Original Research Article

Elevated red blood cell counts are associated with hormonal contraceptive usage among women in the Cape Coast Metropolis, Ghana

ABSTRACT

Background: The widespread use of hormonal contraceptives gives grounds for assessing their influence on various biochemical parameters of the human system since its safety has become controversial. This study assessed the effects of hormonal contraceptives on haematological parameters among users in the Cape Coast Metropolis.

Methods and Material: A simple randomized case-control study approach was used to recruit 94 healthy women of which 54 were hormonal contraceptive users and 40 healthy age-matched non-contraceptive users served as controls. Venous blood samples were taken for full blood count (FBC) analyses using an automated haematology analyser. Data was analysed using SPSS (V.22.0). Data was expressed in means (Mean ±SD) for the different variables. T-test statistic was used to compare the mean scores of two groups whilst one-way ANOVA was used to compare more than two groups. Pearson correlation was used to determine association between the various parameters. *P*-value <0.05 was considered statistically significant.

Results: The study observed mean red blood cell (RBC) count to be significantly higher among hormonal contraceptive users compared to non-users (*P*= 0.030). Additionally, the duration of contraceptive usage had an influence on the blood cell parameters in various ways, with a significant negative correlation between duration of contraceptive use and red cell distribution width (RDW) (r= -0.303, *P*= 0.026).
Conclusion and Recommendation: Hormonal contraceptives cause significant increase in red blood cell (RBC) count among users. Its effects also depend largely on duration of contraceptive use. Additionally, the main limitation to this study was the fact that blood films were not prepared to actually confirm the results presented by the haematology analyser, hence further study is recommended with the incorporation of blood films to the test panel.

Keywords: Hormonal contraceptives, haematological parameters, full blood count.

1. INTRODUCTION

Hormonal contraceptives are birth control methods that influence the endocrine system. Their purpose is to block ovulation by inhibiting the secretion of follicle stimulating hormone and luteinizing hormone. They also thicken the cervical mucus, making it a barrier to sperm transport, thereby blocking fertilization.[1] Hormonal contraceptives may comprise a combination of estrogen and progesterone or progesterone-only and can as well be administered via different routes (oral, intramuscular, vaginal, transdermal implants and associated with the intra-uterine device).

Over the years, there has been growing interests in the safety of hormonal contraceptives among users. More concern has been about the impact of oestrogen and progesterone components of hormonal contraceptives on various biochemical and physiological processes in the bodies of users.[2] Available information indicates that hormonal contraceptives are associated with alterations in some trace elements and vitamins which influence blood production in humans.[3-7] Further, some studies have reported various haematological changes associated with the use of hormonal contraceptives.[2, 8, 9] These changes include high platelet count which increases the risk of thromboembolism, myocardial infarction, arterial disease and carcinogenicity.[10-17] These side effects may range from mild to severe but without a doubt may greatly influence the health status of users.[18] 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 vital. We examined the effect of hormonal contraceptive use on the haematological profile of females in the Cape Coast metropolis.

SUBJECTS AND METHODS:
STUDY DESIGN/STUDY SITE

This simple randomised case-control study was carried out within Cape Coast Metropolis in the Central Region of Ghana. Participants were recruited from the family planning units of the University of Cape Coast Hospital, Planned Parenthood Association of Ghana (PPAG) Clinic and Cape Coast Metropolitan Hospital, all within the Cape Coast Metropolis. Laboratory analyses of samples were done at the University of Cape Coast Hospital laboratory in Cape Coast. Cape Coast is the administrative capital of **Cape Coast** Metropolitan Assembly. It forms part of the twenty (20) Metropolitan, Municipal and District Assemblies in the Central Region of Ghana. The Cape Coast Metropolis is bounded on the south by the Gulf of Guinea, west by Komenda/ Edina/ Eguafo/ Abrem Municipal assembly, east by the Abura/ Asebu/ Kwamankese District and north by the Twifu/ Hemang/ Lower Denkyira District. The Metropolis covers an area of 122 square kilometres and it is the smallest metropolis in the country [19]

STUDY POPULATION/ ELIGIBILITY CRITERIA

Ninety four (94) non pregnant, non-lactating healthy women within the age range of 16-45 years comprising 54 on hormonal contraceptives (cases) and 40 women not on any hormonal contraceptives (controls) were recruited for the study. The fifty-four (54) women on hormonal contraceptives comprised 36 injectable Depo provera users, 11 Jadelle implant users and 7 combined oral contraceptives pills users. Apparently healthy women with no known haematological conditions were recruited as controls. Particularly, only those who had used hormonal contraceptives for at least six months were included as cases. The following categories of women were excluded; women with any known haematological disorder, menopausal and post-menopausal women, pregnant women, lactating mothers, those menstruating, those who were not within the age range of interest, and women who had used hormonal contraceptives for less than six months.

