Correlation between Duration of Oral Contraceptives and Hypercoagulability in Bangladeshi Women

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Md. Atiquzzaman⁵, Dilruba Akther⁶

Abstract:
This study was done to assess the hypercoagulability and the risk of thromboembolism in women taking oral contraceptive pill for prolonged period of time. This cross sectional study was done in the department of Physiology, Dhaka Medical College, Dhaka from Jan 2012 to Dec 2012. Ninety female subjects with the age range from 25-45 years, were taken as a study population. Among them, 60 women taking oral contraceptives for prolonged period of time (>1 years) were included for the study group and age matched 30 women of OCP nonusers were taken as a control. Study subjects were divided into two groups according to their duration of oral pill use: group B1 (1 to 5 years users) were 30 women and group B2 (>5 to 10 years users) were 30 women. Prothrombin time and activated partial thromboplastin time were estimated in all groups. Statistical analysis was done by unpaired Student's 't' test and Pearson's Correlation Coefficient test. In this study, the mean (±SD) PT levels in group B1 & B2 were shortened than that of group A which were statistically highly significant (P < 0.001). Within the study groups, PT levels were positively correlated (r=+0.027) with the group B1 and negatively correlated (r=-0.163) with the group B2. But both the relationships were statistically non significant. The mean (±SD) APTT level in group B1 was shortened than that of group A but the result was not statistically significant. The mean (±SD) APTT level in group B2 was shortened than that of group A but the result was statistically highly significant (P<0.001). Within the study groups, APPT levels were negatively correlated with the group B1 (r=-0.268) and also group B2 (r=-0.122). But both the relationships were statistically non significant. My present study revealed that prolonged duration of OCP use (at least for 5 years) increases the risk of hypercoagulable state and thromboembolism in women.

Introduction:
Oral contraceptives are used for the prevention of conception. Although oral contraceptive pills (OCPs) have been in use for over 30 years and despite innumerable analyses of their risk and benefits, disagreement continues about their safety and adverse effects. Currently prescribed low dose oral contraceptives contain a smaller amount of estrogen (<50μg/day)¹. Most studies indicate that newer low-dose oral contraceptives are clearly associated with a 3 to 6 fold increased

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risk of venous thrombosis and pulmonary thromboembolism. Hepatic synthesis of coagulation factors are increased in the OCP users that may produced hypercoagulability\textsuperscript{2}. Hypercoagulability is related to the reduced synthesis of antithrombin II and also seen with advancing age. According to the duration of OCP use, PT levels were increased significantly after longer duration (\textgreater{}2 yrs) of OCP use than short duration (<1 yrs) of use\textsuperscript{3}. Some other group of investigators also reported according to the duration of OCP use. They divided them into different groups like group I for 1 year; group II for 1 to 4 years; group III for more than 4 years of OCP use. But among the groups, non significant shortened of PT and APTT levels were observed\textsuperscript{4}. Different researchers demonstrated that PT and APTT levels were remain unchanged in short (<1 yrs) and long (>3 yrs) duration of OCP use which was also statistically non significant\textsuperscript{5,6}.

Several studies have been done abroad to observe the thromboembolic effects & hypercoagulable state in women who are taking oral contraceptives for prolonged period of time at least \textgreater{}5 years. But a few published data has been available in our country regarding the hypercoagulability in OCP users. Again we need our own standard baseline from which we can compare these parameters in our own population. Therefore, the present study has been undertaken to estimate PT and APTT in women of OCP users in different period of time that will help us to detect the risk for future thromboembolism. It is expected that findings of this study would give a guideline to the physician for better management of women who were taking oral contraceptives for prolonged period of time. Again this study will also help to build awareness about thromboembolism which is now-a-days an utmost importance worldwide. Moreover early detection & prevention of it can reduce morbidity & mortality and thus reduce burden on our health budget.

**Materials and method:**

This cross sectional study was carried out in the Department of Physiology, Dhaka Medical College, Dhaka between January 2012 and December 2012. The protocol of this study was approved by the Ethical Review Committee of Dhaka Medical College, Dhaka. Sixty apparently healthy women taking hormonal oral contraceptives (Shukhi) for 1 to 10 years with age range between 25 to 45 years were taken as study group (group B). Study group was further divided into 1 to 5 years user group (group B1, n=30) and >5 to 10 years user group (group B2, n=30). In addition, 30 apparently healthy women of OCP nonusers aged 25 to 45 years were included as control group (group A). All the study subjects and controls were selected from family planning clinics of Nari Maitree (Second urban primary health care project, P.A-6, Dhaka city corporation) & from personal contact in different area of Dhaka city.

**Inclusion criteria:**

i) women with age ranging from 25-45 years.

ii) women with the history of taking OCP for 1 to 5 years were included in group B1 & women who were taking OCP for >5 to 10 years included in group B2.
iii) women with no history of taking oral or hormonal contraceptives were included in group A.

Exclusion criteria:

i) Women with age more than 45 years & less than 25 years.

ii) Women with heart, liver, kidney & any endocrine disease like thyroid disease, TB, malignancy.

iii) Women with taking hormone replacement therapy, steroid, aspirin & anti platelet aggregator.

