

Effects of Contraceptives on Serum Trace Elements, Calcium and Phosphorus Levels

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ABSTRACT

Background: Women on different contraceptive methods have been linked with the development of various diseases and possible changes in serum trace elements and vitamins of women on contraceptives have been postulated. Therefore, the relationship between contraceptive use and trace elements needs to be investigated.

Methods: This is a cross-sectional randomized study. After informed consent was obtained, blood samples were collected from a total of 100 women of child-bearing age on different contraceptive methods: 50 on oral contraceptives, 25 on injectables and another 25 on intra-uterine device. Blood samples were also collected from another 50 age-matched non-contraceptive users to serve as control. Serum was analysed using atomic absorption spectrophotometer for zinc, copper, manganese, iron, selenium, cadmium, lead and magnesium while colorimetric method was used for phosphorus and calcium. Body mass index (BMI) was calculated as weight in kilogram/height in meter squared. Results obtained from laboratory analysis and anthropometric measurements were analysed using computer SPSS package.

Results: The mean serum zinc, selenium, phosphorus and magnesium levels obtained from subjects on contraceptives were significantly lower ($p < 0.01$, $p < 0.05$, $p < 0.05$ and $p < 0.05$ respectively) than those of the control group. However, the mean serum copper, iron, calcium and cadmium levels were significantly higher ($p < 0.05$) in participants on contraceptive when compared with the control group. Manganese and lead levels were similar in participants and control groups. Correlation analysis shows significant association between some trace elements and the duration of contraception and body mass index of the participants.

Conclusion: The study showed and confirmed reduced levels of trace elements in women on contraceptives. The reduction is proportional to the duration of contraceptive use.

Keywords: Contraceptives, metabolic processes, Nigeria, trace elements, women

Efectos de los Contraceptivos sobre los Elementos Traza en Suero, y los Niveles de Calcio y Fósforo

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RESUMEN

Antecedentes: Mujeres que usan diferentes métodos anticonceptivos han sido vinculadas al desarrollo de varias enfermedades, y se han presupuesto cambios en los elementos traza en suero y las vitaminas de mujeres en torno a los contraceptivos. Por lo tanto, se hace necesario investigar la relación entre el uso de contraceptivos y los elementos traza.

Métodos: Éste es un estudio transversal randomizado. Después de obtener el consentimiento informado, se recogieron muestras de sangre de un total de 100 mujeres de edad de maternidad en relación

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con diferentes métodos anticonceptivos: 50 con contraceptivos orales, 25 con inyectables, y otras 25 con dispositivos intrauterinos. También se tomaron muestras de sangre de otras 50 mujeres pareadas por edad y no usuarias de anticonceptivos, para servir de control. Se analizó el suero usando el espectrofotómetro de absorción atómico para zinc, cobre, manganeso, hierro, selenio, cadmio, plomo, y magnesio, mientras que el método colorimétrico se usó para el fósforo y el calcio. El índice de masa corporal (IMC) fue calculado como el peso en altura/kilogramo en metro cuadrado. Los resultados obtenidos del análisis de laboratorio así como las dimensiones antropométricas, se analizaron usando el paquete computacional SPSS.

Resultados: Los niveles promedio en suero de zinc, selenio, fósforo y los niveles de magnesio obtenidos de sujetos bajo el uso de contraceptivos fueron significativamente más bajos ($p < 0.01$, $p < 0.05$, $p < 0.05$ y $p < 0.05$ respectivamente) que aquéllos del grupo de control. Sin embargo, los niveles promedio en suero de cobre, hierro, calcio y cadmio fueron significativamente más altos ($p < 0.05$) en los participantes bajo el uso de contraceptivos, en comparación con el grupo de control. Los niveles de manganeso y plomo fueron similares en los participantes y los grupos de control. El análisis de la correlación muestra una asociación significativa entre algunos elementos traza, y la duración de la contracepción y el índice de masa corporal de los participantes.

Conclusión: El estudio mostró y confirmó niveles reducidos de elementos traza en las mujeres bajo contraceptivos. La reducción es proporcional a la duración del uso de contraceptivos.