ETHICAL CONSIDERATION

Ethical clearance was obtained from the Institutional Review Board of the University of Cape Coast (IRB/UCC) concerning this research and approval was sought from the authorities of the various health facilities that were involved in this research. Informed consent was obtained from of all participants by enlightening them on the nature and relevance of the study. They were also informed of their right to participate or not in the study.

BLOOD SAMPLE COLLECTION

With the aid of syringe and needle, three millilitres (3ml) of venous blood was taken from each participant into labelled tri-potassium ethylene diamine tetra-acetic acid (K_3EDTA) tubes according to standard protocol.[20]

HAEMATOLOGICAL TEST

Full blood count (red blood cells, haemoglobin, haematocrit, mean corpuscular volume, mean corpuscular haemoglobin concentration, mean corpuscular haemoglobin, red cell distribution width, platelet count, white blood cell, lymphocytes, monocytes, neutrophils, eosinophils and basophils)

analysis was done on each blood sample using automated haematology analyser according to the principles of operation of the analyser and their respective results were recorded. The haematology analyser used was ABX Pentra 60 (Horiba ABX Diagnostics, France).

DATA ANALYSIS

Data was entered into Microsoft Excel (v. 15.0) and analysed with SPSS (V.22.0). Data was expressed in means (Mean ±SD) and percentages for the different variables. T-test statistic was used to compare the mean scores of two groups whilst one-way ANOVA was used to compare more than two groups. Additionally, Pearson correlation was used to determine association between the various parameters. *P*-value <0.05 was considered statistically significant.

RESULTS

Table 1 shows the general characteristics of participants and compares the haematological parameters of study participants. Additionally, red blood cells (RBC) (*P*=0.030) was particularly higher in hormonal contraceptive (HC) users compared to non-users.

Table 2 compares haematological parameters of the various hormonal contraceptive users (injectable Depo provera, combined oral contraceptive pills and Jadelle implant). The study observed that in spite of fluctuations in the blood parameters among the various users, there was generally no significant difference in haematological parameters among users of the various types of hormonal contraceptives (*P*>0.05).

Table 3 compares haematological parameters of different groups of hormonal contraceptive users based on duration of use. MCV and MCH were higher among women who had used HC for more than 2 years compared to those who had used HC for 2 years or less. The major difference in these parameters (MCV and MCH) were observed between those who had used for 2 years or less and those who had used for 3 to 6 years were statistically significant (*P*=0.031 and *P*=0.033 respectively). RDW was higher among those who had used for 2 years or less compared to those who had used for higher years, with the difference between those had used for 2 years or less and those who had used for 3 to 6 years showing statistical significance (*P*=0.011).

Table 4 compares haematological parameters of hormonal contraceptive users according to their age groups. Monocyte count was significantly higher (*P*=0.013) among contraceptive users at the age of 40 or above as compared to those within the age range of 25 to 29.

Table 5 shows correlation between duration of contraceptive use and haematological parameters among HC users. There was a significant negative correlation between duration of contraceptive use and RDW (r= -0.303, *P*= 0.026).

Table 1: Demographic and haematological profile of study participants

Variable	Cases (n = 54)	Controls (n = 40)	*P*-value

Age (years)	30.04 ± 5.76	29.18 ± 8.15	0.549
Marital status			
Single	21 (38.9)	20 (50.0)	0.283
Married	33 (61.1)	20 (50.0)	
Haematological profile			
RBC × 10^{12}/mm^3	4.35 ± 0.48	4.14 ± 0.42	**0.030**
HGB (g/dl)	12.32 ± 0.81	11.93 ± 1.20	0.061
HCT (%)	37.64 ± 2.46	36.52 ± 3.56	0.075
MCV (fl)	87.04 ± 5.92	88.03 ± 4.56	0.382
MCH (pg)	28.73 ± 2.16	28.47 ± 1.76	0.534
MCHC (g/dl)	32.71 ± 0.90	32.55 ± 0.93	0.382
RDW (%)	13.05 ± 1.35	12.89 ± 1.61	0.597
PLT ×10^9/l	206.28 ± 39.08	196.65 ± 35.12	0.221
WBC ×10^9/l	6.07 ± 1.29	6.19 ± 1.33	0.651
LYM (%)	32.69 ± 3.83	32.81 ± 4.11	0.880
MON (%)	8.04 ± 1.63	8.30 ± 1.82	0.464
NEU (%)	56.12 ± 3.70	55.67 ± 4.14	0.579
EOS (%)	2.35 ± 1.10	2.16 ± 0.83	0.362
BAS (%)	0.91 ± 0.25	1.00 ± 0.34	0.126

