13	11.49	53.10	11.16	0.15
*: Significant p-value					

Table 2 Characteristics of participants in cases and controls groups

		Case (n=70)		Control (n=210)		p-value
		Number	%	Number	%	
Hypertension	Yes	25.00	35.71	109.00	51.90	0.019*
	No	45.00	64.29	101.00	48.10	
Diabetes mellitus	Yes	22.00	31.43	109.00	51.90	0.003*
	No	48.00	68.57	101.00	48.10	
Hypothyroidism	Yes	15.00	21.43	34.00	16.19	0.32
	No	55.00	78.57	176.00	83.81	
Asthma	Yes	4.00	5.71	24.00	11.43	0.17
	No	66.00	94.29	186.00	88.57	
Ischemic heart disease	Yes	3.00	4.29	3.00	1.43	0.17
	No	67.00	95.71	207.00	98.57	
Stroke	Yes	5.00	7.14	0	0	<0.001*
	No	65.00	92.90	210.00	100.00	
Chronic Kidney Disease	Yes	7.00	10.00	1	0.48	<0.001*
	No	63.00	90.00	209.00	99.52	
Pulmonary Embolism	Yes	7.00	10.00	0	0	<0.001*
	No	63.00	90.00	210.00	100.0	
Statin use	Yes	38.00	54.29	164.00	78.10	<0.001*
	No	32.00	45.71	46.00	21.90	
*: Significant p-value						

Assessment of the lipid profiles among DVT patients and controls is shown in Figure 1. The mean (SD) total cholesterol was significantly greater in cases than in controls at 5.55 (1.23) and 5.17 (1.08), with a p-value <0.014. Likewise, the prevalence of abnormal TCH (≥ 5.2) was higher in the case group than in the control group at 65.7% *vs.* 50%, respectively.

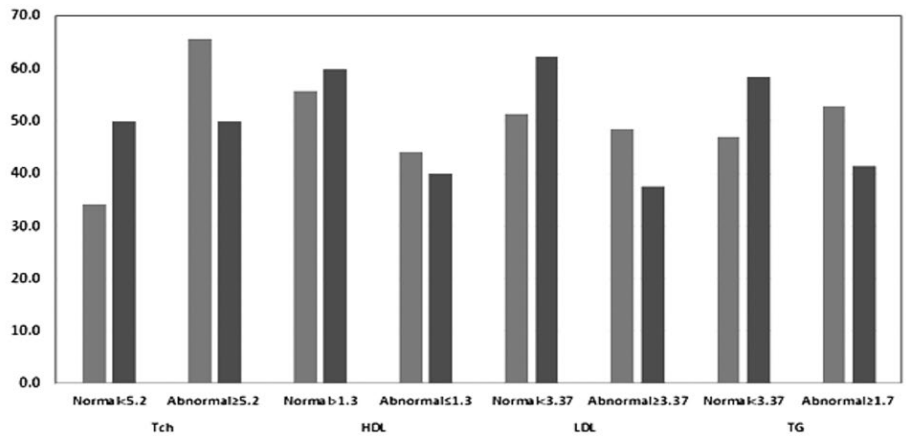

Figure 1 Prevalence of lipid profile alterations

Similar results were obtained for triglycerides, with a mean of 2.04 (1.09) for cases and 1.65 (0.78) for the control group, and a p-value <0.007. However, HDL and LDL levels were similar between the case and control groups.

The Association between CHC and DVT in Dyslipidemia

Table 3 shows the univariate logistic regression for CHC as a risk factor for venous thrombosis in dyslipidemic patients. Results showed that CHC use was significantly associated with a more than two-fold (OR=2.591, p<0.011, 95% CI 1.244-5.396) increased risk of venous thrombosis.

Table 3 Univariate logistic regression for CHC as a risk factor of venous thrombosis

Combined Hormonal Contraception use	Odds ratio	95% CI		p-value
		Lower	Upper	
Yes	2.591	1.244	5.396	0.011*
No**	1.00			
*: Significant p-value; **: used as a reference				

Table 4 shows the univariate logistic regression for various kinds of CHC and venous thrombosis risk factors in dyslipidemic patients. The older generation of oral CHC was associated with a more than eight-fold (OR=8.58, p<0.001, 95% CI 2.60-28.35) significantly increased DVT risk compared to other types of CHC used by participants.