Palabras claves: Contraceptivos, procesos metabólicos, Nigeria, elementos traza, mujeres

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INTRODUCTION

Contraceptives are devices or techniques that permit sexual union without resultant pregnancy (1, 2). There has been interest in recent years about alterations in various metabolic processes and trace element profiles associated with the use of contraceptives. Alterations in metabolic processes and trace element profiles are governed by genetic disposition as well as environmental factors. Changes in lifestyle, environmental factors, dietary habits and active ingredients of hormonal agents have been known to affect status of micronutrients in humans. For instance, contraceptives (compounds with oestrogen-progesterone-like actions) have been used by women in Nigeria to control fertility and such use has been shown to interfere with the absorption of some micronutrients such as trace elements and vitamins (2, 3). Possible changes in serum trace elements and vitamins of women on contraceptives have been postulated (4). Some of these micronutrients *eg* manganese, vitamin B₁₂ and magnesium are co-factors and co-enzymes which are involved in important metabolic pathways. Changes in the tissue level or bioavailability of these elements could play a significant role in health risk and the pathogenesis of some disorders such as cardiovascular complications; the aging process and certain cancers have been associated with the use of contraceptives (3). Some of these trace elements for example, selenium and manganese are potent antioxidants known to be involved in preventing free-radical induced damage. These antioxidants are involved in preventing the formation of free radicals induced damage, preventing the formation of radicals, scavenging them or promoting free

radical decomposition in the body (5). Zinc and copper have been shown to boost immune response and their importance in the malnourished persons have been documented (2, 5). Disruption in the blood levels of these trace elements could be an important health risk. There is scanty information and data on Nigerian women who are using contraceptives even though observed side effects of contraceptives have been linked with disturbance in the bioavailability of trace elements. Therefore, it is important to investigate possible changes in the serum levels of these elements among contraceptive users and determine possible association between duration of contraceptive use and trace element levels.

Ethical approval

Ethical approval was obtained from the Ethical Review Committee of Ladoke Akintola University of Technology Teaching Hospital (LAUTECHTH), Osogbo, Nigeria, to use the clients of the Family Planning Clinic of the hospital for the study.

Participants' consent

The consent of all participants was obtained after they were informed of the nature and relevance of the study. An informed consent form was then given to the participants to fill after it was read to them in both English and the local language (Yoruba). Participants were informed of their right to participate or not in the study. Only consented participants were recruited into the study. All participants were assured of confidentiality of data collected from them.

SUBJECTS AND METHODS

This was a cross-sectional randomized study conducted on non-lactating, non-pregnant women who were on different methods of contraceptives for at least a period of 12 months and were attending the Family Planning Clinic at Osogbo, Western Nigeria. The study population consisted of an urban population with the majority of study subjects being civil servants and who lived an average modest lifestyle.

One hundred, non-lactating, non-pregnant women, aged 18–40 years who were on contraceptives for not less than 12 months participated in the study. Fifty of these women were on oral contraceptive (OCP), 25 on injectables and 25 on uterine device (IUD). Fifty non-lactating, non-pregnant women, aged 18–40 years, not on any contraceptive method participated as control individuals.

A well structured questionnaire was used to collect information on sociodemographic profile, personal biodata and health status of the subjects. The questionnaire had different sections: personal data, demographic data, history, duration of contraceptive use and other relevant data. The questionnaire was given to each participant to complete in a private room to ensure confidentiality.

About 10 milliliters of venous blood was obtained by aseptic procedure from all the participants and control group and placed into already acidified plain specimen tubes prepared in line with the guidelines for sample collection for trace elements as described by Cornelis *et al* (6). The blood was spun at 3000 revolutions per minute (3000 rpm) for five minutes to obtain serum. Serum from both participants and control group were immediately stored at -20°C till analysis was done.

The levels of trace elements in serum samples were determined by Atomic Absorption Spectrophotometry (ASS) using Beck Model 200 SN115863752DJ (Beckman, Germany) Spectrophotometer and using a direct method as described by Kaneko (7). Serum samples were diluted 1:25 for estimation of magnesium while samples for other trace elements were aspirated directly into ASS. This method also complies with the specification for standardized flame AAS quick procedure for metals using Beck Model 200 Atomic absorption system. Samples were assayed for Zinc (Zn), Copper (Cu), Selenium (Se), Cadmium (Cd), Lead (Pb), Manganese (Mn), Iron (Fe) and Magnesium (Mg) with wavelength of 214, 325, 196, 228, 358, 236, 248 and 285 respectively. For Zn, high standard and ABS energy, 0.5 ppm/0.26 detection limit, 0.005, linear range 1.0 and typical stability ± 0.003 . For Cu, high standard and ABS energy, 5 ppm/0.75 detection limit, 0.005, linear range 5.0 and typical stability ± 0.005 . Also, 25 ppm/0.3, 0.15, 100 and ± 0.01 for Se respectively and 1 ppm/0.75, 0.01, 2.0 and ± 0.005 for Cd, 5 ppm/0.75, 0.005, 5.0 and ± 0.005 for Pb, 2 ppm/0.3, 0.01, 2.0 and ± 0.005 for Mn, 4 ppm/0.55, 0.01, 2.0 and ± 0.005 for Fe and 0.5 ppm/0.75, 0.005, 2.0, ± 0.005 for Mg.

