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Article *in* British Journal of Medicine and Medical Research · January 2017

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British Journal of Medicine & Medical Research
20(11): 1-7, 2017; Article no.BJMMR.32565
ISSN: 2231-0614, NLM ID: 101570965

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Trace Elements Levels and Blood Pressure in Ghanaian Women Using Depot Medroxyprogesterone Acetate Contraceptive

Justice Afrifa[1*], Samuel Essien-Baidoo[1], Eric Gyamerah Ofori[2] and Albert Abaka-Yawson[1]

[1]Department of Medical Laboratory Technology, University of Cape Coast, Cape Coast, Ghana.
[2]Department of Biochemistry, University of Cape Coast, Cape Coast, Ghana.

Authors' contributions

This work was carried out in collaboration between all authors. Authors JA and SEB designed the study, performed the statistical analysis, wrote the protocol and wrote the first draft of the manuscript. Authors EGO and JA managed the analyses of the study. Authors JA and EGO managed the literature searches. All authors read and approved the final manuscript.

Article Information

DOI: 10.9734/BJMMR/2017/32565
Editor(s):
(1) Sinan Ince, Department of Pharmacology and Toxicology, University of Afyon Kocatepe, Turkey.
Reviewers:
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Complete Peer review History: http://www.sciencedomain.org/review-history/18608

Original Research Article

Received 2nd March 2017
Accepted 30th March 2017
Published 13th April 2017

ABSTRACT

Background: The benefit of depot medroxyprogesterone acetate (DMPA) (an injectable contraceptive) relate to the fact that it has a very high efficacy in pregnancy prevention.
Aim: We investigated the effect of the hormonal contraceptive, DMPA on the levels of trace elements: (Selenium (Se), Copper (Cu), Zinc (Zn)) and blood pressure.
Materials and Methods: Fifty (50) women on DMPA and thirty (30) controls (who were not on DPMA) were recruited from the Kasoa Polyclinic in the Central Region of Ghana. Blood was collected for the estimation of trace elements using mass spectrometry. Blood pressure was measured and body mass index (BMI) calculated.
Results: Serum levels of Cu was found to be significantly elevated among participants on DMPA compared to healthy controls (P=0.002). Se levels were however slightly but insignificantly reduced

**Corresponding author: E-mail: jafrifa@ucc.edu.gh;*

(P=0.316) among participants on DMPA. There was also a significantly elevated diastolic blood pressure (76.00 ± 11.95 mmHg, P=0.03) among DMPA users compared to the controls. Serum Cu correlated positively with Zn(r=0.463) (P=0.001) among the DMPA users.
Conclusion: DMPA users had an increase in Cu with reduced Se levels as well as an increased blood pressure. However, no change in serum Zn concentration was seen among DMPA users compared to the controls.

Keywords: Trace elements; depot medroxyprogesterone acetate; copper; blood pressure.

1. INTRODUCTION

The contraceptive, depot medroxyprogesterone acetate (DMPA) has played a very important role in birth control over the past few decades. It has proven to be a reliable contraceptive with it failure rate being less than one pregnancy per 100 women per year [1]. The benefit of DMPA relates to the fact that it is 99% effective at preventing pregnancy when used properly, it also requires only one injection every 3 months, and offers extended protection due to the crystallized progestin that slowly dissolves into the bloodstream [2,3]. Notwithstanding bleeding irregularities; headache is the most commonly reported adverse health effect of hormonal contraceptives [4]. Mood changes and weight gain have also been reported in a couple of cases [4]. Of much more concern is the fact that studies have found decreases in high density lipoprotein (HDL) levels and increases in low density lipoprotein (LDL) levels as well as decreased bone density in contraceptive use [5]. The DMPA label for contraceptive injection has a "black box" warning an increased risk of osteoporosis [6]. In addition, women using DMPA have been reported to have a double risk of developing breast cancer [7].

Trace elements have long been suggested to be the missing link in atherosclerosis, osteoporosis and hypertension [8]. Se, Cu and Zn have antioxidant properties and theoretically protect the body from cardiovascular diseases [9]. Therefore, their alterations may play a role in atherosclerosis and hypertension. Cu deficiency has also been observed in the early stages of osteoporosis [10]. Various studies have documented the relationship amid trace elements, blood pressure and contraceptive use, bringing to light some of the mechanisms by which contraceptives influence these parameters [11]. There is however scarcity of data on the use of DMPA especially in Africa where greater population of DMPA users live. We therefore sought to investigate the effects of the hormonal contraceptive DMPA on the levels of trace elements (Se, Cu and Zn) and blood pressure among women in Ghana.