RBC= Red blood cells, HGB= Haemoglobin, HCT= Haematocrit, MCV= Mean corpuscular volume, MCH= Mean corpuscular haemoglobin, MCHC= Mean corpuscular haemoglobin concentration, RDW= Red cell distribution width, PLT= Platelets, WBC= White blood cells, LYM= Lymphocytes, MON= Monocytes, NEU= Neutrophils, EOS= Eosinophils, BAS= Basophils

Table 2: Haematological profile of hormonal contraceptive users based on the types of contraceptives

Parameter	Type of HC			*P*-value
	Depo Provera (n = 36)	**COCP** (n = 7)	**Jadelle** (n = 11)	
RBC × 10^{12}/mm^3	4.41 ± 0.47	4.25 ± 0.40	4.18 ± 0.51	0.297
HGB (g/dl)	12.44 ± 0.79	12.01 ± 0.74	12.10 ± 0.91	0.274
HCT (%)	38.07 ± 2.50	36.59 ± 2.07	36.92 ± 2.38	0.192
MCV (fl)	86.58 ± 5.74	86.57 ± 7.30	88.82 ± 5.83	0.544
MCH (pg)	28.28 ± 2.19	28.57 ± 2.67	29.03 ± 1.78	0.604
MCHC (g/dl)	32.69 ± 1.01	32.83 ± 0.35	32.72 ± 0.81	0.935
RDW (%)	13.24 ± 1.35	13.37 ± 1.29	12.22 ± 1.16	0.070
PLT ×10^9/l	203.72 ± 41.07	214.86 ± 49.22	209.18 ± 25.59	0.766
WBC ×10^9/l	5.91 ± 1.19	5.89 ± 0.97	6.70 ± 1.68	0.195
LYM (%)	33.36 ± 4.03	31.66 ± 3.09	31.14 ± 3.20	0.183
MON (%)	7.92 ± 1.27	8.56 ± 1.82	8.09 ± 2.49	0.642
NEU (%)	55.55 ± 3.91	57.04 ± 4.40	57.42 ± 1.92	0.269
EOS (%)	2.39 ± 1.20	1.90 ± 0.59	2.51 ± 1.01	0.494
BAS (%)	0.91 ± 0.27	0.84 ± 0.21	0.94 ± 0.23	0.750

HC= Hormonal contraceptive, COCP= Combined oral contraceptive pills

Table 3: Haematological profile of hormonal contraceptive users stratified by the duration of contraceptive use

Parameter	Duration of use (years)			*P*-value
	≤ 2 (n = 30)	**3-6** (n= 21)	**≥ 6** (n = 3)	
RBC × 10^{12}/mm^3	4.45 ± 0.48	4.41 ± 0.46	4.20 ± 0.48	0.176
HGB (g/dl)	12.27 ± 0.88	12.30 ± 0.73	12.93 ± 0.71	0.411
HCT (%)	37.71 ± 2.83	37.32 ± 1.86	39.27 ± 2.25	0.438
MCV (fl)	85.17 ± 5.01	89.43 ± 6.52*	89.00 ± 4.58	**0.031**
MCH (pg)	27.79 ± 1.97	29.33 ± 2.26*	29.20 ± 0.98	**0.033**
MCHC (g/dl)	32.53 ± 1.05	32.94 ± 0.66	32.93 ± 0.31	0.269
RDW (%)	13.52 ± 1.34	12.52 ± 1.20*	12.00 ± 0.36	**0.011**
PLT ×10^9/l	200.70 ± 41.22	213.00 ± 34.48	215.00 ± 53.84	0.510
WBC ×10^9/l	5.93 ± 1.24	6.27 ± 1.41	6.03 ± 1.31	0.671
LYM (%)	32.13 ± 3.97	33.01 ± 3.68	35.90 ± 2.15	0.240
MON (%)	7.95 ± 1.86	8.25 ± 1.31	7.43 ± 1.34	0.655
NEU (%)	56.72 ± 3.54	55.67 ± 3.80	53.27 ± 4.05	0.239
EOS (%)	2.30 ± 1.08	2.24 ± 0.91	3.63 ± 2.06	0.112
BAS (%)	0.93 ± 0.28	0.89 ± 0.23	0.77 ± 0.06	0.543