Controls for all metals included human or bovine blood spiked with known quantities of each metal. In addition, we

analysed Cd, Pb, and Mercury (Hg) with regard to standardized human reference blood containing known quantities of each metal.

Serum Calcium (Ca) level was estimated by the colorimetric, endpoint, Arsenazo III reaction (8) and inorganic phosphate by the phosphomolybdic acid reaction as described elsewhere (9).

Height was measured in meter using an appropriate rule with the participants standing erect, bare-footed and looking straight ahead. Weight of each participant was determined with each of them wearing minimal clothing using Uniscope simple scale. Body mass index was calculated as follows:

$$\text{Body mass index} = \frac{\text{Weight (kg)}}{\text{Height (m)}^2} = \text{kg/m}^2$$

Statistical analysis was performed on data using computer SPSS software package and results expressed as mean and standard deviation. Student's "t" test was used to determine the significant difference between the mean values with p value set at $p < 0.05$. Pearson correlation was used to determine association between the various parameters.

RESULT

Serum zinc, copper, iron, selenium, cadmium, magnesium, phosphate and calcium levels were analysed in 100 women of reproductive age (18–40 years) who were on different contraceptive methods: 50 on oral contraceptives (OCP), 25 on injectables and 25 on intra-uterine devices (IUD). Fifty (18–40 years) non-pregnant, non-lactating women who are not on any contraceptive methods served as the control group. Demographic characteristics of participants are summarized in Table 1.

Table 2 shows the mean and standard deviation of trace elements determined in all the participants (contraceptive and control groups). When all the parameters were compared between contraceptive and control groups, there was a significant difference between the two groups in body mass index being higher in the contraceptive group than in the control group. Serum manganese and lead showed no significant difference ($p > 0.05$) between the two groups. However, age, zinc, copper, iron, selenium, cadmium, phosphorus, calcium, and magnesium showed a significant ($p < 0.05$) difference between contraceptive users and the control group.

Table 3 shows the mean and standard deviation of zinc, copper, manganese, iron, selenium, cadmium, phosphate, calcium, lead and magnesium levels in contraceptive (oral contraceptives, injectables and intra-uterine device) users and in the control group.

Table 4 shows comparison between the contraceptive and control groups. Participants on oral contraceptive were compared with the control group while those on injectables were compared with participants on intra-uterine device separately. Manganese and lead levels of participants on OCP showed no significant difference when compared with

Table 1: Mean, standard deviation and range values of age, body mass index (BMI) and serum trace elements in women using contraceptive and the control group

| Parameters | Mean ± SD | Range |
|---|--------------|---------------|
| Control participants (n = 50) | | |
| Age (Year) | 34.52 ± 4.25 | 24.00 – 42.00 |
| Body mass index (BMI) | 22.01 ± 2.40 | 19.16 – 28.31 |
| Oral contraceptive pills (OCP) n = 50 | | |
| Age (Year) | 27.78 ± 3.46 | 22.00 – 34.00 |
| Body mass index (BMI) | 22.15 ± 1.58 | 19.33 – 26.44 |
| Duration of contraception | 15.82 ± 3.13 | 12.00 – 24.00 |
| Injectables n = 25 | | |
| Age (Year) | 29.04 ± 3.06 | 22.00 – 36.00 |
| Body mass index (BMI) | 22.89 ± 2.46 | 20.30 – 32.37 |
| Duration of contraception | 16.44 ± 4.98 | 12.00 – 36.00 |
| Intra-uterine device (IUD) n = 25 | | |
| Age (Year) | 35.36 ± 4.29 | 28.00 – 44.00 |
| Body mass index (BMI) | 23.37 ± 3.70 | 21.09 – 25.10 |
| Duration of Contraception | 19.16 ± 5.85 | 12.00 – 30.00 |
| Total contraceptive participants (n = 100) | | |
| Age (Year) | 29.99 ± 4.76 | 22.00 – 44.00 |
| Body mass index (BMI) | 22.64 ± 1.84 | 19.33 – 32.37 |
| Duration of contraception | 16.81 ± 4.59 | 12.00 – 36.00 |

Contraception ($r = -0.46$, $p < 0.05$).