2. MATERIALS AND METHODS

2.1 Study Design and Setting

This simple randomized case-control study was conducted at the Family Planning and Laboratory Departments of the Kasoa Polyclinic from December 2013 to March 2014.The Polyclinic is located in Kasoa Central. Kasoa is the capital of the Awutu Senya East Municipality, in the Central Region of Ghana.

2.2 Study Population

One hundred and twenty (120) women met the criteria for inclusion after initial screening. Out of this, 20 refused to participate, 10 refused to give written informed consent and another 10 refused to give blood samples for the study. The remaining 80 participants were adequately informed of the procedures, risks and benefits involved. Socio-demographic data (age, marital status, educational background and occupation among others) were gathered using a pre-tested questionnaire.

2.3 Inclusion and Exclusion Criteria

Women within the reproductive ages (15-49) years and have been using the injectable DMPA for at least three months were considered for the study. Fifty (50) participants chosen from this population were selected as case, and thirty (30) non-contraceptive (women not on any form of contraception as at the time of the study) within the same age category who were attending the outpatient department for routine check-up and to seek advice on family planning were also recruited as controls. DMPA users who have previously used other forms of contraception were excluded from the study. Also women who had diabetes, and infections like human immunodeficiency virus (HIV), hepatitis B and C as well as hypertension and were on DMPA were excluded.

2.4 Ethical Consideration

Ethical approval was sought from authorities at Kasoa Polyclinic and the Institutional Review Board (IRB) of University of Cape Coast. Written informed consent was sought from the participants prior to the study with vivid explanations of the need to carry out the research.

2.5 Measurement of Blood Pressure

The blood pressure measurement was performed with an automatic validated device (Omron HEM711DLX, UK), on the superior left limb, sitting position with the legs uncrossed, with the arm supported at the height of the heart and a cuff adapted to the arm size. All measurements were in accordance with recommendations of the American Heart Association [12]. Mean values of duplicate measurements were recorded as the blood pressure. Hypertension was graded as "normal" when the systolic blood pressure (SBP) < 120 mmHg and diastolic blood pressure (DBP) <80 mmHg "pre-hypertension" when SBP = 120-139 or DBP = 80-89 and "hypertension" when SBP = 140-159 or DBP = 90-99 [13].

2.6 Sample Collection and Processing

Five milliliters (5 ml) of venous blood sample was collected from each participant by aseptic means and transferred immediately into a dipotassium ethylenediamine tetra acetic acid (K_2 EDTA) tube. The samples were centrifuge at 1500g for 5-8 minutes and the plasma transferred into cryovials and stored at -80^{o}C until assayed. The samples for assay were stored in cold chest and transported to the Chemistry Laboratory of Ghana Atomic Energy Commission (GAEC), Kwabenya for analysis.

2.7 Digestion and Estimation of Trace Elements in Serum (Se, Cu and Zn)

The Digestion Protocol for serum samples using milestone acid digestion microwave ETOS 900 was employed. (Milestone Acid Digestion Cookbook update 1st January 1996). The digestate was made up to 20 ml with double distilled water and assayed for the presence of Zn and Cu using Atomic Absorption Spectrometer (VARIAN AA 240FS/ Australia) in an acetylene- air flame and in acetylene-nitric acid for Se.

2.8 Reporting Results

The atomic absorption spectrophotometer VARIAN AA 240FS produces values in both absorbance and concentrations. Classification of trace element cut-offs was done according to Rukgauer and co [14].

It however does not factor in the nominal volume (volume of digested solution) and the volume of the sample. The final concentration of the trace elements was calculated as follows;

Final Concentration, mg/L = $\frac{A \times B}{C}$

Where: A = Concentration of trace elements in digested sample, mg/L
B = Volume of digested solution, ml
C = Sample volume, ml

2.9 Anthropometric Measurement and Calculation of BMI

Height (to the nearest centimeter) without shoes was measured using a stadiometer (seca 217, 40 Barn Street B5 5QB Birmingham, United Kingdom) and weight (to the nearest 0.1 kg), was measured using bathroom scale (Zhongshan Camry Electronic Co. Ltd, Guangdong, China). Body mass index (BMI) was estimated as a ratio of weight (kg) to height squared (m^2). according to WHO criteria. Participants were categorized as underweight (<18 Kg/m^2), normal (18-24 Kg/m^2), overweight (25-29.9 Kg/m^2) and obese (>30 Kg/m^2) [15].

