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Some Haematological parameters of Female Students on Oral Contraceptives. A Case Study in University of Calabar, Calabar, Cross River State, Nigeria.

Okafor Ifeyinwa Maryann* [1], Etura Joyce Ezekiel[1] and Ogar, Agnes Oka [1]
Department of Haematology and Blood Transfusion Science, Faculty of Medical Laboratory Science, University of Calabar, P.O Box 1115, Calabar, Nigeria.
Author for correspondence*: +234-808-068-0620/okaforify@unical.edu.ng
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Abstract
The rapid growth in the use of hormonal contraceptives gives grounds for assessing their influence on various biochemical parameters of the human system since its safety has become arguable and in doubt. This study investigated the effects of oral contraceptives on some haematological parameters among female students in University of Calabar, Nigeria. A simple randomized study approach was used to recruit 100 healthy women; of which 50 were oral contraceptive users as subjects and 50 non-contraceptives users as controls. A well-constructed questionnaire was developed to gather data on socio-demography, knowledge and frequency of use of contraceptives by female students in UNICAL Hostels. Blood samples were collected for blood count analyses using an automated haematology analyzer. Data was analyzed using SPSS (V.20.0). Data was expressed in means (Mean ± SD) for the different variables. T-test of association statistic was used to compare the mean scores of the subjects and the controls. P-value < 0.05 was considered statistically significant. The study observed mean of WBC (P = 0.100) to be statistically insignificant while red blood cell (RBC) and platelet count were significantly higher among oral contraceptive users compared to non-users (P = 0.001) and (P = 0.007) respectively. Conclusively, this study has shown that the effects of oral contraceptives on users are both ways; some decrease (WBC) while others increase (RBC and PLT). Despite resulting in increase or decrease, in the haematological parameters, the alterations in this study were all within the reference ranges of haematological parameters.

Keywords: Haematological parameters, Oral contraceptives, Hormonal Contraceptives, Biochemical Parameters, Influence, Knowledge

Introduction

Contraceptives were first introduced in the 1960s; the birth control pill has been a popular and extremely effective form of contraception (Akinloye, 2011). The pill is easy to use and, when taken correctly, it is 95% to 99.9% successful at preventing pregnancy. Contraceptives are hormonal agents. Oral contraceptives (OCs) contain both estrogen and progestogen. Endogenous estrogens are largely responsible for the development and maintenance of female reproductive system and secondary sexual characteristics. Estrogens act through binding to nuclear receptors in estrogen responsive tissues. Circulating estrogens modulate the pituitary secretion of the gonadotropins, luteinizing hormone (LH) and follicle stimulating hormone (FSH), through a negative feedback mechanism (Palmary, 2013; Okafor *et al.,* 2013). Modern progestogens such as gemstone have been developed in order to provide women with an oral contraceptive agent with more selective pregestational activity that improves cycle control, minimizes metabolic changes and adverse events and effectively prevents pregnancy (Okafor *et al.,* 2018; Brito *et al.,* 2011).

Over the years, there has been growing interest in the safety of oral contraceptives among users. More concern has been about the impact of estrogen and progesterone components of hormonal contraceptives on various biochemical

and physiological processes in the bodies of users (Afrifa, 2013). Available information indicates that oral contraceptives are associated with alterations in some trace elements and vitamins which influence blood production in humans (Akinloye, 2011). Further, some studies have reported various haematological changes associated with the use of oral contraceptives (Akinloye, 2011; Zebut & Han, 2012; Okafor *et al.,* 2013). These changes include high platelet count which increases the risk of thromboembolism, myocardial infarction, arterial disease and carcinogenicity (Afrifa, 2013). These side effects may range from mild to severe but without a doubt may greatly influence the health status of users (Martin & Elliot, 2016). The potential risk these types of contraceptives pose on the health of users raises some degree of health concern. Since the effects of these contraceptives vary from population to population, continual research is very important.

Study area and design: This study was conducted in University of Calabar, Calabar, Cross River State, Nigeria. A simple randomized case- control study design was adopted for this research.

