Short–term effect of Oral Contraceptive Pills on some Haemostatic parameters in Healthy Nigerian Women.

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The objective of this study was to determine the effect of low–dose combined oral contraceptive pill, Lo–femenal, on the following haemostatic parameters: platelet count (PC), prothrombin time (PT), activated partial thromboplastin time (APTT), thrombin time (TT) and fibrinogen, of apparently healthy Nigerian women over a period of three months. A total of sixty–seven women were recruited for the study consisting of forty–seven subjects and twenty age–matched controls, who were aged between 17 and 37 years. All haemostatic parameters were determined using standard haematological techniques described by Dacie and Lewis, before, and three months after continuous use of oral contraceptive pills in the subjects. The same parameters were determined three months apart in control subjects who were on oral contraceptive pills. Statistical analysis of data was done using the chi–squared test and statistical significance was based on p value <0.05. The mean values of platelet count and fibrinogen were significantly increased (p=0.0000 and 0.0003 respectively), while the PT and TT reduced significantly (p=0.007 and 0.0000 respectively) after three months of contraceptive use. There was no significant difference in the value of APTT (p=0.17) before and after oral contraceptive use. No differences were observed in the values in the controls. The findings in this study indicate some degree of pro–coagulant activity in the subjects, and the need to properly assess and monitor haemostatic parameters in pills users before commencement and while on them

KEY WORDS: oral contraceptive pills, haemostasis

In many third world countries, rapid population growth and its attendant consequences have necessitated continuous search for suitable birth control methods. With a failure rate of about 0.34 pregnancies per 100–woman years[1], oral contraceptives had been reported to be the most effective form of birth control presently available. This failure rate is the lowest when compared with other forms of contraceptive methods.

In addition, oral contraceptives have been reported to have beneficial effects in reducing the incidence of pelvic inflammatory disease[2,3], benign breast lesions[4], ovarian and endometrial cancer[5,6] and rheumatoid arthritis[7] among the pill users. Despite the general acceptability, and the obvious advantages that have been attributed to oral contraceptive use, some serious side effects have been reported in women taking the pill.

Epidemiologic studies have indicated a relationship between oral contraceptive use and cardiovascular phenomenom[8,9,10]. These associations have been identified and extensively documented among Caucasian subjects.

Furthermore, the possible danger of intravascular coagulation resulting from the use of oral contraceptive pill had been extensively studied among the Caucasian women by laboratory measurements of coagulation and platelet changes in women taking the combined oestrogen–progestogen oral contraceptive pill[11,12]. Oral contraceptives have been reported to shorten the prothrombin time[12,13], the partial thromboplastin time and the thromboplastin generation test[14]. Increased levels of factors VII, VIII, IX, X and fibrinogen have also been reported[12,15,16].

Platelet adhesiveness and aggregation are said to be increased[17] whereas antithrombin III levels and fibrinolysis are reduced in women taking oral contraceptives[12,14,18]. Jack *et al* (1988) reported a reduction in antithrombin III levels and prolonged euglobulin lysis time in their study of women

on oral contraceptive pills in Lagos, Nigeria.

Closely linked with these changes in the coagulation profile and platelet behavior are the risks of thromboembolism, myocardial infarction and other cardiovascular diseases which have been reported to be higher in young women on oral contraceptive pills compared to non-users[18,20,21,22,23].

However, the use of oral contraceptives is still being strongly undertaken and promoted in our environment where there is paucity of studies on their effects on the coagulation profiles.

We have therefore, in this study examined the effects of a low dose combined oral contraceptive (OC) pill on some basic coagulation parameters of apparently healthy Nigerian women over a three month period. It is hoped that the result will throw some light on the need or otherwise of monitoring coagulation system in women taking these pills.

Subjects, Materials and Methods

Forty seven apparently healthy women who were aged between 17 – 37years, and who were reporting for the first time for the purpose of oral contraceptive, were recruited from 3 different family planning clinics within the Ilorin metropolis. After informed consents had been obtained from them, a detailed history was taken from each of them with emphasis on medical, gynaecological and haematological aspects.

Each subject was then physically examined, and sequel to the above, only subjects without a history or signs and symptoms suggestive of thromboembolic disease, other cardiovascular diseases, diabetes mellitus or any chronic condition in which oral contraceptives were contraindicated were included in the study. None of the subjects had been pregnant in the last six months preceding their inclusion in the study, or on any other form of drug therapy or steroid use.