Table 4 Univariate logistic regression for the type of combined contraceptive and venous thrombosis

Combined Hormonal Contraception	Odds ratio	95% CI		p-value
		Lower	Upper	
Yasmin OCP				
Yes	2.03	0.33	12.4	0.443
No**	1			
Gynera OCP				
Yes	1.3	0.33	5.16	0.711
No**	1			
Dian OCP				
Yes	3.09	0.61	15.67	0.173
No**	1			
Nordette OCP				
Yes	8.58	2.6	28.35	<.001*
No**	1			
*: Significant p-value; **: used as a reference				

Table 5 demonstrates the association between CHC duration of use and DVT risk. Compared to nonusers, CHC users of 1 year or less and 1 to 5 years had a five-fold elevated DVT risk, while users of >5 years had a 0.86 risk of DVT. Adjustment for BMI did not affect the risk estimate, but the result was statistically significant only for the 1-5 year duration of use.

Table 5 Association between duration of exposure to combined contraception and risk of DVT among cases and control

Duration of use	Cases	Control	Odds ratio				Adjusted[$] Odds ratio			
			OR	95% CI		p-value	OR	95% CI		p-value
				Lower	Upper			Lower	Upper	
Non-user	55	190	Ref.				Ref.			
≤ 1 year	3	2	5.18	0.84	31.8	0.076	5.58	0.9	34.59	0.065
1 to 5 years	9	6	5.18	1.77	15.19	0.003	5.05	1.71	14.86	0.003
> 5 years	3	12	0.86	0.24	3.17	0.825	0.98	0.26	3.68	0.974
Ref.: Reference group; [$]: Adjusted for BMI										

Associated Factors of Deep Vein Thrombosis

As shown in Figure 2, and Figure 3, a high triglyceride level (>2.22) and no statin use were linked to additional risk for deep vein thrombosis with OR=2.301 (95% CI 1.092-4.847) and OR=3.002 (95% CI 0.693-5.324), with p-values <0.028 and <0.001, respectively. In contrast, HTN and DM exhibited a lower venous thrombosis risk, with OR values of 0.55 and 0.425, respectively, with significant p-values <0.05. Moreover, age, BMI, HDL, total cholesterol, and LDL showed no correlation with the risk for venous thrombosis.