Table 2: Mean and standard deviation of trace elements of participants on different contraceptive and control groups

| Parameters measured | Participants n = 100 Mean ± SD | Control n = 50 Mean ± SD | T- test | p-Value |
|-----------------------------|--------------------------------------|--------------------------------|---------|-------------|
| Zinc (Zn) mg/dl | 0.70 ± 0.23 | 1.00 ± 0.15 | 0.000 | $p < 0.001$ |
| Copper (Cu) mg/dl | 1.69 ± 0.25 | 0.98 ± 0.16 | 0.000 | $p < 0.001$ |
| Manganese (Mn) µg/L | 7.96 ± 1.04 | 7.98 ± 1.00 | 0.911 | $p > 0.05$ |
| Iron (Fe) µg/L | 98.64 ± 17.33 | 89.80 ± 2.89 | 0.000 | $p < 0.001$ |
| Selenium (Se) µg/L | 74.52 ± 9.36 | 89.68 ± 2.98 | 0.000 | $p < 0.001$ |
| Cadmium (Cd) µg/L | 2.51 ± 0.22 | 2.3 ± 0.33 | 0.002 | $p < 0.05$ |
| Phosphorus (P) mg/dl | 2.75 ± 0.61 | 3.31 ± 0.23 | 0.000 | $p < 0.001$ |
| Calcium (Ca) mg/dl | 2.43 ± 0.46 | 2.10 ± 0.28 | 0.000 | $p < 0.001$ |
| Lead (Pb) µg/L | 8.42 ± 0.21 | 8.42 ± 0.36 | 0.863 | $p > 0.05$ |
| Magnesium (Mg) µg/L | 1.84 ± 0.39 | 2.05 ± 0.27 | 0.001 | $p < 0.05$ |

n = number of subject

kg = Kilogram

mg/dL = Milligram per deciliter

µg/L = Microgram per liter

Mean±SD = Mean ± standard deviation

pattern to that of cadmium. Serum magnesium level showed significant ($p < 0.05$) difference in participants on OCP, IUD and the control group but insignificant difference between control group *versus* injectables.

Table 5 shows correlation between age, body mass index and duration of contraception and serum levels of trace

Table 3: Mean and standard deviation of trace elements in participants on oral contraceptives, injectables, intra-uterine device and control group

| Parameter | OCP n = 50 mean ± SD | Injectables n = 25 mean ± SD | IUD n = 25 mean ± SD | Control n = 50 mean ± SD |
|-----------------------------|----------------------------|------------------------------------|----------------------------|--------------------------------|
| Zinc (Zn) mg/dL | 0.59 ± 0.14 | 0.61 ± 0.14 | 1.00 ± 0.17 | 1.00 ± 0.15 |
| Copper (Cu) mg/dL | 1.58 ± 0.14 | 1.58 ± 0.17 | 2.00 ± 0.23 | 0.98 ± 0.16 |
| Manganese (Mn) µg/L | 8.04 ± 0.99 | 7.92 ± 1.04 | 7.84 ± 1.18 | 7.98 ± 1.00 |
| Iron (Fe) µg/L | 109.9 ± 1.3 | 105.7 ± 1.8 | 69.1 ± 2.9 | 89.8 ± 2.8 |
| Selenium (Se) µg/L | 69.3 ± 3.3 | 69.8 ± 2.9 | 89.7 ± 3.4 | 89.7 ± 2.9 |
| Cadmium (Cd) µg/L | 2.49 ± 0.23 | 2.47 ± 0.23 | 2.58 ± 0.16 | 2.36 ± 0.33 |
| Phosphorus (P) mg/dL | 2.18 ± 0.26 | 3.34 ± 0.25 | 3.28 ± 0.21 | 3.31 ± 0.23 |
| Calcium (Ca) mg/dL | 2.80 ± 0.31 | 2.10 ± 0.26 | 2.04 ± 0.28 | 2.10 ± 0.28 |
| Lead (Pb) µg/L | 8.40 ± 0.18 | 8.40 ± 0.21 | 8.48 ± 0.25 | 8.43 ± 0.36 |
| Magnesium (Mg) µg/L | 1.60 ± 0.23 | 1.98 ± 0.40 | 2.25 ± 0.19 | 2.05 ± 0.27 |