Twenty age-matched women, who were selected from amongst medical students and student nurses served as controls. Exclusion criteria were the same as for the study group and none of them had used OC pill or any steroidal preparation previously. Informed consents were also obtained from the control group. All the subjects had their blood samples taken, after an overnight fast (between 8 – 10am) before commencement of oral contraceptive therapy i.e. just before the start of their next menstruation, and thereafter at three months on the pill. The combined oral contraceptive pill used in this study was LO-FEMENAL (product of WYETH-AYERST CANADA INC. Montreal, Canada).

The control group also had their blood samples taken three months apart but without oral contraceptive therapy. About 7ml of blood was collected from both the subjects and controls and distributed as follows: 4.5ml of blood into a clean tube containing 0.5ml of 3.8% trisodium citrate. The sample was mixed thoroughly and spun at 2000g for 10 minutes at 25°C and the plasma separated into another clean tube and immediately placed in a jar containing ice cubes until it was used for the coagulation tests (within 2 hours).

The remaining 2.5ml of blood was placed in a tube containing ethylene diamine tetra acetic acid (EDTA) as anticoagulant. The sample was thoroughly mixed and used for the platelet counts. The samples that were taken from both groups were three months apart and were treated as described above.

The platelet count was estimated manually by the method of Brecher and Cronkite[24]. Prothrombin time (PT). Activated partial thromboplastin time (APTT) and thrombin time (TT) were estimated using commercially prepared kits (obtained from Diagnostic Reagents Ltd., Thame, Oxon England) and were based on methods described by Dacie and Lewis[25]. Fibrinogen estimation was carried out by the dry clot weight method of Ingram[26].

Each of the procedures above was carried out on the test and control plasma in duplicate at the same time, and the results were expressed as the mean of the paired values for the test and control. The results were analysed by generating mean and frequency distribution for the different variables which were then displayed in tables. Comparisons of the variables were done using the chi square test and statistical significance of data was based on p-value <0.05.

Results

A total of sixty-seven women, made up of forty-seven subjects and twenty controls, were studied. Their ages ranged between 17 and 37years with a mean age of 26.9 $\pm$ 4.8years. Forty-five (95.7%) of the women in the study group, representing a majority, were in their third and fourth decades of life. Clinical evaluation of subjects just before OC pill treatment and after the three months of OC use did not reveal any significant changes in terms of menstrual flow, body weight and blood pressure.

The means of platelet counts, PT, APTT, TT and fibrinogen in the subjects before commencement of OC pill were 143.6 $\pm$ 15.9 x 10^9/L, 12.2 $\pm$ 10 seconds, 33.2 $\pm$ 9.4 seconds, 15.7 $\pm$ 2.9 seconds and 1.8 $\pm$ 0.5g/L respectively. In the control group, the means of platelet counts, PT, APTT, TT and fibrinogen at the beginning of the study were 149.6 $\pm$ 22.2 x 109/L, 12.5 $\pm$ 1.0 seconds, 30.4 $\pm$ 6.9 seconds, 1.8 $\pm$ 0.4g/L respectively. There was no significant difference between the mean values of coagulation parameters in the subjects and the controls at the commencement of the study (Table i).

The means values of coagulation parameters in the subjects after 3 months of OC use were platelet count (179.8 $\pm$ 29.6 x 10^9/L), PT (11.7 $\pm$ 0.8 seconds), APTT (31.2 $\pm$ 3.2 seconds), TT (12.1 $\pm$ 2.2 seconds) and fibrinogen (2.1 $\pm$ 0.3g/L). In the controls without oral contraceptive use, the means of platelet count, PT, APTT, TT and fibrinogen were 163.3 $\pm$ 21.8 x 10^9/L, 12.3 $\pm$ 0.5seconds, 32.1 $\pm$ 3.2

***Table i*: Baseline coagulation parameters of subjects and controls before study.**

Parameter	Subject (n=47) Mean (±SD)	Control (n=20) Mean (±SD)	p–value	Remark
Platelet Count (x 10^9/L	143.6±15.9	149.6±22.2	0.22	NS
PT (seconds)	12.2±1.0	12.5±1.0	0.23	NS
APTT (seconds)	33.3±9.4	30.4±6.9	0.23	NS
TT (seconds)	15.7±2.9	16.9±1.7	0.16	NS
Fibrinogen (g/L)	1.8±0.5	1.8±0.4	0.95	NS

*NS = Not Significant.

seconds, 15.8 ± 3.7 seconds and 1.8 ± 0.4g1L respectively after the 3 months period.

