Introduction

Oral contraceptives (OCs) are widely utilized method to prevent ovulation, implantation and therefore pregnancy. The high estrogen content (0.05 mg ethinyl estradiol) was though to be the main reason for increased risk of thrombosis. This subsequently led to the development of new oral contraceptives with lower estrogen content (0.03 mg ethinylestradiol). They were considered safer, but recent studies have challenged the concept that reducing the dose of estrogen in oral contraceptives eliminates the risk of thrombosis (23). In the last decade several new synthetic progestins were introduced in combined oral contraceptive preparations. Dienogest (hybrid progestin close to the pregnane group) and drospirenon (derived from spironolactone) are new generation progestins with good ovulation inhibition, cycle control, tolerability and safety profile (12). They have significant antiandrogenic activity. It is still debated whether this property has resulted in lower risk in arterial or venous thromboembolism (20).

Thrombosis caused by OCs can be venous or arterial; in the pulmonary, systemic or splanchnic circulation. Arterial thrombosis is mainly associated with heightened platelet reactivity and damage to the vessel wall, although venous thrombosis has been traditionally associated with blood stasis and hypercoagulability. Accordingly, classic risk factors for arterial and venous thrombosis are usually considered distinct. Risk factors of arterial thrombosis include smoking, hypertension, diabetes, the metabolic syndrome, and hyperlipidemia. However, a number of studies have recently challenged this dichotomy. It is now recognized that venous and arterial thromboses share several risk factors, suggesting a closer link between the two clinical conditions (1, 4, 9, 13, 17). Although the use of oral contraceptives might contribute to the development of thrombosis, it would appear that smoking can independently increase the risk of thromboembolism (10).

The morbidity and mortality of venous thromboembolism and arterial thrombosis in Bulgaria is substantial. Deep venous thrombosis (DVT) accounts for a great part of hospitalizations in the vascular surgery clinics in Bulgaria. The most serious complication of DVT is pulmonary embolism (PE). We therefore evaluated the age specific incidence of deep venous thrombosis, pulmonary thromboembolism and arterial thrombosis, and the recent impact of hormone therapy (combined low-dose oral contraceptives, containing estrogen component with new generation progestins) and smoking habits on these pathologies in Bulgarian women under the age of 50 years.
Materials and Methods
A case-control study of venous thrombosis was conducted in National Heart Hospital in Sofia. The study included evaluation of registry records of Bulgarian women discharged from the hospital from January 2005 until December 2009 after a thromboembolic event.

Patients were interviewed about demographic characteristics, personal habits (including smoking and alcohol consumption) and history of medication. Diagnoses at discharge were later obtained from the hospital records. We confined our analyses to patients who were women 20-50 years of age receiving OCs. The patients reported the use of “low dose” contraceptives (estrogen content of 0.03 mg ethinylestradiol) combined with progestin component norgest (2 mg) or drospirenon (3 mg).

We further excluded patients with diabetes mellitus, obesity, acute myocardial infarction, lipid abnormalities, varicose veins or pulmonary disease other than thromboembolic - all conditions which might predispose to the development of thromboembolism. Patients whose thromboembolism was secondary to trauma or surgical procedures were also excluded.

Cases were women with diagnosis of a DVT or arterial thrombosis admitted to the vascular surgery clinic of the participating hospital. A total of 65 cases of DVT and 43 cases with arterial thrombosis at age 20 to 50 years (mean age 33) were included in the study.

Controls were women admitted to the same hospital during the same period, for diseases other than VTE or arterial thrombosis, and not related to known potential risk factors. There were 76 control women for DVT group and 51 controls for arterial thrombosis groups. The women in the control group were comparable with the study cases in terms of age. Patients were matched for age within a five year tolerance.

Standard methods of analysis, based on unconditional logistic regression, were used to derive odds ratios (OR), and the corresponding 95% confidence intervals (CI) (2).

Results and Discussion
Impact of oral contraceptives on development of DVT and arterial thrombosis
Table 1 presents distribution of DVT according to the hormone therapy (OCs). Seventeen patients with DVT (26.20%) reported the use of OCs. The risk for developing DVT increases after hormonal therapy. The OR was 2.3 compared to the group of non users. Within the hormone treated group, a total of 7.63% of the cases with DVT versus 4.61% of controls were current users of hormonal treatment and 18.46% versus 10.79% were past users. The risk of DVT decreases as the time since last hormonal use increases, although it still remained high.