participants on injectables, intra-uterine device and the control group. However, zinc and selenium levels showed significant ($p < 0.05$) difference between the groups but no significant difference ($p > 0.05$) between the IUD group *versus* control and OCP *versus* injectables. Copper showed significant difference ($p < 0.05$) in all the groups except in OCP *versus* injectable ($p > 0.05$). Serum iron level showed significant difference ($p < 0.05$) in all the groups. Serum cadmium showed no significant value ($p > 0.05$) except in participants on IUD when compared with control participants ($p < 0.05$). Serum calcium and phosphorus showed similar

elements in contraceptive participants. Serum zinc, copper, selenium, cadmium, phosphorus and magnesium showed significant positive correlation with age ($p < 0.01$). However, iron and calcium show significant negative correlation ($p < 0.01$) whilst manganese and lead showed non-significant negative correlation with age of participants. Most trace elements showed insignificant negative correlation with BMI except phosphorus and magnesium that showed significant positive correlation ($p < 0.01$). A significant positive correlation was observed between body mass index (BMI) and zinc ($p < 0.05$) and significant negative correlation with iron

Table 4: Comparative difference between contraceptive and control groups using student “t” test (p values)

| Parameter | Control vs OCP (p-value) | Control vs Injectables (p-value) | Control vs IUD (p-value) | OCP vs Injectables (p-value) | OCP vs IUD (p-Value) | Injectables vs IUD (p-value) |
|----------------------|--------------------------|----------------------------------|--------------------------|------------------------------|----------------------|------------------------------|
| Zinc (Zn) mg/dL | 0.000 | 0.000 | 1.000 | 0.995 | 0.000 | 0.000 |
| Copper (Cu) mg/dL | 0.000 | 0.000 | 0.000 | 1.000 | 0.000 | 0.000 |
| Manganese (Mn) µg/L | 1.000 | 1.000 | 0.997 | 0.998 | 0.978 | 1.000 |
| Iron (Fe) µg/L | 0.000 | 0.000 | 0.000 | 0.000 | 0.000 | 0.000 |
| Selenium (Se) µg/L | 0.000 | 0.000 | 1.000 | 0.976 | 0.000 | 0.000 |
| Cadmium (Cd) µg/L | 0.183 | 0.534 | 0.002 | 1.000 | 0.306 | 0.306 |
| Phosphorus (P) mg/dL | 0.000 | 0.997 | 0.995 | 0.000 | 0.000 | 0.997 |
| Calcium (Ca) mg/dL | 0.000 | 1.000 | 0.951 | 0.000 | 0.000 | 0.983 |
| Lead (Pb) µg/L | 0.996 | 0.996 | 0.968 | 1.000 | 0.584 | 0.756 |
| Magnesium (Mg) µg/L | 0.000 | 0.958 | 0.003 | 0.000 | 0.000 | 0.022 |

Table 5: Correlation between serum trace elements and duration on contraceptives, age and body mass index in participants as a whole

| Parameters | Age (Year) | Body Mass index (Kg/m ²) | Duration of contraception (Months) |
|----------------------|-----------------|--------------------------------------|------------------------------------|
| Zinc (Zn) mg/dL | 0.387 p < 0.01 | 0.304 p < 0.05 | 0.226 p < 0.05 |
| Copper (Cu) mg/dL | 0.389 p < 0.01 | 0.163 p > 0.05 | 0.272 p < 0.01 |
| Manganese (Mn) µg/L | -0.006 p > 0.05 | 0.190 p > 0.05 | -0.143 p > 0.05 |
| Iron (Fe) µg/L | -0.662 p < 0.01 | -0.271 p < 0.05 | -0.293 p < 0.01 |
| Selenium (Se) µg/L | 0.574 p < 0.01 | 0.141 p > 0.05 | 0.293 p < 0.01 |
| Cadmium (Cd) µg/L | 0.348 p < 0.01 | -0.092 p > 0.052 | 0.111 p > 0.05 |
| Phosphorus (P) mg/dL | 0.466 p < 0.01 | 0.242 p < 0.05 | 0.202 p < 0.05 |
| Calcium (Ca) mg/dL | -0.356 p < 0.01 | -0.245 p < 0.05 | -0.167 p > 0.05 |
| Lead (Pb) µg/L | 0.064 p > 0.05 | -0.132 p > 0.05 | -0.055 p > 0.05 |
| Magnesium (Mg) µg/L | 0.414 p < 0.01 | 0.059 p > 0.05 | 0.259 p < 0.01 |

and calcium ($p < 0.05$). The duration of contraception showed significant correlation ($p < 0.05$) with zinc, phosphorus and also with copper, iron, selenium and magnesium at $p < 0.01$.

