Steroidal contraceptives and changes in individual plasma phospholipids: possible role in thrombosis

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Abstract

The changes in the levels of individual phospholipids were studied in women during prolonged use of three types of steroidal contraceptive preparation: high-dose combined pills (Noriday 1 + 50 Fe); low-dose combined pills (Nominest Fe) and progestin-only injectables (Depo-Provera). Women on high-dose combined pills had significantly higher (p < 0.05) mean lysophosphatidylcholine (LPC), sphingomyelin (SPH), phosphatidylserine (PS) and phosphatidylethanolamine (PE) levels, respectively, than the women on low-dose combined pills, progestin-only injectables and the controls, respectively. Women on low-dose combined pills had significantly lower (p < 0.01) mean LPC and PS levels, respectively, than the controls, while women on progestin-only injectables had significantly lower (p < 0.01) mean PS and PE levels, respectively, than the controls. Based on the reported high activities of PS and PE in hemostasis, the PE/total plasma phospholipids, PS/total plasma phospholipids and the sum of PE and PS/total plasma phospholipids ratios were calculated to assess the possible overall effect of the changes in plasma phospholipids in steroidal contraceptive users. The results obtained using these indices agree with some earlier reports of an estrogen dose-dependent risk/incidence of thrombosis in steroidal contraceptive users. It is concluded that the observed dose-dependent estrogen-induced alterations in phospholipids, and, most especially, the PE and PS fractions may bear a relationship with thrombotic conditions.

Introduction

The use of steroidal contraceptives is one of the commonest methods of preventing unwanted pregnancies in Nigeria today. Yet epidemiological studies in steroidal contraceptive users have shown significant changes in some biochemical parameters [1], increased risk of cardiovascular disease [2–5] and thromboembolic disease [6–9].
The hemostatic system involves the blood vessels, platelets, blood coagulation and fibrinolytic system. Abnormalities have been reported in one or more of these basic components in women who take steroidal contraceptives [10].

Phospholipids are essential cofactors in the blood coagulation cascade; most of the steps of the clotting system require the formation of a complex composed of phospholipid surfaces onto which calcium binds and activate the clotting factors [10–13]. Phospholipids are also the active component of platelet factor 3, which becomes available to the coagulation enzymes and cofactors of the plasma following platelet aggregation or trauma [14].

Phosphatidylethanolamine and phosphatidylserine are the specific phospholipids that have been shown to be active in most of the hemostatic reactions [15–19]. For example, pure phosphatidylserine has been shown to mimic platelet coagulant activity in coagulation tests in vitro [20–23]. Some of the other phospholipids are not as active because they probably bind the coagulation factors in an inactive complex formed without the participation of calcium [23–25].

This study was aimed at assessing the changes in the individual phospholipids in Nigerian women who have used one of three different types of steroidal contraceptive products for at least twelve months.

Subjects and methods

One hundred and two (102) randomly selected healthy Nigerian women aged between 22–40 years who were receiving steroidal contraceptives at Ile-Ife clinics of the family planning project center volunteered for this study. They had used a type of steroidal contraceptive for at least twelve months prior to the time of the study. They were divided into three groups on the basis of the type of steroidal contraceptive they were using:

Group 1: This consisted of thirty-six (36) women on high-dose combined pills (Noriday\textsuperscript{R} 1 + 50 Fe, Syntex Laboratories Inc., USA). Each cycle contained 21 tablets of 0.05 mg mestranol and 1.0 mg norethindrone per tablet, and 7 placebos containing 75 mg ferrous fumarate a tablet.

Group 2: This consisted of thirty-two (32) women on low-dose combined pills (Nomine\textsuperscript{R} g Fe, Syntex Laboratories Inc., USA). Each cycle contained 21 tablets of 0.035 mg ethinylestradiol and 0.5 mg norethindrone per tablet, and 7 placebos containing 75 mg ferrous fumarate a tablet.

Group 3: This consisted of thirty-four (34) women on progestin-only injectables (Depo-Provera\textsuperscript{R}, Upjohn Co., Belgium). Each ampoule contained 150 mg medroxyprogesterone acetate which is administered intramuscularly once in three months as a depot injection.