Fibrinolytic activity in women on oral contraceptive pills: variation due to haemoglobin genotype

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Plasma fibrinogen levels and euglobulin lysis time (ELT) were determined in 84 women with haemoglobin genotype AA (HbAA) and in 38 with haemoglobin genotype AS (HbAS), aged 17–35 years, who were on oral contraceptive pills (OCP). The control group included 23 HbAA and 27 HbAS age-matched, apparently healthy women, who had regular menstruation and no history of OCP usage. The controls showed statistically significant elevations in fibrinogen levels in women with genotype HbAS (+13%; \( P < 0.05 \)) compared with women with genotype HbAA. Among OCP users, the difference in fibrinogen levels (+5%) between HbAS and HbAA women was not statistically significant. The elevation in fibrinogen levels which was restricted to the HbAA women, was probably caused by OCP use, and may be dependent on the Hb genotype. In contrast, the observed elevations in euglobulin lysis time among OCP users \( (P < 0.005) \) were independent of Hb genotype. Thus, while OCP may constitute a risk factor for the development of thromboembolism in women, the S-gene may confer partial protection against this development in women who have the HbAS genotype.

Key words: Hemoglobin AA, AS; Fibrinolytic activity; Oral contraceptive pill; Contraception

Introduction

Several epidemiological studies have shown that women on oral contraceptive pills (OCP) have a higher risk of developing thrombosis (Poller and Thomson, 1966; Vessey and Doll, 1969 and Famodu et al., in press). Recently, significantly increased fibrinogen levels (Famodu and Reid, 1987 and Famodu et al., 1991) and decreased fibrinolytic activities (Famodu, 1988) were observed in healthy homozygous HbSS individuals. Such changes in fibrinogen levels and in fibrinolytic activities may indeed contribute to the severity of vascular disorders with the added use of OCP. Most of the published epidemiological investigations and haemostasis studies on women on OCP have been on Caucasians with genotype AA. There is a dearth of information on Black Africans, who have the highest incidence of haemoglobinopathies, particularly the sickle-cell trait (HbAS; HbAC) and sickle-cell disease (HbSS; HbSC). The number of African women currently using OCP as a means of birth control is increasing. In this connection, the fact that the HbAS trait occurs in 20–40% of the

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Black African population (Fleming 1982) is a cause for concern. The present study is therefore designed to investigate the possible association between the haemoglobin S-gene and OCP as an added risk factor in the development of thrombosis.

Materials and Methods

The study group included 122 women (84 with genotype HbAA and 38 with genotype HbAS, aged 17–35 years) on oral contraceptive pills, and 50 healthy normal women with regular menstruation and no previous hormonal therapy (23 with HbAA and 27 with HbAS, aged 18–38 years).

Venous blood was withdrawn from an arm vein with a minimum of stasis into a clean disposable plastic syringe. 10 ml of blood was collected from women on oral contraceptive pills and from controls. 9 ml of blood was mixed with 1 ml of sodium citrate solution (31.3 g/l). After mixing, the blood was spun at 2500 x g for 10 min in a bench centrifuge to separate the plasma. The plasma was then decanted and kept at room temperature (25–26°C) until the tests were done.

The plasma fibrinogen level was measured by the clot weight procedure of Ingram (1961). Measurements were made on the day the samples were collected. The haemoglobin genotype was determined by electrophoresis using filter paper (Whatman No. 1) with barbitone buffer (pH 8.6), run at a constant emf of 180 V for between 12 and 15 h. Haemolysates of blood from known genotypes HbAS and HbSS were used as controls. Euglobin lysis time (ELT) was measured by the modified method of Von Kaulla (1963).

Results are expressed as mean ± S.D. Student's t-test for paired means was used for statistical comparisons.

Results

Table 1 shows the mean plasma fibrinogen and euglobulin lysis time for women on OCP and controls without OCP. Fibrinogen levels in HbAA OCP users was significantly higher than in HbAA controls (P < 0.05). There was no significant difference between fibrinogen levels of HbAS OCP users compared with HbAS controls.

The control group showed statistically significant differences in fibrinogen levels in an intra-group comparison (+ 13%; P < 0.05). However, in the group using OCP the difference in fibrinogen levels (+ 5%) between HbAS and HbAA women was not statistically significant.

The ELT was increased in women on OCP (HbAA and HbAS; P < 0.005) when compared with the respective control populations. Intra-group variation in ELT was not observed in the OCP users or the controls.

Discussion

The study showed that women with HbAS, who constitute 26–40% of the female population, have higher fibrinogen levels than those with HbAA. This increase (+ 13%) in fibrinogen level could be a consequence of the presence of the S-gene.
TABLE 1
Mean ± S.D. of plasma fibrinogen level and euglobulin lysis time for women on OCP and controls without OCP

Numbers in parentheses represent number of women.

<table>
<thead>
<tr>
<th></th>
<th>Plasma fibrinogen level (g/l)</th>
<th>Euglobulin lysis time (min)</th>
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<tbody>
<tr>
<td>Control HbAA (22)</td>
<td>3.82 ± 1.23</td>
<td>167.58 ± 8.50</td>
</tr>
<tr>
<td>Control HbAS (27)</td>
<td>4.33 ± 1.05*</td>
<td>170.60 ± 4.10</td>
</tr>
<tr>
<td>Women on OCP HbAA (84)</td>
<td>4.11 ± 1.25**</td>
<td>188.26 ± 9.57***</td>
</tr>
<tr>
<td>Women on OCP HbAS (38)</td>
<td>4.32 ± 1.45</td>
<td>189.13 ± 8.63****</td>
</tr>
</tbody>
</table>

*  P < 0.05; control HbAS compared with control HbAA.
** P < 0.05; OCP HbAA compared with control HbAA.
*** P < 0.005; OCP HbAA compared with control HbAA.
**** P < 0.005; OCP HbAS compared with control HbAS.

This is not unlikely, since homozygous HbSS individuals have already been shown to have significantly increased fibrinogen levels (Famodu and Reid, 1987 and Famodu et al., 1990). Interestingly, increased fibrinogen concentrations were not observed among the women on OCP. Clearly, an unexplained interaction between OCP and the S-gene must be exerting an inhibitory influence on the synthesis of fibrinogen, and possibly on other clotting factors. The observed lack of increased fibrinogen levels among the HbAS OCP users could possibly provide some protection against thromboembolism.

It is equally striking that the depressed fibrinolytic activity observed in the group using OCP was probably a consequence of OCP usage alone, and was not influenced by the S-gene. In the light of this finding, women with the HbAA genotype who are on OCP may be more prone to vascular and circulatory disorders than women with the HbAS genotype. This hypothesis is derived from the observed increased fibrinogen levels, coupled with the decreased fibrinolytic activities as assessed by the euglobulin lysis time, in the HbAA genotype OCP users. However, further studies in Africa and in other areas of the world with varying haemoglobinopathies, among users of various types of OCP as a birth control method, are needed to confirm whether such levels of fibrinogen and of impaired fibrinolytic activities really have clinical significance and constitute a risk factor for thromboembolism.

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References