Ethical Consideration/ informed consent
Ethical clearance was obtained from the Research Ethics Committee of the Ministry of Health, Cross River State. All participants recruited for the study were properly intimated on the process and procedure of taking samples, the reason for taking the samples and assured of confidentiality. Nevertheless, participation was voluntary as well as responded to administered questionnaires.

Study Subjects: A total of one hundred (100) female students of the University of Calabar aged 16- 35 years were enrolled in this study. Those who gave consent and volunteered to participate were included while those who did not consent were excluded.

Sample Analysis
With the aid of syringe and needle, three milliliters (3mls) of venous blood were taken from each participant into well labeled tri-potassium ethylene diamine tetra-acetic acid (K_3EDTA) tubes according to standard protocol (Turgeon, 2012).

Haematological Test
The following haematological parameters were done; Full blood count (red blood cells, haemoglobin, haematocrit, mean cell volume, mean cell haemoglobin concentration, mean cell haemoglobin, red cell distribution width, platelet count, white blood cell, lymphocytes, monocytes, neutrophils, eosinophils and basophils) using automated haematology analyzer (Mythic 22 Auto Haematology Analyzer). The mythic 22 auto haematology analyzer is a five-parts differentiation machine that relies on impedance technology. This involves cells in suspension passing through a tiny aperture across which an electrical current is applied. The size of the aperture differs for red blood cells, white blood cells and platelets. Each cell that passes through the aperture alters the electrical impedance. The change in electrical impedance is proportional to the cell volume which results in a cell count. A nucleating agent is added which shrinks lymphocytes more than other white blood cells, thus making it possible to differentiate lymphocytes by volume. The accuracy of the impedance technology is further improved by the principle of hydrodynamic focusing. This ensures that cells pass through the aperture in a single file, thereby eliminating false size estimates.

Results
Socio-demography and Knowledge of Female Students on Oral Contraceptives and Controls
Table 1 and 2 shows the socio-demographic data and knowledge of females in UNICAL female hostels about oral contraceptives collected from the administered questionnaire. Majority of the controls and subjects were between the age of 21 – 25 years (Control; 70%, subjects; 68%) while the other age brackets were distributed as follows 16 – 20 years (controls 14%; Subjects 16%), 26 – 30 years (controls 6%; subjects 2%) and 31 – 35 years (controls 10%; subjects 6%). The marital status of the respondents showed that 80% and 70% were single for subjects and controls respectively, while 20% and 30% were married for both subjects and controls respectively. This table also showed that all the respondents were

fully aware of what contraception and contraceptives are. Table 2 shows that none of the controls had ever used oral contraceptives, while 100% of the subjects were users of oral contraceptives. 76% of the female students on oral contraceptives, had used POPs while the remaining 24% had used COCs. Majority of the subjects used contraceptives monthly (84%), few use them quarterly (16%) while no subject used daily or weekly. Furthermore, in some of the subjects; 72% and 28% had taken OCs within the last 1 – 3 months and 4 – 6 months respectively.

Furthermore, the results in Table 2 indicate that a higher (82%) population of the subjects had no observable changes, whereas few of the subjects (16%) affirmed observable changes. From those who accepted to have had observable changes; Majority (10%) of the subjects who agreed to observable changes had delayed menstrual flow and (6%) had changes in menstrual cycle. The table shows that the entire subjects and controls (100%) were not patients of any form of haematological disorders nor pregnant or having their monthly flow as at the time this survey was conducted.

Furthermore, from table 2; few (16%) of the subjects accepted to have observable changes as a result of the use of oral contraceptives. Six percent (6%) of them said there experienced alteration in menstrual cycle, while the remaining ten percent (10%) had delayed flow. None of the subjects agreed to any haematological disorder.

Table 3: Shows WBC of female students on oral contraceptives. The table shows that Mono (P = 0.001) is significantly reduced in the subjects when compared to the controls. WBC (P = 0.100), Neut (P = 0.078) and Eosin (P = 0.272) are less in the subjects when compared to the controls although not statistically significant. The difference in Lymph (P = 0.561) was not significant. Baso (P = 0.934) is statistically indifferent among the subjects and controls.