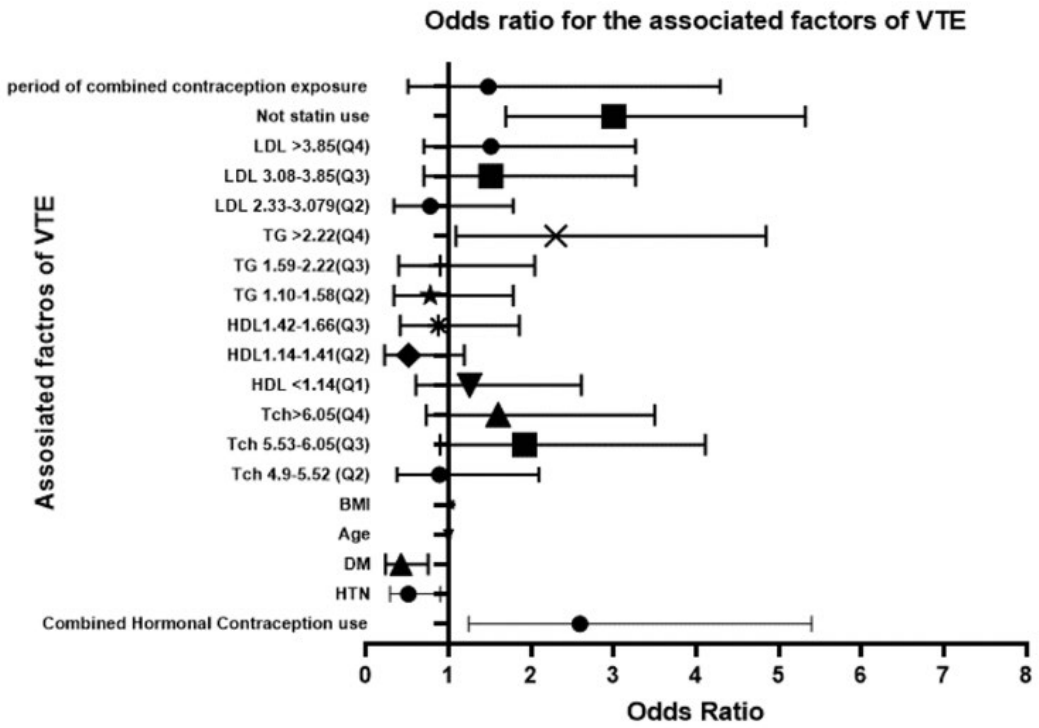

Figure 2 Forest plot of odds ratios for univariate logistic regression for the associated factors of venous thrombosis

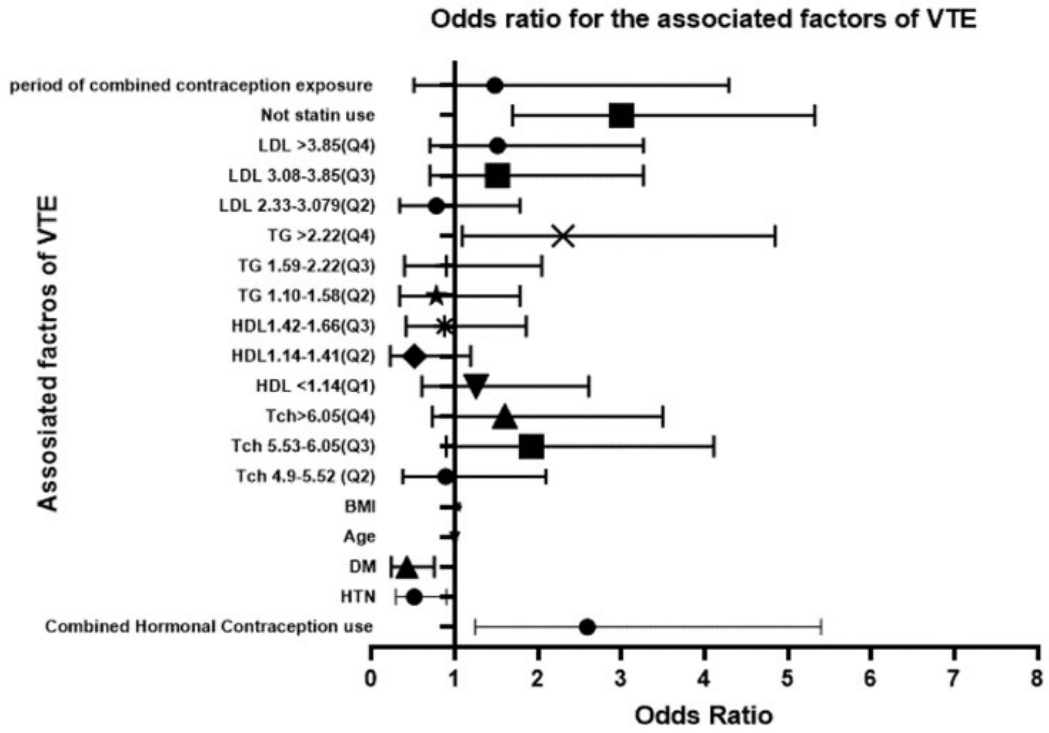

Figure 3 Forest plot of odds ratios for multivariate logistic regression for the associated factors of deep venous thrombosis

Contraception and Altered Lipid Parameters

The association between CHC use and abnormal lipid levels was not statistically significant, since all p-values were >0.05, as shown in Table 6. The odds ratios for total cholesterol, LDL, and TG were slightly more than 1; however, these increments were not statistically significant.