Table 2 presents distribution of arterial thrombosis according to the hormone therapy. Nineteen patients with arterial thrombosis (44.2%) had received OCs. Hormonal therapy increases the risk of arterial thrombosis. The OR was 3.6 compared to the group of non users. The risk of arterial thrombosis decreases as the time since last hormonal use increases.

Effect of smoking on thromboembolic events
Out of the patients with DVT 41.5% were non-smokers compared with 43.1% of smokers (Table 3).

In 15.4% of the cases with DVT a complication of PE occurred. With reference to the effect of smoking compared with non smokers, the OR of pulmonary embolism was 1.4 (95 CI 0.9-3.0). PE occurred more often when smoking was combined with hormonal therapy (66.11% in patients with hormonal therapy vs. 33.9% in patients without hormonal therapy). Thus no clear evidence of a relation between venous thromboembolism and smoking habits was observed, while pulmonary embolisms were more often in smokers, who used therapy with hormones.

In the group with arterial thrombosis the smokers were 53.5% vs. 46.5% of non smokers. With reference to the effect of smoking compared with non smokers, the OR of arterial thrombosis in smokers was 2.7 (95 CI 1.4-3.7).

Age specific incidence of deep venous and arterial thrombosis
Venous thromboembolic events incidence (femoropopliteal, iliofemoral venous thrombosis and arterial thrombosis) among smoking women was modelled from the smoothed age specific incidence rates.

Patients were matched for age within five year tolerance. Incidence of femoropopliteal venous thrombosis among all women increased with age. It rose from 9.8% at age 20-24 years to 28.5% at age 45-50 years. Similar effects were observed in cases of iliofemoral venous thrombosis. In this patient group the incidence rose from 7.1% at age 20-24 years, to 38% at age over 45 years (Fig. 1). The smoking habits increased significantly the risk of developing arterial thromboembolic events with the age. It sharply increased from approximately 5% at age 20-24 years to almost 73% at age of 45-50 years.

![Fig. 1. Age specific incidence of femoropopliteal, iliofemoral and arterial thrombosis in smoking women under 50 years of age](image-url)
Distribution of 65 cases of deep venous thrombosis (DVT) and 76 controls and odd ratios (with 95 confidence intervals, CI) according to OCs use in the period 2005-2009

<table>
<thead>
<tr>
<th>Hormone use (OCs)</th>
<th>DVT</th>
<th>Controls</th>
<th>Odd ratios (OR, 95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patients (number)</td>
<td>%</td>
<td>Patients (number)</td>
<td>%</td>
</tr>
<tr>
<td>Never user</td>
<td>48</td>
<td>73.80</td>
<td>66</td>
</tr>
<tr>
<td>Ever user</td>
<td>17</td>
<td>26.20</td>
<td>10</td>
</tr>
</tbody>
</table>

*Reference category

Distribution of 43 cases of arterial thrombosis and 51 controls and odd ratios (with 95 confidence intervals, CI) according to the hormonal therapy (OCs) in the period 2005-2009

<table>
<thead>
<tr>
<th>Hormone use (OCs)</th>
<th>Arterial thrombosis</th>
<th>Controls</th>
<th>Odd ratios (OR, 95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patients (number)</td>
<td>%</td>
<td>Patients (number)</td>
<td>%</td>
</tr>
<tr>
<td>Never user</td>
<td>24</td>
<td>56.8</td>
<td>42</td>
</tr>
<tr>
<td>Ever user</td>
<td>19</td>
<td>44.2</td>
<td>9</td>
</tr>
</tbody>
</table>

*Reference category

Relation between smoking habits and deep venous thromboembolism with pulmonary embolism

<table>
<thead>
<tr>
<th>Patients with femoropopliteal and iliofemoral venous thrombosis</th>
<th>Patients with thromboembolism complicated with pulmonary thromboembolism</th>
<th>Odd ratios (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>number</td>
<td>%</td>
<td>number</td>
</tr>
<tr>
<td>Non smokers*</td>
<td>27</td>
<td>41.5</td>
</tr>
<tr>
<td>Smokers</td>
<td>28</td>
<td>43.1</td>
</tr>
</tbody>
</table>

*Including former smokers who had currently abstained for over one year.
**Reference category

in women with venous thromboembolism. There is strong synergism between the use of OCs and other recognized risk factors such as tobacco smoking (15).