P< 0.05, *significantly different from groups on contraceptive for ≤ 2 years

Table 4: Haematological profile of hormonal contraceptive users stratified by age groups

Parameter	Age group					*P*-value
	<25 (n =10)	**25-29** (n = 17)	**30-34** (n = 13)	**35-39** (n = 12)	**≥ 40** (n = 2)	
RBC ×10^{12}/mm^3	4.33 ± 0.33	4.47 ± 0.42	4.33 ± 0.59	4.16 ± 0.31	4.65 ± 1.40	0.412
HGB (g/dl)	12.28 ± 0.82	12.46 ± 0.84	12.27 ± 1.00	12.16 ± 0.62	12.80 ± 0.85	0.824
HCT (%)	37.33 ± 2.30	37.99 ± 2.29	37.28 ± 2.82	37.22 ± 1.55	41.10 ± 6.08	0.283
MCV (fl)	86.60 ± 4.45	85.12 ± 4.27	86.92 ± 7.99	89.67 ± 4.94	90.50 ± 13.44	0.303
MCH (pg)	28.53 ± 1.25	27.85 ± 1.73	28.32 ± 2.71	29.38 ± 1.67	28.80 ± 7.07	0.469
MCHC (g/dl)	32.84 ± 0.55	32.74 ± 1.14	32.84 ± 0.45	32.66 ±0.77	31.35 ± 2.62	0.287
RDW (%)	12.94 ± 1.16	13.54 ± 1.40	13.17 ± 1.24	12.28 ± 1.25	13.25 ± 2.62	0.177
PLT ×10^9/l	198.60 ± 46.64	201.29 ± 35.10	217.23 ± 41.41	206.42 ± 30.02	215.00 ± 91.92	0.789
WBC ×10^9/l	5.70 ± 1.06	6.19 ± 1.64	6.04 ± 1.05	6.05 ± 1.26	7.15 ± 1.06	0.682
LYM (%)	31.14 ± 3.22	32.86 ± 4.04	32.35 ± 4.84	33.62 ± 2.76	35.45 ± 2.76	0.489

MON (%)	8.49 ± 1.44	7.21 ±1.07	8.35 ± 2.15	8.02 ± 1.09	10.90 ± 1.98*****	**0.013**
NEU (%)	56.72 ± 2.71	56.98 ± 3.86	55.81 ± 4.27	55.50 ± 3.35	51.60 ± 3.82	0.337
EOS (%)	2.86 ± 1.37	2.19 ± 1.00	2.52 ± 1.36	2.14 ± 0.49	1.30 ± 0.71	0.283
BAS (%)	0.85 ± 0.18	0.85 ± 0.22	0.98 ± 0.32	0.98 ± 0.26	0.75 ± 0.21	0.376

P< 0.05, *significantly different from age group (25-29) years

Table 5: Correlation analysis of haematological profile of hormonal contraceptive users

PMT		DU	RBC	HGB	HCT	MCV	MCH	MCHC	RDW	PLT	WBC	LYM	MON	NEU	EOS	BAS
DU	R	1	-0.073	0.189	0.130	0.230	0.219	0.155	-0.303	0.262	0.146	0.183	0.001	-0.177	0.113	-0.156
	P-value		0.600	0.172	0.349	0.095	0.112	0.262	**0.026**	0.055	0.292	0.186	0.996	0.201	0.415	0.259
RBC	R		1	0.724	0.819	-0.818	-0.787	-0.150	0.596	0.245	-0.062	-0.278	-0.185	0.289	0.204	0.108
	P-value			**0.000**	**0.000**	**0.000**	**0.000**	**0.000**	**0.000**	**0.000**	1.000	**0.000**	**0.000**	**0.000**	0.139	0.438
HGB	R			1	0.896	-0.312	-0.177	0.297	0.120	0.139	-0.096	-0.099	-0.134	0.106	0.212	-0.139
	P-value				**0.000**	**0.000**	**0.000**	**0.000**	**0.000**	**0.000**	**0.000**	**0.000**	**0.000**	**0.000**	0.124	0.315
HCT	R				1	-0.340	-0.369	-0.153	0.223	0.143	0.003	-0.097	-0.094	0.077	0.204	-0.043
	P-value					**0.000**	**0.000**	**0.000**	**0.000**	**0.000**	1.000	**0.000**	**0.000**	1.000	0.140	0.756
MCV	R					1	0.916	0.056	-0.731	-0.243	0.105	0.339	0.258	-0.393	-0.169	-0.186
	P-value						**0.000**	**1.000**	**0.000**	**0.000**	**0.000**	**0.000**	**0.000**	**0.000**	0.222	0.178