Table 6 shows the correlation between age, body mass index, duration of contraception and serum trace elements in OCP, injectables and IUD participants. No significant correlation exists between BMI and zinc ($r = 0.223, p > 0.05$) and manganese ($r = 0.373, p > 0.05$). A positive significant correlation was observed between iron and BMI ($r = -0.590, p < 0.01$). Selenium level was inversely significantly correlated with age ($r = -0.398, p < 0.01$) and body mass index ($r = -0.427, p < 0.01$). Similarly, lead level was significantly negatively correlated with age ($r = -0.478, p < 0.01$) and magnesium showed a negative relationship with age but insignificant negative correlation with BMI ($r = -0.172, p > 0.05$).

Zinc showed negative significant correlation with age ($r = -0.187, p < 0.01$), iron with age ($r = -0.552, p < 0.01$) and selenium with age ($r = -0.564, p < 0.01$). Cadmium showed positive significant correlation with age and duration of contraception. Likewise magnesium showed positive cor-

relation with age ($r = 0.399, p < 0.05$). Manganese showed a negative significant relationship with duration of contraception.

DISCUSSION

Zinc

In this study, serum zinc level was significantly reduced in participants on contraceptives compared to that of the control group. This result is similar to that of Ynsa *et al* (10) in which low levels of zinc was reported for individuals on oral and injectable contraceptive methods.

Holt (11) also reported that oral contraceptives were associated with decreased zinc levels. The reason for this reduction in zinc level is not well known but it may be attributed to redistribution of blood zinc with resultant increase in erythrocyte zinc as a result of oral contraceptive use (2, 12). The physiological implications of the alterations in serum zinc levels in women using contraceptives are not well documented. Decrease in serum zinc levels are reported to result not only in increased platelet aggregation but may also increase serotonin release (13). The incidence of venous thrombus in combination pill users is known to be four to seven times higher than in a control population. As a whole, contraceptive may alter the post-absorptive utilization of zinc. Circulating zinc level may be reduced while some tissue level may be increased. Also the release of zinc from tissues may be depressed in OCP users. It is suggested that these changes may alter the dietary zinc requirement. Zinc level in intra-uterine device users showed no significant difference with that of the control group. Adequate zinc level is believed to be important in immune function. Thus, the low level of zinc reported in our study consequent to oral contraceptive pill or the injectable may promote zinc deficiency which may have negative impact on immune function and integrity and nutritional status of contraceptive users.

Copper

Since the introduction of oral contraceptives, many metabolic side effects have been reported. Among the documented

Table 6: Correlation between serum trace elements and age, body mass index and duration on contraceptives in participants on oral contraceptives, injectable and uterine devices