Table 4 shows that RBC (P = 0.001), HGB (P = 0.006), HCT (P = 0.034), MCV (P = 0.001), MCH (P = 0.001), RDW-CV (P = 0.001), and RDW-SD (P = 0.001) are significantly increased in subjects as compared to controls, while MCHC (P = 0.210) is statistically insignificant for both subjects and controls.

Table 5 shows that platelet count (P = 0.007) of female students on oral contraceptives are significantly increased as compared to controls, while MPV (P = 0.063), PDW (P = 0.846) and PCT (P = 0.089) of subjects shows no significant difference when compared to the controls,

Table 1: Socio-demographic Characteristics of Female Students on Oral Contraceptives and Controls (N = 100)

Items	Controls		Subjects	
	Frequency	Percentage (%)	Frequency	Percentage (%)
Age				
16 – 20	7	14	8	16
21 – 25	35	70	34	68
26 – 30	3	6	1	2
31 – 35	5	10	3	6
Total	**50**	**100**	**50**	**100**
Marital Status				
Single	35	70	40	80
Married	15	30	10	20
Total	**50**	**100**	**50**	**100**
Any notable Haematological Disorder?				
Yes	-		-	-
No	50	100	50	100
Total	**50**	**100**	**50**	**100**
Are You menstruating presently?				
Yes	-	-	-	-
No	50	100	50	100
Total	**50**	**100**	**50**	**100**
Are you pregnant?				
Yes	-	-	-	-
No	50	100	50	100
Total	**50**	**100**	**50**	**100**

Table 2: Knowledge of Females in Unical Female Hostels about Oral Contraceptives (N = 100)

Items	Controls		Subjects	
	Frequency	Percentage (%)	Frequency	Percentage (%)
Do you know about contraceptives?				
Yes	50	100	50	100
No	-	-	-	-
Total	**50**	**100**	**50**	**100**
Do you use oral contraceptives?				
Yes	-	-	50	100
No	50	100	-	-
Total	**50**	**100**	**50**	**100**
type of Oral contraceptives used?				
POPS	-	-	38	76
COCs	-	-	12	24
Total	**-**	**-**	**50**	**100**
Frequency of OC used?				
Daily	-	-	-	
Weekly	-	-	-	
Monthly	-	-	42	84
Quarterly	-	-	8	16
Total	**-**	**-**	**50**	**100**
last time you used contraceptives?				
1 – 3 months	-	-	36	72
4 – 6 months	-	-	14	28
7 – 9 months	-	-	-	-
10 – 12 months	-	-	-	
Total	**-**	**-**	**50**	**100**
Any observable Changes?				
Yes			8	16
No	50	100	42	84
Total	**50**	**100**	**50**	**100**
If Any Observable Changes, What kind?				
Change in Menstrual Cycle.			3	6
Delayed flow			5	10
Others			-	-
Total			**8**	**16**

Table 3: White Blood Cell Parameters of Female Students on Oral Contraceptives and Controls

Parameters	Controls	Subjects	*P*-value
WBC ($\times 10^9$/L)	5.77 ± 1.26	5.31 ± 1.67	0.100
Lymph ($\times 10^9$/L)	2.86 ± 0.70	2.94 ± 0.78	0.561
Mono ($\times 10^9$/L)	0.27 ± 0.11	0.18 ± 0.08	0.001
Baso ($\times 10^9$/L)	0.09 ± 0.07	0.09 ± 0.06	0.934
Eosin ($\times 10^9$/L)	0.11 ± 0.07	0.09 ± 0.07	0.272
Neut ($\times 10^9$/L)	2.38 ± 0.85	2.02 ± 1.04	0.078

Table 4: Red Blood Cell Parameters of Female Students on Oral Contraceptives and Controls

Parameters	Controls	Subjects	*P*-value
RBC ($\times 10^{12}$/L)	4.57 ± 0.46	4.97 ± 0.32	0.001
HGB g/dL	12.42 ± 0.87	14.93 ± 1.02	0.006
HCT (%)	38.87 ± 3.27	39.51 ± 2.89	0.034
MCV (fL)	84.11 ± 3.08	75.57 ± 5.47	0.001
MCH (pg)	27. 07 ± 1.42	23.93 ± 2.26	0.001
MCHC (g/dL)	32.13 ± 0.77	31.62 ± 1.27	0.210
RDW-CV (%)	14.74 ± 0.99	16.23 ± 1.66	0.001
RDW-SD (fL)	45.18 ± 3.20	48.33 ± 2.52	0.001