2.10 Statistical Analysis

Data was de-identified before entry into Microsoft excel. Data was analyzed with SPSS version 16 (SPSS Inc. Chicago). Independent sample t-test was used to compare mean scores between DMPA users and controls. Chi-square was used to test association between proportions of categorical variables. Correlations between trace elements and blood pressure were performed using Pearson's correlation coefficient test. P<0.05 were considered statistically significant.

3. RESULTS

The study recruited fifty (50) depot medroxyprogesterone acetate (DMPA) users and thirty (30) non-contraceptive users. In general, 50% and 46.7% of the subjects were within age range of 20-29 for cases and controls respectively. Majority of the cases 40(80.0%) were married compared to the controls

15(50.0%). High levels of serum Cu was predominantly associated (P<0.0001) with the cases 48(96%) compared to the controls. Also 8(16%) of the cases were found to be hypertensive compared to 1(3.3%) of the controls as illustrated in Table 1.

Table 2 shows mean values of demographic, clinical and biochemical characteristics of the study participants. BMI(P=0.001), DBP(P=0.03) and Cu(P=0.002) were significantly elevated among cases as compared to the controls. However, there were no significant differences in serum Zn, Se and SBP (P> 0.05).

Age correlated positively with Se, Zn, BMI and blood pressure, but negatively with Cu, though none of them was significant. Serum Se correlated negatively with Zn, and blood pressure but showed a significant positive (*P=0.001*) correlation with Cu. Also SBP correlated positively (P<0.001) with DPB (Table 3).

4. DISCUSSION

We aimed to determine the effects of DMPA on trace element levels and blood pressure among women of reproductive age. Our results indicate an insignificantly reduced serum Se levels among participants on DMPA. In contrast serum Cu levels among cases were significantly higher, however there was no change in Zn levels between cases and controls. There was also a significantly elevated diastolic blood pressure among participants on DMPA. Serum Cu positively correlated with Zn. Our results also indicated a higher participation of married women among the study participants.

Table 1. Sociodemographic characteristics of study participants

Parameter	Cases (50)	Control (30)	*P*-value
	N (%)	N (%)	
Age			0.46
<20	1 (2.0)	1 (3.3)	
20-29	25 (50.0)	14 (46.7)	
30-39	22 (44.0)	11 (36.7)	
≥40	2 (4.0)	4 (13.3)	
Marital status			0.02
Single	9 (18.0)	14 (46.7)	
Married	40 (80.0)	15 (50.0)	
Divorced	1 (2.0)	1 (3.3)	
Level of education			0.43
None	8 (16.0)	4 (13.3)	
Primary	2 (4.0)	1 (3.3)	
Basic	27 (54.0)	13 (43.3)	
Secondary	9 (18.0)	11 (36.7)	
Tertiary	4 (8.0)	1 (3.3)	
Se level			0.09
Low	38 (76.0)	17 (56.7)	
Normal	2 (4.0)	5 (16.6)	
High	10 (20.0)	8 (26.7)	
Cu level			<0.0001
Low	0 (0.0)	2 (6.6)	
Normal	2 (4.0)	11 (36.7)	
High	48 (96.0)	17 (56.7)	
Zn level			0.73
Low	23 (46.0)	15 (50.0)	
Normal	27 (54.0)	15 (50.0)	
Hypertension status			0.038
Normal	41(82.0)	25 (83.33)	
Pre-hypertension	1 (2.0)	4 (13.3)	
Hypertension	8 (16.0)	1 (3.3)	
BMI			0.02
Normal	17 (34.0)	17 (56.7)	
Overweight	17 (34.0)	11 (36.7)	
Obese	16 (32.0)	2 (6.6)	

Table 2. Comparison of mean trace element levels, blood pressure and age among cases and controls