| Parameters | Oral contraceptives | | | Injectables contraceptives | | | Uterine device | | |
|------------|---------------------|--------------------------|--------------------|----------------------------|--------------------|--------------------|--------------------|--------------------------|--------------------|
| | Age (Year) | BMI (Kg/m ²) | Duration (months) | Age (Year) | BMI (Kg/m) | Duration (Months) | Age (Year) | BMI (Kg/m ²) | Duration (Months) |
| Zn mg/dL | -0.187 p > 0.05 | 0.223 p > 0.05 | 0.059 p > 0.05 | -0.187 p < 0.01 | 0.098 p > 0.05 | -0.333 p > 0.05 | -0.070 p > 0.05 | 0.349 p > 0.05 | 0.144 p < 0.05 |
| Cu mg/dL | 0.010 p > 0.05 | -0.024 p > 0.05 | -0.128 p > 0.05 | -0.242 p > 0.05 | 0.029 p > 0.05 | 0.268 p > 0.05 | -0.358 p > 0.05 | -0.054 p > 0.05 | 0.103 p < 0.05 |
| Mn µg/L | 0.003 p > 0.05 | 0.373 p < 0.01 | -0.050 p > 0.05 | 0.158 p > 0.05 | 0.070 p > 0.05 | 0.144 p > 0.05 | 0.070 p > 0.05 | 0.209 p > 0.05 | -0.406 p < 0.05 |
| Fe µg/L | 0.110 p > 0.05 | 0.590 p < 0.01 | 0.113 p > 0.05 | -0.552 p < 0.01 | 0.153 p > 0.05 | -0.275 p > 0.05 | 0.033 p < 0.05 | -0.432 p < 0.05 | 0.179 p > 0.05 |
| Se µg/L | -0.398 p < 0.01 | -0.427 p < 0.01 | 0.142 p > 0.05 | -0.564 p < 0.01 | -0.390 p > 0.05 | 0.041 p > 0.05 | -0.279 p > 0.05 | 0.410 p < 0.05 | -0.031 p < 0.05 |
| Cd µg/L | 0.221 p > 0.05 | -0.159 p > 0.05 | -0.271 p > 0.05 | 0.431 p < 0.05 | -0.049 p > 0.05 | 0.591 p < 0.01 | 0.453 p > 0.05 | -0.318 p > 0.05 | -0.036 p > 0.05 |
| Ph mg/dL | 0.205 p > 0.05 | -0.092 p > 0.05 | -0.100 p > 0.05 | 0.170 p > 0.05 | -0.028 p > 0.05 | 0.160 p > 0.05 | 0.165 p > 0.05 | 0.375 p > 0.05 | 0.075 p > 0.05 |
| Ca mg/dL | 0.110 p > 0.05 | 0.146 p > 0.05 | -0.005 p > 0.05 | 0.242 p > 0.05 | -0.239 p > 0.05 | 0.198 p > 0.05 | -0.148 p > 0.05 | -0.305 p > 0.05 | -0.092 p > 0.05 |
| Pb µg/L | -0.478 p < 0.01 | -0.039 p > 0.05 | -0.133 p > 0.05 | 0.372 p > 0.05 | -0.122 p > 0.05 | -0.083 p > 0.05 | 0.125 p > 0.05 | -0.569 p < 0.05 | -0.128 p > 0.05 |
| Mg µg/L | -0.388 p < 0.01 | -0.172 p > 0.05 | -0.192 p > 0.05 | 0.399 p < 0.05 | -0.390 p > 0.05 | -0.184 p > 0.05 | -0.040 p > 0.05 | -0.254 p > 0.05 | -0.188 p > 0.05 |

Zn – Zinc, Cu – Copper, Mn – Manganese, Fe – Iron, Se – Selenium, Cd – Cadmium, Ph – Phosphorus, Ca – Calcium, Pb – Lead, Mg – Magnesium.

effects of oral contraceptives are elevations in serum levels of copper (12). This study showed that contraceptives are associated with increased serum copper level. The mean serum level of copper was significantly higher in all the contraceptive groups than in the control group. The increase in serum copper level in intra-uterine device users is much higher than those on oral contraceptives and injectables. This may suggest an extra source of copper, possibly from a slow release of copper from the copper coil on copper T into the blood stream. This may further explain the weak (but significant) positive correlation between serum copper and the duration of contraception. Liukko *et al* (14) noted that copper levels rose significantly while using oral contraceptives over a two-year period but returned to initial levels after the contraceptives were discontinued. Berg *et al* (4) reported that while elevated serum copper level was found in users of most types of contraceptives, the elevation was more pronounced among women on intra-uterine device. Increased serum copper levels are usually mopped up by its binding to ceruloplasmin. Increased level of copper by individuals on contraceptives may be related to a saturation of ceruloplasmin or a reduction in plasma ceruloplasmin level. Excess level of circulating copper may have adverse effects on liver which may lead to hepatolenticular degeneration (12). The effects of contraceptives on nutritional status have received little attention in Nigeria and effects of contraceptive agents on copper levels have not been examined under controlled conditions. Whether changes in copper levels reflect the consequence of nutritional utilization or that

of contraceptives remain an important question and needs to be investigated further.

Manganese

Heese *et al* (15) reported no significant effect of any contraceptive on the serum manganese level but agreed that oral contraceptives may interfere with manganese absorption. The clinical implication of this potential interaction is yet uncertain. In this study, the findings are similar to those of Heese *et al* (15).

Iron

A significant increased level of iron was observed in participants on contraceptives compared with the control group. However, oral contraceptive users and injectable users showed significant increase when compared with those on IUD (IUD showed significant lower levels than the control group).

The increased iron level observed in participants on oral contraceptives or injectables may be associated with the decreased menstrual blood flow which usually occurs in these subjects (16).