Table 5: Platelet Count of Female Students on Oral Contraceptives and Controls

Parameters	Controls	Subjects	*P*-value
PLT ($\times 10^9$/L)	332.82 ± 65.11	366.52 ± 74.23	0.007
MPV (fL)	8.09 ± 0.60	8.33 ± 0.48	0.063
PDW (%)	14.98 ± 0.53	14.96 ± 0.51	0.846
PCT (%)	0.28 ± 0.07	0.30 ± 0.49	0.089

Discussion

The study of the effects of oral contraceptives on users is very vital in the prescription and recommendations of methods for birth control and family planning. The use of contraceptives have effects on various biochemical and physiological processes in the bodies of users resulting in high risks of liver diseases, kidney diseases, cerebrovascular diseases and cervical diseases (Coffee *et. al.,* 2020). These effects may be linked to alterations in some hormones, elements and vitamins, which influence blood production in human, (Kelada *et al.,* 2012 and Kaabulat & Uzunlar, 2012). Some scientists reported haematological changes associated with OC use, these changes include high platelet count which increases the risk of thromboembolism, myocardial infarction, arterial disease and carcinogenicity (Adamssons *et al.,* 2014, Enawgaw *et al.,* 2017).

WBC has been inconsistent (Increase and decrease) with no clear reasons. The results from this research, shows an insignificant decrease in the WBC of the female students who use pills. The cause of this reduction is not clear. Our finding is at variance with a previous report which reported a decrease in the WBCs of users on oral contraceptives (Adamssons *et al.,* 2014). Even scientists that have reported increment of WBCs in users of contraceptives could only manage to explain that when estrogen is elevated, resting peripheral blood monocytes release less interleukin 1β and TNFα properly, resulting in increase in white blood cells (Kelada *et al.,* 2012). However, the inability to explain the decrease in WBC calls for further investigations.

Nevertheless, the results from the comparison of the mean values of the RBC of female students who were subjects and controls showed that there was significant increase in the value of the RBC of the subjects. Generally, the use of oral contraceptives is associated with lighter menstrual periods due to better indicators of iron status (Enawgaw *et al.,* 2017). Poor iron status indicators (low levels of Serum ferritin and HGB) have been linked to menstrual blood loss (Coffie *et al.,* 2020). Also, the endometrium shrinks as a result of progestogenic tablets, endometrial atrophy and their usage results in scanty withdrawal bleeding that is less than in a typical cycle (Coffie *et al.,* 2020). However, some scientists asserted that longevity of use could affect parameters such as MCV, MCH and RDW (Sutterlin, 2013). In a study, Okeke (2011) reported that there was significant increase in MCV and MCH with a significant decrease in RDW for those who had used contraceptives for 3 to 6 years compared to those who had used for only two years and below. This shows that the effects in RDW is duration of use dependent.

Additionally, the study showed a statistically significant increase in platelet of female students on oral contraceptives. However, estrogen, like many lipophilic hormones affects the gene transcription of various proteins, this estrogen increases platelet count. Also, this increase in the number of PLT may be explained by the fact that estrogen administration significantly increases the division and proliferation of the HSCs in women during their reproductive years. For some other scientists (Zia *et al.,* 2015 and Coffie *et al.,* 2020) PLT and MPV among OC users remained stable. However, the lack of substantial alteration may be attributed to the use of smaller sample sizes or the short durations of oral contraceptives usage which may not produce differences in these parameters.

Conclusion

This study has shown that the effects of oral contraceptives on users are both ways; some decrease (WBC) while others increase (RBC and PLT). Despite resulting in increase or decrease, in the haematological parameters, the alterations in this study were all within the reference ranges of haematological parameters. Additionally, the major limitation to the study was that blood films were not prepared to confirm results from the haematological analyzer.

Conflict of interest: None declared.

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