Table 6 Association between contraception and lipid profile

		Odds ratio	95% CI		p-value
			Lower	Upper	
TCH	Normal <5.2**	1			
	Abnormal ≥ 5.2	1.071	0.669	1.715	0.776
HDL	Normal >1.03**				
	Abnormal ≤ 1.03	0.669	0.414	1.079	0.099
LDL	Normal<3.37**				
	Abnormal ≥ 3.37	1.016	0.630	1.640	0.947
TG	Normal <1.7**				
	Abnormal ≥ 1.7	1.154	0.719	1.851	0.554
**: used as a reference					

DVT risk by quartiles of lipid measurement is shown in Table 7. As demonstrated, the risk for DVT was elevated as the levels of total cholesterol, TG, and LDL increased or if HDL levels decreased. However, this association was only significant with TGs and LDL. Women with high TGs had a 4.75-fold increased risk for DVT compared to those with lower levels, with a 95% CI 1.82-12.42 and a p-value <0.001. For LDL, patients with high levels had an OR of 1.514 (95% CI 0.703-3.264) for venous thrombosis compared to lower-level patients, with a p-value <0.028.

Table 7 Risk of venous thrombosis by quartiles of lipid levels

	Odds ratio	95% CI		p-value
		Lower	Upper	
Total cholesterol				
<4.33 (Q1)**	1			
4.33-5.25 (Q2)	0.889	0.377	2.094	0.788
5.26-5.98 (Q3)	1.92	0.897	4.112	0.093
>5.98 (Q4)	1.6	0.732	3.498	0.239
HDL				
<1.13 (Q1)	1.256	0.605	2.609	0.54
1.13-1.36 (Q2)	0.518	0.225	1.192	0.122
1.37-1.59 (Q3)	0.878	0.415	1.858	0.735
>1.59 (Q4)**	1			
TG				
<1.10 (Q1)**	1			
1.10-1.56 (Q2)	1.16	0.42	3.22	0.771
1.57-2.12 (Q3)	0.99	0.35	2.77	0.983
>2.12 (Q4)	4.75	1.82	12.42	.001*
LDL				
<2.29 (Q1)**	1			
2.29-3.05 (Q2)	0.779	0.339	1.786	0.554
3.06-3.83 (Q3)	1.514	0.703	3.264	0.8
>3.83 (Q4)	1.514	0.703	3.264	.028*

*: Significant p-value; **: used as a reference; Q1=first quartile, Q2=second quartile, Q3=third quartile, Q4=fourth quartile

DISCUSSION

Combined hormonal contraception use is a well-recognized risk factor for deep vein thrombosis. Given the insufficient data addressing the risk for DVT in CHC users with dyslipidemia, this study was initiated. We performed this case-control study primarily to evaluate the risk for deep vein thrombosis in women with dyslipidemia who were exposed to combined hormonal contraception compared to non-exposed women.

Cases and controls were matched for age group and were similar in demographic and other characteristics, except for DM, HTN, and statin use, which were greater in controls than in cases. Additionally, CHC use was higher in cases than in controls.

The primary findings indicate that current CHC use in women with dyslipidemia is considerably associated with a more than the two-fold increased risk for DVT in univariate analysis (OR=2.591, p<0.011, 95% CI 1.244-5.396). Such risk remained high after multivariate adjustment. Our result was in line with a systematic review in 2015 performed by Dragoman, et al. showing that dyslipidemic women using combined hormonal contraceptives may experience a minimal increase in risk for venous thromboembolism [26].

In our study, average total cholesterol and triglyceride levels were markedly greater in cases than in controls, as shown in Figure 1. Moreover, the risk for venous thrombosis was increased with increasing levels of total cholesterol, triglyceride, and LDL or with decreasing HDL level with a significant association only for TG and LDL, as shown in Table 7. Women with high TG levels had a 4.75-fold higher risk for DVT with a 95% CI (1.82-12.42) and a p-value <0.001. Similarly, women with high LDL had an OR of 1.514 (95% CI 0.703-3.264) for venous thrombosis, with a p-value <0.028.