MCH	R	1	0.398	-0.742	-0.246	-0.014	0.291	0.211	-0.321	-0.141	-0.221
	P-value		**0.000**	**0.000**	**0.000**	**1.000**	**0.000**	**0.000**	**0.000**	0.309	0.108
MCHC	R		1	-0.218	0.033	-0.211	-0.016	-0.089	0.071	0.043	-0.231
	P-value			**0.000**	1.000	0.000	1.000	1.000	1.000	0.759	0.094
RDW	R			1	0.143	-0.052	-0.187	-0.193	0.301	-0.175	0.170
	P-values				**0.000**	**1.000**	**0.000**	**0.000**	**0.000**	0.260	0.219
PLT	R				1	0.200	-0.278	0.121	0.217	0.016	0.098
	P-value					**0.000**	**0.000**	**0.000**	**0.000**	0.908	0.481
WBC	R					1	-0.086	0.079	0.093	-0.209	0.094
	P-value						1.000	1.000	1.000	0.129	0.498
LYM	R						1	-0.251	-0.856	-0.132	-0.222
	P-value							**0.000**	**0.000**	0.340	0.107
MON	R							1	-0.191	-0.105	0.241
	P-value								**0.000**	0.448	0.079
NEU	R								1	-0.094	0.073
	P-value									0.498	0.602
EOS	R									1	-0.086
	P-value										0.536
BAS	R										1
	P-value										

DU= Duration of contraceptive use, PMT=Parameter

3.2 DISCUSSION

This study assessed the effect of hormonal contraceptives (HC) on full blood count parameters (RBC, HGB, HCT, MCV, MCH, MCHC, RDW, platelets, WBC, lymphocytes, monocytes, neutrophils, eosinophils and basophils) among women within the Cape Coast Metropolis. Our study observed a significantly elevated RBC count among HC users compared to non-users. This finding is however contrary to that of similar studies conducted in Pakistan and Gaza.[2, 9] Our observation may be due to reduced menstrual blood flow which is known to be common among HC users.[2, 3]

Additionally, slight increases in RDW were observed among HC users compared to non-users. This result is however contrary to that reported in Gaza.[18] In their study, they found significantly lower RDW among users of progestogen-only contraceptives compared to controls in Gaza city. The variation in results may be due to oestrogenic effect of the combined oestrogen-progestogen contraceptives included in this study. This may account for RDW values in this present study being slightly higher among combined oestrogen-progestogen users compared to the progestogen-only contraceptives users.

Further, duration of contraceptive use was seen to influence MCV, MCH and RDW. There was a significant increase in MCV and MCH, and a significant decrease in RDW among those who had used HC for 3 to 6 years compared to those who had use for 2 years or less. This was further seen in correlation analysis where there was a significant negative correlation between duration of contraceptive use and RDW. This shows a duration-dependent effect of HC on RDW. From the MCV results, it is possible that long-term use of these contraceptives may have macrocytic effect on the red blood cells, perhaps when the negative effect HC on vitamin B12 and folate suggested by some studies begins to manifest.[4-6]

Lastly, HC users at the age of 40 and above had significantly higher monocyte count compared to those within the ages of 25 to 29 years. The reason for this observation is however not immediately apparent.

CONCLUSION AND RECOMMENDATION

Hormonal contraceptives cause significant increase in red blood cell (RBC) count among users. Its effects also depend largely on duration of contraceptive use. Additionally, the main limitation to this study was the fact that blood films were not prepared to actually confirm the results presented by the haematology analyser, hence further study is recommended with the incorporation of blood films to the test panel.

CONSENT (WHERE EVER APPLICABLE)

Written informed consent was obtained from participants before the study took place and these documents are preserved by the authors.

ETHICAL APPROVAL (WHERE EVER APPLICABLE)

Ethical clearance was sought from the Institutional Review Board of the University of Cape Coast (IRB/UCC) and administrators of the Hospital before the study was commenced. In addition, all women recruited into the study gave informed consent after thorough explanation of the rationale of the study has been given.

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