This study assesses the effects of oral contraceptives and cigarette smoking on incidence of venous and arterial thromboembolic disease among women at age 20-50 years. The patients reported the use of combined hormone preparations with low-estrogen (0.03 mg) and progestin component (dienogest or drospirenone). Although in the past the lower estrogen contraceptives combined with progestin component were considered to be relatively safe, recent studies have challenged that concept. Several studies suggested that certain progestins may increase the risk of thrombosis associated with low-estrogen preparations (11, 24). Whereas the beneficial effects of new generation progestins (desogestrel, gestogen) on the level of high density lipoprotein cholesterol suggested that they might lower the risk of arterial thrombosis, studies demonstrated that the relative risk of venous thrombosis in users of these oral contraceptives was much higher than the risk of second generation progestins (levonorgestrel, norgestrel) (21).

Results from the study showed that the risk of thrombosis among hormone users was higher than in non users. The relative risk of confirmed arterial thrombosis associated with OCs was 3.6 (CI 1.3-6.8); the risk of venous thrombosis was lower: OR 2.3 (CI 1.3-4.0). The results confirm the existence of an increased risk associated with the use of modern oral contraceptives. The most serious adverse events of combined estrogen and progestin preparations are related to distribution along major vascular trunks (celiac, superior and inferior mesenteric) to the side of thrombus in either the arterial or venous system. Several pathophysiological mechanisms have been proposed to explain the relationship between oral contraceptive use and “hypercoagulable” state: estrogen increase the procoagulant factors like prothrombin, factor VII, X, XII and XIII; estrogens have an effect on anticoagulant pathway by causing resistance to activated protein C; estrogens increase fibrinolysis; progestin exacerbate the effects of estrogens on procoagulant, anticoagulant and fibrinolytic pathways (7, 8, 22).

Smoking is an important risk factor for cardiovascular diseases. Since there were considerable differences in the
smoking habits of patients in different age groups, we took this factor into account by a matching procedure. No clear evidence of relation between venous thrombotic events and smoking habits in non OCs users were observed. Nevertheless, the risk of complications, like pulmonary thromboembolism, substantially increased in smoking women who used OCs. It suggested an action of both risk factors on similar aspects of the pathogenic process (5, 8). Some evidence implicates smoking directly in the pathogenesis of thromboembolic states in the less platelet-dependent venous side of circulation (6, 14). Potential procoagulant mechanisms that might be associated with smoking are: increased fibrinogen level from increased interleukin-6, increased catecholamine release, increased tissue factor level, impaired fibrinolysis, impaired platelet activation (3, 6, 18). The above mechanisms are interrelated, and it is difficult to determine which abnormalities clearly result from smoking and also clinically increase the risk for VTE.

We found a clear association between smoking habits with the risk of arterial thrombosis. This may be related to the dose-dependent and reversible association of smoking with activation of coagulation and inflammation (25). Smoking has a direct effect on arterial walls, which range from endothelial dysfunction to atherosclerosis.

We further analyzed the age specific incidence of DVT and arterial thrombosis among smoking women at the age 20-50 years. There was an exponential increase in risk of arterial thrombotic disease with age. We found that the relative effect of smoking on arterial thrombosis became significant when combined with OCs in women older than 40 years. Possible mechanisms might include cumulative effects of risk factors on the arterial wall, decreased regular exercise increasing immobility that results in venous stasis and increasing systemic activation of blood coagulation (19). Smoking is an additional risk factor. In combination with OCs smoking aggravates the stage of arterial disease, especially in higher age (16).

This multifactor set of conditions that favor vascular narrowing or occlusion seem to be the explanation for the association between DVT, PE, oral contraceptives and smoking. In conclusion, women older than 35 years should be assessed for thrombogenic risk factors including smoking, hypertension, metabolic syndrome, and other vascular diseases prior to oral contraceptive use. Further long-term vascular follow-up, especially of women at the age 40-50 years, with regard to prior hormone therapy is needed.

Conclusions

Both non-clinical and clinical studies suggest a possible link of oral contraceptives to abnormalities in coagulation and fibrinolysis. The emphasis of researches connecting smoking to various aspects of coagulation and fibrinolysis has tended to focus primarily on the potential impact on atherosclerosis and do not deal with deep venous thrombosis and arterial thrombosis. This retrospective case-control study was performed to evaluate the age-specific effects of both oral contraceptives and smoking on the risk of deep venous thrombosis and arterial thrombosis in women under 50 years of age. We found that the use of low dose oral contraceptives is associated with higher risk of both arterial and venous thrombosis. The effect was more evident in women over 35 years. We found clear evidence that smoking increases the risk of arterial thrombosis and that this effect was age-dependent. The incidence of deep venous thrombosis was also higher in oral contraceptive users compared to non-users.

The present study will allow a decision-based analyses and rational contraceptive use to individual woman taking into consideration their age and smoking habits.

REFERENCES