Our results indicated an increased risk for DVT with elevated triglyceride levels. A previous population-based case-control study reported a similar association. Two-fold increased risk for deep vein thrombosis in patients with elevated triglyceride levels as per Doggen, et al. study [21]. However, the Morelli, et al. case-control study disagreed with the above findings and reported no association between various kinds of cholesterol or triglycerides and venous thrombosis risk [22].

Carine JM, et al. found that elevation in total cholesterol levels or HDL cholesterol is concomitant with a reduced risk of venous thromboembolism [21]. In contrast, the Framingham Heart prospective cohort study reported that females diagnosed with VTE had greater levels of total cholesterol [30].

Additionally, a Japanese case-control study reported that hypercholesterolemia was concurrent with increased risk for deep vein thrombosis [20].

The present study assessed the risk for deep vein thrombosis in dyslipidemic patients using various types of combined hormone contraception. Our results showed that Nordette oral contraceptive containing (levonorgestrel/ethinyl estradiol) was significantly associated with a more than eight-fold (OR=8.58, p<0.001, 95% CI 2.60-28.35) elevated risk for DVT compared to the other types used by participants, as shown in Table 4. This was in line with a population-based cohort study of 573,680 females using CHC that indicated a high risk for a venous thromboembolic event for drospirenone-containing pill use with high-dose estrogen compared to CHC with a lower estrogen dose [12]. Furthermore, a case-control study by Cole JA, et al. detected a more than two-fold increase in the risk of VTE with transdermal patch use compared to other modalities [10]. On the other hand, Jick, et al. reported an odds ratio of 0.9 for VTE related to transdermal contraception [11]. In our study, the use of transdermal patches was not common, and we cannot comment on its association with DVT.

An evaluation was performed for the association between CHC duration of use and DVT risk. Our result was compatible with the published studies that DVT risk predominates early in CHC use. In the current study, the initial year of CHC use had a five-fold higher DVT risk than nonusers and more than 5-year users, as represented in Table 5. This was in line with the Martinelli, et al. case-control study in 2016, which demonstrated a venous thromboembolism Odds Ratio (OR) of 9.0 (95% CI 6.9-12.2) in oral contraception users for one year or less compared to longer duration users. They suggested a decrease in VTE risk over time in CHC users [17]. Another population-based case-control study in the Netherlands supports this assertion as well. DVT risk was highest in the earliest 6 months to one year of CHC use. The initial 6 months had a three-fold higher risk, while the first 12 months had a two-fold higher DVT risk compared to a longer duration of use [18].

In the present study, a protective effect against DVT was found with statin use. As shown in Figure 2, and Figure 3, not using statins was related to higher DVT risk with OR=3.002 (95% CI 0.693-5.324), with p-values <0.001. This was in parallel to a meta-analysis of a randomized control trial and 9 observational studies in 2010 that evaluated 971,307 patients for statin's role in deep vein thrombosis prevention. A significant 41% DVT risk reduction was observed (Odds Ratio (OR) 0.59, 95% CI 0.43- 0.82) among statin users [23].

Unexpectedly, HTN and DM were associated with a reduced risk for deep vein thrombosis with ORs of 0.55 and 0.425, respectively, significant p-values <0.05. The varied prevalence of DM and HTN between cases and controls with a higher percentage of controls having DM and HTN can explain this result. Additionally, this might be because of the effect of treatment use and regular follow-up. Moreover, age, BMI, HDL, total cholesterol, and LDL showed no correlation in univariate logistic regression for the factors associated with venous thrombosis.

As with any research study, our study has limitations, including the small sample size, difficulty finding a case with both deep vein thrombosis and dyslipidemia, recall struggles with respect to contraception history and the variable prevalence of some DVT confounders between cases and controls.

CONCLUSION

Overall, data from this case-control study indicates that females with dyslipidemia who use combined hormonal contraceptives may be at a higher risk for deep vein thrombosis. Similarly, a high level of triglycerides was considerably associated with DVT. Given the findings of this study, the use of CHCs in women with dyslipidemia is concerning. Additional, thorough research is needed to confirm these associations.

DECLARATIONS

Conflicts of Interest

The authors declared no potential conflicts of interest concerning the research, authorship, and/or publication of this article.

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