There was no significant difference noticed in the control groups between the beginning and after the 3 months period (Table ii). However, there were statistically significant differences observed in the means of platelet count, thrombin time and fibrinogen levels of subjects compared with the controls after the 3 months period of study (Table iii). Also, statistically significant differences were observed in the means of platelet count, PT, TT and fibrinogen levels of the subjects before and after the 3 months of oral contraceptive pill therapy (Table iv).

***Table iii*: Baseline coagulation parameters of subjects and controls after 3 months of study.**

Parameter	Subject (n=47) Mean (±SD)	Control (n=20) Mean (±SD)	p–value	Remark
Platelet Count (x 10^9/L	179.8±29.6	163.6±21.8	0.03	S
PT (seconds)	11.7±0.8	12.3±0.5	0.07	NS
APTT (seconds)	31.2±3.2	32.1±3.2	0.30	NS
TT (seconds)	12.1±2.2	15.8±3.7	0.04	S
Fibrinogen (g/L)	2.1±0.3	1.8±0.4	0.01	S

*NS = Not Significant.

***Table ii*: Comparison of coagulation parameters in controls before and after 3 months.**

Parameter	Baseline Mean ± SD	Mean ± SD after 3 months of study	p–value	Remark
Platelet Count (x 10^9/L	149.6±22.2	163.3±21.8	0.55	NS
PT (seconds)	12.5±1.0	12.3±0.5	0.38	NS
APTT (seconds)	30.3±6.9	32.1±3.2	0.33	NS
TT (seconds)	16.9±1.7	15.8±3.7	0.28	NS
Fibrinogen (g/L)	1.8±0.4	1.8±0.4	0.93	NS

*NS = Not Significant.

***Table iv*: Comparison of coagulation parameters of subjects before and after 3 months of oral contraceptive pill (OCP)**

Parameter	Baseline Mean ± SD before OCP	Mean ± SD after 3 months of study of OCP	p–value	Remark
Platelet Count (x 10^9/L	143.6±15.9	179.8±29.6	0.000	S
PT (seconds)	12.2±1.0	11.7±0.8	0.007	S
APTT (seconds)	33.2±9.4	31.2±3.2	0.17	NS
TT (seconds)	15.7±2.9	12.1±2.2	0.000	S
Fibrinogen (g/L)	1.8±0.5	2.1±0.3	0.0003	S

*NS = Not Significant.

Discussion

The need to limit family size has been recognised in the developed and the developing societies of the world since the ancient times. In spite of the various side effects, and the more serious complications that have been associated with the use of combined OC pill, Oestrogen–progestogen combined pill is still regarded as a safe and highly effective method of contraception[27,28].

The Oestrogen component of the combined OC pill has been implicated as being responsible for most of the adverse effects attributed to the combined pill[28,29]. In recent times, however, combined OC pills with low oestrogen content are being recommended to minimise the side effects. The combined OC pill that was used in this study contains 30mg ethinyloestradiol, thereby complying with the recommended oestrogen dose of

between 0.02–0.5μg[28].

Throughout the study period, none of the subjects developed any clinical side effects that could warrant discontinuation of treatment except for a patient who became pregnant after the first cycle on the pill, and had to be excluded. That little or no side effect was observed among the subjects during the period of treatment with OC pill may be due to the low content of oestrogen in the pill. Similar observation had been made in Nigeria and elsewhere: Marvelon Van Dierendonk *et al*[30] in a multicentre clinical trial carried out in Nigeria with a low dose combined OC pill reported no significant side effects in their patients.

The women in this study were all treated with the same type of OC pill so as to remove any variation that may arise from using different preparations, as well as individual genetic differences, which may produce different outcomes in the subjects. Laboratory methods have been extensively employed in studying the effects on coagulation, fibrinolysis, and platelets by oral contraceptives among users[11,12,13,18]. In the present study, dynamic tests of the extrinsic and intrinsic coagulation pathways i.e. prothrombin time (PT), activated partial thromboplastin time (APTT) and thrombin time (TT), as well as platelet counts and fibrinogen estimation were carried out in order to determine the effects of OC pill on these parameters.

The mean PT and TT of the subjects were both significantly shortened after OC pill use when compared with their baseline values. The mean APTT however did not show any significant change from the baseline mean values after OC pill use The above findings agree with some previous reports where similar shortening of the PT and TT were observed[15,18], but at variance with those reports which showed significant shortening of the APTT.