Parameter	Case (50)	Control (30)	*p*-value
	Mean ± SD	Mean ± SD	
Age (years)	29.94 ± 5.46	30.37 ± 6.24	0.75
Se (mg/l)	0.06 ± 0.11	0.08 ± 0.10	0.32
Zn (mg/l)	0.66 ± 0.25	0.66 ± 0.38	0.96
Cu (mg/l)	2.18 ± 0.66	1.68 ± 0.65	0.002
SBP (mmHg)	115.20 ± 12.49	116.33 ± 9.28	0.67
DBP (mmHg)	76.00 ± 11.95	70.33 ± 8.50	0.03
BMI (Kg/m^2)	27.90 ± 5.08	24.59 ± 2.69	0.001

SBP: Systolic Blood Pressure; DBP: Diastolic Blood Pressure, Se = 0.08-0.13 mg/l, Cu = 0.70-1.40 mg/l, Zn = 0.70-1.20 mg/l

Table 3. Correlation of biochemical parameters, trace elements and age among study participants who are on DMPA

		Correlations					
		Age	Se	Cu	Zn	SBP	DBP
Age	Pearson correlation	1	0.061	-0.04	0.137	0.109	0.156
	P-value		0.675	0.784	0.344	0.450	0.280
Se	Pearson correlation		1	0.463	-0.043	-0.225	-0.175
	P-value			0.001*	0.767	0.117	0.225
Cu	Pearson correlation			1	0.135	-0.004	-0.069
	P-value				0.351	0.976	0.635
Zn	Pearson correlation				1	-0.092	-0.188
	P-value					0.523	0.191
SBP	Pearson correlation					1	0.825
	P-value						<0.0001
DBP	Pearson correlation						1
	P-value						

** Correlation is significant at the <0.05 level (2-tailed)*

Serum Se has been known to offer some level of antioxidant protection against hypertension and cancers [16]. The low Se levels reported among participants on DMPA in this study is in line with findings of earlier studies [17,18] which also reported a reduced but insignificant levels of serum Se among contraceptive users. Elsewhere low serum Se levels have been linked with a reduced antioxidant protection against hypertension and cancer [9] among injectable contraceptive users.

Consistent with a previous study [17], we observed high Cu levels among DMPA users as compared to controls, emphasizing the high levels of Cu in women using hormonal contraception. This is suggestive of the link between DMPA and increased absorption of Cu into the bloodstream. Studies have shown that excess serum Cu may be due to the synthesis of estrogen induced ceruloplasmin in the liver [19] and this has been associated with conditions such as nausea, abdominal pain and vomiting [20].

Zn levels were found to be low in both cases and controls, however, there were no significant differences between the cases and controls. Cu is a competitive antagonist for the absorption of Zn [21,22]. Therefore, the high Cu levels observed in this study could be a function of the low zinc levels. Previous studies on the influence of hormonal contraceptives on plasma Zinc concentration have shown either no effects [23] or a decrease in their levels [24]. This makes the influence of hormonal contraceptives on serum Zn levels inconclusive.

Progesterone containing contraceptives are known to stimulate appetite and eating behavior, this has been demonstrated by previous studies which reported appetite stimulating effect of synthetic progesterone like DMPA [25,26]. However, our current study may be limited by our inability to assess dietary habits of the study participants.

Whiles we report an increased DBP among our study participants, Taneepanichskul et al. [27]

also reported no change in blood pressure in a study that compares weight and blood pressure among women on DMPA and those using intrauterine device (IUD). The difference may be due to the different study design and nature of the study participants used. We report no difference in the measured parameters with respect to the different age group categories. Our study was a smaller sample size case-control design and this could have accounted for insignificant differences in both Zinc and Se.

5. CONCLUSION

We conclude that among our study participants, DMPA usage is associated with increased Cu, reduced Se levels and an increase in blood pressure. However, DMPA had no effect on serum Zinc levels. It is therefore important that baseline (for DMPA, naive women) as well routine assessment of trace elements are carried out among women on DMPA to ensure a continuous trace element balance. We recommend that future inquest into DMPA dynamics should involve larger multicultural cross dimensional populations as well as a comparison of different contraceptive types.

ACKNOWLEDGEMENT

The authors grateful to the laboratory staff of Kasoa Polyclinic.

COMPETING INTERESTS

Authors have declared that no competing interests exist.

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Peer-review history:
The peer review history for this paper can be accessed here:
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