Data were collected through written questionnaire, clinical examination and relevant investigation. PT and APTT level were analyzed on automated coagulation analyzer, Sysmex CA - 500 series by using the Thromborel ® S(Human thromboplastin containing calcium) reagent and the Dade ® Actin ® FSL Activated PTT reagent respectively. Statistical analysis was done by Unpaired Student's ' t ' test and Pearson's Correlation Coefficient tests as applicable and p value <0.05 was considered as level of significant.

Results:

The mean (±SD) PT levels in group B1 & B2 were shortened than that of group A which were statistically highly significant (P < 0.001). Within the study groups, PT levels were positively correlated (r=+0.027) with the group B1 and negatively correlated (r = -0.163) with the group B2. But both the relationships were statistically non-significant (Table I, II and Figure I, II).

Unpaired Student's ' t ' test was performed to compare between groups. The test of significance was calculated and p values <0.05 was accepted as level of significance.

### Table I: Prothrombin time and activated partial thromboplastin time in different groups (n=90)

<table>
<thead>
<tr>
<th>Groups</th>
<th>N</th>
<th>PT(sec)</th>
<th>P value for PT</th>
<th>APTT(sec)</th>
<th>P value for APTT</th>
</tr>
</thead>
<tbody>
<tr>
<td>A</td>
<td>30</td>
<td>11.1±0.42</td>
<td></td>
<td>32.2±2.46</td>
<td></td>
</tr>
<tr>
<td>B1</td>
<td>30</td>
<td>9.7±0.38</td>
<td>(A vs B) 0.001</td>
<td>25.6±2.34</td>
<td>(A vs B) 0.093*</td>
</tr>
<tr>
<td>B2</td>
<td>30</td>
<td>9.5±0.72</td>
<td>(A vs B) 0.001</td>
<td>24.5±2.24</td>
<td>(A vs B) 0.801**</td>
</tr>
</tbody>
</table>

Group A: OCP nonusers
Group B1: OCP users 1 5 years
Group B2: OCP users >5 10 years
ns=Not significant
*Significant at P<0.05
**Significant at P<0.001

### Table-II : Correlations of duration of OCP use with different study parameters in different study groups (n=60)

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Group B1 (n=30)</th>
<th>Group B2 (n=30)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>r</td>
<td>p</td>
</tr>
<tr>
<td>PT</td>
<td>0.027</td>
<td>0.889*</td>
</tr>
<tr>
<td>APTT</td>
<td>-0.268</td>
<td>0.153*</td>
</tr>
</tbody>
</table>
Discussion:

In the present study, findings of PT and APTT levels in OCP users were almost within normal range. But the levels were more shortened in >5 to 10 years OCP user group than 1 to 5 years user group.

In the present study, PT and APTT levels in women of OCP users were shortened than that of nonusers and the result was statistically highly significant. This finding was in agreement with those of different researchers of different countries.\(^6\text{,}^7\text{,}^8\text{,}^9\text{,}10\text{,}11\).

In between study groups, PT levels were positively \((r=+0.027)\) correlated with the group B1 and negatively \((r=-0.163)\) correlated with the group B2. Here PT levels were progressively shortened along the duration of OCP use. But the relationships were statistically non-significant. Similar type of observations were reported by the different researchers of different countries.\(^4\text{,}5\text{,}6\).

In the present study, APPT levels were negatively correlated with the group B1 \((r=-0.268)\) and group B2 \((r=-0.122)\). Here APPT levels were progressively shortened along the duration of OCP use. But all these relationships were statistically non-significant. Similar type of observations were reported by the different researchers of different countries.\(^4\text{,}5\text{,}6\). In our study, above findings of correlations showed that the duration of OCP use (1-5 years and >5-10 years) did not show any statistically significant difference on study parameters. Smaller sample size of the present study may be the cause of these above findings.

Many explanations are suggested by different investigators for the shortened PT and APTT level in women taking oral contraceptive for
longer duration of time but the exact mechanism is not yet clear. It has been suggested that estrogen present in combined oral contraceptive pills acts as a contributory factor for significant shortening of PT and APTT. Hypercoagulability due to hyper estrogenic state is probably caused by increased hepatic synthesis of coagulation factors and reduced anticoagulant synthesis. These condition might play an important role in development of thromboembolism.

The pathogenesis underlying this apparent prothrombotic state is not clear. It has been suggested that increased plasma concentration of several markers of coagulation (clotting factors of intrinsic and extrinsic blood coagulation) factors are thought to be a primary factor in the increased thrombotic risk associated with OCP.

Any hormonal therapy, including oral contraception may increases the risk for venous thromboembolism. Careful and individual risk-to-benefit analysis is needed in any woman taking oral contraceptives. But the factors and mechanism by which prolonged use of oral contraceptive leads to a prothrombotic state are complex and cannot be find out from this present study due to time and financial constrains. So, a further study on this field is required for clarification.

From this study, it can be concluded that the longer duration of OCP use causes non-significant increase of PT and APTT among >5 to 10 years OCP users than 1 to 5 years user group. This altered results of above parameters were more profound with advanced age specially after 30 years of women taking oral pills for prolonged period of time. Thus it may be stated that prolonged duration of OCP users are susceptible to develop hypercoagulability and increased risk of thromboembolism. To establish the findings of our study, further studies with involvement of larger population are needed for clarification.

References:


