EVALUATION OF ELEVATED FACTOR VIII IN ORAL CONTRACEPTIVE USERS

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ABSTRACT
Background: Recently elevated factor VIII become increasingly the most common cause of thrombosis, many studies reported a 10% of normal population with elevated factor VIII more than 150iu/ml. Sustained Increase in factor VIII level reported in response to acute phase reaction, malignancy, inflammation, pregnancy, estrogen and in response to oral contraceptive pills. Many studies report 4-6 folds increase risk of thrombosis in women on oral contraception and elevated factor VIII level, furthermore there is still a familial tendency for high factor VIII level for which no cause has yet been found within factor VIII gene. Objectives: This study was designed to assess the level of factor VIII in women on oral contraceptive pills and correlate this level with duration of drug intake. Methods: Forty women on oral contraceptions for more than one year had been invistegated for factor VIII level using one stage factor assay. This study done in Geodon lab.in period between Sept. 2008 till April 2013. Results: Thirteen women on oral contraception for more than one year show elevated level of factor VIII more than 150% activity compared to only two cases elevation in the control group, furthermore higher level of factor VIII correlate clearly with duration of drug intake. Conclusion: Oral contraceptive pill has unexplained role on elevation of factor VIII level which correlate with duration of drug intake, careful and routine follow up for thromboembolic markers is recommended.

Key words: Oral contraceptives (OCS), venous thromboembolism (VTE), factor VIII level.
INTRODUCTION
Hypercoagulable states can be defined as a group of inherited or acquired conditions associated with a predisposition to venous thrombosis (including upper and lower extremity deep venous thrombosis with or without pulmonary embolism, cerebral venous thrombosis, and intra-abdominal venous thrombosis), arterial thrombosis (including myocardial infarction, stroke, acute limb ischemia, and splanchnic ischemia), or both (1). Venous thromboembolic disease is the most common clinical manifestation resulting from hypercoagulable states. Although most inherited conditions appear to increase only the risk of venous thromboembolic events (VTEs), some of the acquired conditions have associated with both VTEs and arterial thrombosis. These include cancer, myeloproliferative syndromes, antiphospholipid antibodies (APAs), hyperhomocysteinemia, and heparin-induced thrombocytopenia (2). Oral contraceptive use is associated with a 2- to 4-fold increase in the risk of venous thromboembolism (3). It has been previously reported that some thrombophilic alterations such as factor V Leiden and G20210A prothrombin mutations display a synergistic interaction with use of oral contraceptives therefore heterozygous carrier of these mutations have a 20- to 40-fold higher risk of thrombosis than non-users who have a normal genotype (4). High levels of factor VIII are another common risk factor for venous thromboembolism. In the Lieden thrombophilia Study Factor VIII procoagulant activity levels in the upper quartile were associated with a 5-fold increase in the risk of venous thrombosis when compared to the risk in subjects with lower levels (5,6). Similar findings have been reported in several independent studies (7,8,9). More recently, it was shown that high factor VIII levels increase the risk of venous thrombosis in women using oral contraceptives (10). In a subset of 155 premenopausal women with DVT enrolled in LETS, Bloemenkamp observed that use of OCPs was associated with an odds ratio of 3·8 (95% CI: 2·4–6·0). In this same cohort, women with high FVIII:C levels were also at significant increased risk of venous thrombosis, with an odds ratio of 4·0 (95% CI: 2·0–8·0). Importantly however, the combination of both OCP and high FVIII resulted in an odds ratio of 10·3 (95% CI: 3·7–28·9) (11). Similarly, in another case–control study, Legnani reported an even more marked synergistic increase in VTE risk (odds ratio 13·0; 95% CI: 4·9–34·3) for women with combined high FVIII levels and OCP usage (12). The combination of high FVIII levels and heterozygosity for the F5 R506Q mutation has also been associated with increased risk of VTE (13,14).
The aim of the study is to detect the increasing evidences about the possible role of oral contraceptive in causing thrombosis by assessing the level of factor VIII in women on oral contraceptive pills and correlate this level with duration of drug intake.

MATERIALS AND METHODS

**Patients:** 40 women on oral contraceptive pills for more than one year, mean age $37.22\pm2.59$ range (23-47) and 20 normal healthy women with no history of contraception controls, mean age $23.95\pm3.1$ range (23-47), participated in the study. Mean duration of drug intake (in years) is $(3.87\pm1.9)$ range (1.5-10). The patients were visiting Geodon laboratory for the period from Sept. 2008 to April 2013. Blood samples were taken from patients and control groups by mixing 1.8 ml blood in 0.2 ml sodium citrate (0.11M). All samples (patients and controls) were tested for factor VIII level by one stag assay. A cutoff point for factor VIII level is 150% (150 IU/100ml).

**Statistical Analysis:** The Statistical Analysis System- SAS (2010) was used to effect of different factors in study parameters. T-test was used for significant comparing between means in this study.

RESULTS AND DISCUSSION

The incidence of Deep vein thrombosis (DVT) in general population has been reported to be around 5 per 10 000 per annum (15). The pathogenesis of DVT is quite complex, hyperactive coagulation pathway or hypoactive anticoagulant mechanism and or hypoactive fibrinolysis being all implicated. DVT appear to be multicausal disease that’s more than single risk factor need to be present simultaneity to cause thrombosis. The risk factor incriminated include acquired and genetic factor. Among genetic factor includes antithrombin III deficiency, protein C deficiency, protein S deficiency, factor V leiden and prothrombin 20210 mutation. Among known acquired risk factors includes immobilization, surgery, trauma, pregnancy, puerperium, lupus anticoagulant, malignancy and female hormone(16,17). Recently elevated factor VIII level was proposed as an additional factor in the development of deep vein thrombosis (18).

In this study we assessed the prevalence of elevated factor VIII in women on oral contraceptive for more than one year mean drug duration $(3.87\pm1.9)$. The study showed that 27.5% of patients group had elevated factor VIII level in excess of 150 compared to only...
10% of control group. Table (1) shows that mean factor VIII is higher in the study group (153.62±5.12) compared to control group (135.15±8.17).

Table (1) factor VIII levels in both study groups.

<table>
<thead>
<tr>
<th>Group</th>
<th>No.</th>
<th>VIII level ± SE</th>
</tr>
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<tbody>
<tr>
<td>Patients</td>
<td>40</td>
<td>153.62 ± 5.12</td>
</tr>
<tr>
<td>Control</td>
<td>20</td>
<td>135.15 ± 8.17</td>
</tr>
<tr>
<td>T-test value</td>
<td>----</td>
<td>13.53 *</td>
</tr>
</tbody>
</table>

* (P<0.05).

Such increase in factor VIII lead to imbalance between procoagulant activity of factor VIII and that of anticoagulant as protein C lead to increase risk of thrombosis 4-6 folds (19). On the other hand there is an obvious correlation between duration of drug intake and age of women (P<0.01) as shown in table (2) which means that elevated factor VIII level is dose and time dependent similar correlation concluded by many studies (20,21,22).

Table (2). Correlation coefficient between duration of drug and VIII level

<table>
<thead>
<tr>
<th>Correlation coefficient (r)</th>
<th>Duration of drug</th>
<th>Age</th>
</tr>
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<tbody>
<tr>
<td>VIII level</td>
<td>0.51 **</td>
<td>0.41 **</td>
</tr>
<tr>
<td>** (P&lt;0.01).</td>
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In contrast to deficiency state in which well known genetic defect within factor VIII gene reported, no recognizable factor VIII gene defect in those with increase factor VIII level is identified yet and subtle changes in regulation of gene activity is probably responsible for elevated level of factor VIII.

Oral contraceptive pill has unexplained role on elevation of factor VIII level which correlate with duration of drug intake, careful and routine follow up for thromboembolic markers is recommended.

REFERENCES