Exogenous oestrogens in the pill have been shown to accumulate in the liver and stimulate the synthesis of the clotting factors, more especially factors II, VI and X[18,31]. The significant shortening of the PT observed in this study is possibly an indication of some degree of enhanced coagulation process in the subjects which may have resulted from increased plasma levels of coagulation factors of the extrinsic pathways as a result of increased synthesis from the liver.

Jack *et al*[19] in Lagos, in their study of forty Nigerian women taking the combined OC pill found their mean platelet count to be slightly higher than for the control group, but the increase was not statistically significant. In this study, significant increase in the mean platelet count of subjects was observed after treatment with OC pill, which supports earlier observation that OC pill has an effect on platelet number[15,19]. The noted increase in the mean platelet count of subjects with OC use may be a reflection of an acute phase response that could follow minimal vascular tissue damage secondary to oestrogen use[32].

This study also demonstrated significant increase in the mean fibrinogen level of subjects after OC use. This finding agrees with previous reports both in Caucasians and African women[19,33,34]. The concentration and reaction of fibrinogen in plasma significantly affect thrombin time[35]. Increased plasma levels of fibrinogen may be accompanied by a shortened TT (an observation that was made in this study), and an increased tendency of the blood to clot. Increased plasma levels of fibrinogen, as well as other clotting factors that are synthesised by the liver, and are induceable by exogenous oestrogen may create a hypercoagulable state in the subjects.

This may increase the risk of thrombosis in them, more so in the presence of additional risk factors such as trauma, infections, surgery, prolonged inactivity and smoking. The hypercoagulability that is seen during treatment with oral contraceptives is said to be similar to that observed during pregnancy[19,32]. However, the incidence of thromboembolism changes in blood coagulation that is seen during treatment with OP pill are of significance with regard to the occurrence of thromboembolism. The risk of thrombosis following oral contraceptive use has been reported to be low but must always be borne in mind[28,32].

In the present study, significant changes in the coagulation profile of subjects have been demonstrated, even with a low dose OC pill, that are capable of promoting thrombosis in them if additional predisposing risk factors were present. Though, none of the subject developed thrombosis clinically, the laboratory findings indicate that Nigerian women using combined OC pill are equally predisposed to thrombotic risks just like their Caucasian and other African counterparts. It is believed that the complication rate with combined oestrogen–progestogen preparations can be reduced to the barest minimum if all "pill" prescribers carefully screen and follow up every user no matter how healthy she may appear to be. Adherence to absolute contraindications, thoughtful weighing of the risk/benefit ratio in the use of OC pills and continuous monitoring of these patients should increase the safety margin and guarantee safe use of this easy and efficient method of birth control

References

1. Namboze J. M: Family Planning In: Principles and Practice of Community Health in Africa. Ed. Shofoluwe G. O., Benneth F. J. University Press Ltd., Ibadan; pp 253– 266.
2. Vessey M. P.: Epidemiology of endometritis in women attending family planning clinics *BMJ* 1993; **306**: 585–590.
3. Pollard I: A guide to reproduction: Social issues and human concerns, 1st edition. London, Cambridge University Press 1994; 274–306.
4. Vessey M. P., Doll R, Sutton P. M: Investigation of the possible relationship between oral contraceptives and benign and malignant breast disease. *Cancer*, 1971; **28**: 1395–1398.
5. Vessey M, Metcalfe A. Wells C: Ovarian neoplasms, functional ovarian cysts and oral conctraceptives. *BMJ* 1987; **294**: 1518.