Selenium

There was a significant reduction in the serum selenium level of participants on oral contraceptives and those on injectables. There seems to be a mechanism induced by the components of either oral contraceptives or injectables which interfere with the absorption or metabolism of selenium (2,

17). Heese *et al* (15) similarly reported a significant reduction in serum selenium levels among 200 female students placed on oral contraceptives for a period of 3 months compared with the control group.

Cadmium

Although serum cadmium levels showed a positive correlation with duration of contraception, its level in the three groups of participants on contraceptives and the control group were not significantly different. This implies that the effect of various contraceptive methods on the absorption, distribution and metabolism of cadmium is minimal. This result is similar to the report of other workers who have stated that no significant variation is associated with the use of contraceptives and observed serum cadmium levels (17).

Calcium

A critical assessment of the participants on contraceptives showed that those on oral contraceptives demonstrated significantly increased serum calcium levels over the control group while serum calcium levels in injectables users and those on intra-uterine device did not differ significantly from those of the control group. Similar significant increase in calcium level was observed in oral contraceptive participants as reported by Hergenroeder *et al* (18) and Hartard *et al* (19). It is possible that the use of oral contraceptives is most often associated with increased absorption of calcium. Serum calcium showed no significant correlation with the duration of contraception in the combined contraceptive participants (oral contraceptive, injectables and intra-uterine device groups).

Meanwhile, a negative significant association existed between serum calcium and age and body mass index in participants on contraceptives. Apart from increased absorption of calcium, it is also possible that oral contraceptives play a role in calcium homeostasis which brings about a net effect of increased calcium mobilization from the bone leading to bone demineralization. This may predispose individuals on these contraceptives to osteoporosis (9).

Phosphorus

There was a significant reduction in the concentration of serum phosphorous in participants on contraceptives as a whole compared to the control group. This observation was also seen in participants on oral contraceptive pills as analysis showed that only the oral contraceptive group had a significantly reduced serum phosphorus level compared with the control group. Those on injectables and intra-uterine device users had similar values to the control group. This observation is related to the fact that calcium and phosphate move in opposite directions therefore significantly elevated serum calcium level is reciprocated by a significantly reduced serum inorganic phosphate level (9). Hameed *et al* (9) also reported significant reduction in the serum phosphorus levels in women on oral contraceptives. This also

may explain the weak negative but significant association observed between oral contraceptive use and duration.

Lead

The effect of contraceptive use on serum lead level is not significant because serum lead levels in the various contraceptive groups were similar to that of the control group. We are therefore tempted to say that the absorption, distribution and metabolism of lead is independent of the use of contraceptives. A similar finding was observed by Heese *et al* (15) who reported that serum lead level was not affected by oral contraceptives.

Magnesium

A significantly decreased serum magnesium level was observed in the combined participants on contraceptives when compared with the control group. This is in agreement with the study of Hameed *et al* (9) who reported significantly decreased serum levels of magnesium. However, it should be noted that only the participants on oral contraceptives showed this trend. This implies that oral contraceptives play some role either at the level of absorption, distribution or metabolism of magnesium. On the other hand, participants on intra-uterine device had significantly elevated serum magnesium levels than the control group.

CONCLUSION

This study established that there is a significant reduction in the levels of some trace elements in individuals on various contraceptive methods when compared with the control group. Our findings confirmed disturbance in the distribution of trace elements in participants on contraceptives. It showed a significant decrease in the serum concentration of zinc, selenium, phosphorus and magnesium while a significant increase in serum level was observed for copper, iron, cadmium and selenium.

Recommendations

- * It is suggested that these contraceptives should be used with care and with proper investigations of the women before and during therapy especially those on long term use.
- * Dietary supplements may be necessary, especially where levels are significantly reduced in some individuals on contraceptives. This should be borne in mind by the prescribing physician, dietician or nutritionally trained healthcare provider.
- * Further research in the field of micronutrients and trace metals in individuals on various methods of contraception is recommended.

Limitation of the study

The perception of women towards the use of contraceptives in the study locality is quite discouraging. During the course of this study, it was apparent that women in the locality have

little information about family planning and those who attended the family planning clinic were afraid of being stigmatized by friends, husbands and their family members for approaching health-workers for education on family planning. Few women hardly attend family planning clinic on a regular basis thereby making it difficult to recruit a large sample size for the study. Further studies on determining vitamins A, C, E and beta-carotene are envisaged.

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