6. Vessey M. P.: Endometrial and ovarian cancer and oral contraceptives: findings in a large cohort study. *Br. J. Cancer* 1995; **71**: 1340–1342.
7. Royal College of General Practitioners' Oral contraceptive study: Reduction in the incidence of rheumatoid arthritis associated with oral contraceptives. *Lancet* 1978; **1**:569–571.
8. Goldzieher J. W.: An assessment of the hazards and metabolic alterations attributed to oral contraceptives. *Contraception* 1970; **1**: 409–445.
9. Epstein S. E., Rosing D. R., Brackman P, Redwood D. R., Astrup T: Impaired fibrinolytic responses to exercise in patients with Type IV hyperliproteinaemia. *Lancet* 1970; **2**: 631–633.
10. Poller L, Thomson J. M., Thomas P. W. Effects of progestogen oral contraception with Norethisterone on blood cloting and platelets *BMJ* 1972; **4**: 391 – 393.
11. Doll R: The long term effects of oral contraceptives. *J. Biosoc Sci* 1970; **2**: 367–389.
12. Ygge J: Variation in the individual subject of some parameters in blood coagulation and fibrinolysis. A longitudinal study in young healthy women. *Scand J Haematol* 1969; **6**: 343–347.
13. Poller L, Tabiowo A, Thomson J. M: Effects of low dose oral contraceptives on blood coagulation. *BMJ* 1968; **3**: 218–219.
14. Hidden M, Amris C. J., Starup J: the haemostatic mechisms in oral contraception. *Acta Obstet. Gynaecol. Scand.* 1967; **46**: 562–571.
15. Thomoson J. M., Poller L: Clotting factors during oral contraception – further report. *BMJ* 1966; **2**: 23–25.
16. Eckst ein P, Whitby M, Fotherby K, Butler C: Clinical and laboratory findinggs in a trial of Norgestrel, a low dose progestogen – only contraceptive. *BMJ* 1972; **3**: 195–200.
17. Poller L, Priest C. M, Thomson J. M: Platelet aggregation during oral contraception. *BMJ* 1969; **4**: 273–274.
18. Poller L, Thomson J. M, Thomas W: Oestogen–Progestogen oral contraception and blood clotting a long time follow -up. *BMJ* 1971; **4**: 648 – 650.
19. Jack M. A., Akinsete I, Onitiri A. C.: Effects of oral contraceptives on serum lipoproteins, coagulation and fibrinolysis in Nigerian women. *Nig. Med. Pract.* 1988; 15: 14–18.
20. Mann J. L., Vessey M. P., Thorogood M, Doll R: Myocardial infarction in young women with special reference to oral contraceptive practice. *BMJ* 1976; **2**: 241 – 245.
21. Goldzieher J. W., Dozier T. S.: Oral contraceptives and thromboembolism – a ressessment. *Am. J. Obstet. Gynaecol.* 1975; **123**: 878–880.
22. Inman W. H. W., Vessey M. P., Westerholm B, Engelund A: Thromboembolic disease and the steriod content of oral contraceptives. A report to the committee on safety of drugs. *BMJ* 1970; **2** 203–209.
23. Beral V, Kay C. R.: Mortality among oral contraceptive users. Lancet 1977; **2**: 727–731.
24. Brecher G, Cronkite E. P.: Morphology and enumeration of human blood platelets. *J. Applied physiol* 1950; **3**: 365–357.
25. Dacie J. V., Lewis S. M: Practical Haematology, 7th Edition, London. Churchill Livingstone, 1991; 55–92.
26. Ingram G. I. C: The determination of plasma fibrinogen by the clot weight method. *Biochemical Journal* 1952; **51**: 583–588.
27. Centres for Disease control and prevention (CDC): Family planning methods and practice: Africa 2nd edition, Atlanta Georgia, Division of Reproductive Health, 2000 pp 295–337.
28. Grimes D. A: The safety of oral contraceptives: Epidemiologic insights from the first 30 years *Am. J. Obstet Gynaecol* 1992; **166**: 1950–1954.
29. Wharton C, Blackburn R: Lower dose pills: - Popul Rep 1989; series A: 1–31.
30. Marvelon Van Dierendonk B, et al: A multicentre clinical trial in Nigeria with a low dose oral contraceptive *Adv Contracept* 1933; **9**: 25–32.
31. Notelowitz M; Sare M: Coagulation risks with post menopausal Oestrogen threrapy: In: Progress in Obstetrics and Gynaecology Vol. 2 J. Studd (ed), Edinburgh, Churchill Livingstone, 1982; 228–240.
32. Wessler S, Gitel S. N, Wan L. S: Oestrogen – containing oral contraceptive agents. A basis for their thrombogenicity. *JAMA* 1976; **231**: 2179–2181.
33. Famodu A. A: effects of oral contraceptive on fibrinogen levels in African women. *Haematologia* 1991; **24**: 135–138.
34. Lee A. J: Plasma fibrinogen in women: relationship with oral contraception, the menospause and hormone replacement therapy. *Br. J. Haematol* 1993; **83**: 616–621.
35. Sknonsberg O. H: Increase thrombin generation during collection of blood from women taking oral contraceptices *Thromb Haemostat* 1987; **58**: 403–407.