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Some biochemical and metabolic alterations associated with selected contraceptive methods in reproductive-age women: A Case-Control Study in Osun state, Nigeria

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Abstract

Background: Contraceptive use, while essential for family planning, has been anecdotally associated with various physiological changes. This study investigated the effects of selected hormonal and non-hormonal contraceptive methods on key biochemical markers of oxidative stress, antioxidant defense, and plasma proteins in reproductive-age women.

Methods: A case-control study was conducted in Osun State, Nigeria, involving 200 women aged 20–49. Participants were divided into four groups (n=50 each): women using injectable contraceptives (Depot Medroxyprogesterone Acetate), women with contraceptive implants, women with an intrauterine contraceptive device (IUCD), and a control group of non-users. Plasma levels of total protein, albumin, antioxidant vitamins (A, C, E), and enzymatic antioxidants (superoxide dismutase [SOD], catalase [CAT], glutathione peroxidase [GPx]), as well as lipid peroxidation (malondialdehyde [MDA]), were measured using standard spectrophotometric methods. Statistical significance was determined using one-way ANOVA, with a p-value < 0.05 considered significant.

Results: No significant changes were observed in any of the measured parameters in the IUCD group when compared to the control group. However, in both the injectable and implant groups, plasma levels of MDA and GPx were significantly increased ($p<0.05$), while levels of SOD, CAT, reduced glutathione (GSH), antioxidant vitamins (A, C, E), total protein, and albumin were significantly decreased ($p<0.05$) compared to the control.

Conclusion: The use of hormonal contraceptives (injectables and implants) is associated with a significant state of oxidative stress, characterized by increased lipid peroxidation and a depleted antioxidant defense system. These findings suggest that steroidal hormones may induce a pro-oxidant state, potentially increasing the long-term risk of related diseases. We recommend routine biochemical monitoring for women on long-term steroidal hormonal contraception.

Keywords: Contraception; Oxidative Stress; Antioxidants; Lipid Peroxidation; Physiological Proteins

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1. Introduction

1.1. Contraception and Global Health

The introduction of modern contraceptive methods has been a major public health achievement, empowering women with control over their fertility and contributing to global health targets, including the reduction of maternal and infant mortality (UNFPA, 2023). These methods, including oral pills, injectables, implants, and intrauterine devices (IUDs), have diverse mechanisms of action and varying levels of efficacy.

1.2. Physiological Effects of Hormonal Contraceptives

While widely used, hormonal contraceptives (HCs) have been linked to a range of physiological and metabolic alterations. The exogenous hormones, primarily progestins and/or estrogens, can influence various bodily systems, including the cardiovascular, hepatic, and metabolic pathways. A growing body of research has focused on the impact of HCs on oxidative balance the equilibrium between pro-oxidants (reactive oxygen species, ROS) and antioxidants (Fallah et al., 2011).

1.3. Oxidative Stress and its Implications

Oxidative stress occurs when there is an imbalance in favor of pro-oxidants, leading to cellular damage. It has been implicated in the pathogenesis of various chronic diseases, including cardiovascular disease, cancer, and neurodegenerative disorders. Hormonal shifts, such as those induced by HCs, can disrupt this delicate balance. Previous studies have shown that synthetic hormones may increase the production of reactive oxygen species or deplete the body's antioxidant reserves (Palan et al., 2010).

1.4. Study Rationale and Objective

Despite extensive research, there is a notable scarcity of data from sub-Saharan African populations, where genetic, nutritional, and environmental factors may influence the physiological response to HCs differently. This study aims to fill this gap by assessing the effects of three widely used contraceptive methods (injectables, implants, and IUCDs) on plasma total protein, albumin, antioxidant status, and lipid peroxidation in a cohort of reproductive-age women in Osun State, Nigeria.

2. Materials and Methods

2.1. Study Area and Population

This study was conducted at the Family Planning Clinic of the State Specialist Hospital in Ilesha, Osun State, Nigeria. The study population consisted of 200 healthy reproductive-age women (20-49 years old).

2.2. Inclusion and Exclusion Criteria

Participants were selected based on their contraceptive method and were confirmed to be in good health, with no history of chronic diseases or concurrent use of other medications, including antioxidant supplements.

2.3. Ethical Considerations and Consent

Ethical approval was obtained from the Ethics and Research Committee of the Osun State Hospitals' Management Board. All participants provided informed written consent after a detailed explanation of the study's objectives and procedures.

2.4. Sample Size

The minimum sample size of 200 was calculated using the formula $n = Z^2PQ/E^2$, based on a contraceptive prevalence rate of 15% in Nigeria (NDHS, 2013).

2.5. Study Design

This was a cross-sectional, case-control study. Participants were grouped as follows:

- Group 1: Injectable Contraceptive users (n=50)
- Group 2: IUCD users (n=50)
- Group 3: Implant users (n=50)

- Group 4: Non-contraceptive users (Control, n=50)

2.6. Sample Collection and Analysis

2.6.1. Sample Collection

5 ml of venous blood was collected from each participant into a lithium-heparinized bottle. Plasma was separated and stored at -40°C.

2.6.2. Biochemical Assays

Proteins: Total protein and albumin concentrations were measured using standard spectrophotometric methods (Cheesbrough, 1999).

2.6.3. Antioxidant Vitamins

Vitamins A (Beta-Carotene Bleaching Assay), C (Briggs, 1981), and E (Desai et al., 1984) were determined spectrophotometrically.

2.6.4. Enzymatic Antioxidants

The activities of Catalase (Aebi, 1984), Superoxide Dismutase (SOD) (McCord and Fridovich, 1969), and Glutathione Peroxidase (GPx) (Rotruck et al., 1973), as well as reduced glutathione (GSH) (Beutler and Kelly, 1963), were measured using spectrophotometric methods.

2.6.5. Lipid Peroxidation

Plasma lipid peroxidation was assessed by measuring malondialdehyde (MDA) levels via the thiobarbituric acid (TBA) method (Ohkawa et al., 1979).

2.6.6. Statistical Analysis

Data were presented as mean ± SEM and analyzed using one-way ANOVA. P-values < 0.05 were considered statistically significant.

3. Results

3.1. Effect of IUCD

As shown in Figure 1 and Table 1, there were no significant differences ($p > 0.05$) in plasma levels of total protein, albumin, antioxidant vitamins, or enzymatic antioxidants (SOD, CAT, GPx, GSH) in the IUCD group compared to the control group. Plasma MDA levels also remained unchanged.

3.1.1. Effect of Hormonal Contraceptives

- **Proteins:** In both the implant and injectable groups (Figures 2 and 3), there was a significant decrease ($p < 0.05$) in plasma levels of total protein and albumin compared to the control.
- **Oxidative Stress Markers:** As detailed in Tables 2 and 3, both implant and injectable contraceptive users showed a significant increase ($p < 0.05$) in plasma MDA levels, indicating elevated lipid peroxidation.
- **Antioxidant Status:** Users of both hormonal contraceptives exhibited a significant decrease ($p < 0.05$) in the activities of SOD, CAT, and the levels of antioxidant vitamins (A, C, E) and GSH. However, a significant increase in GPx activity was observed in these groups.

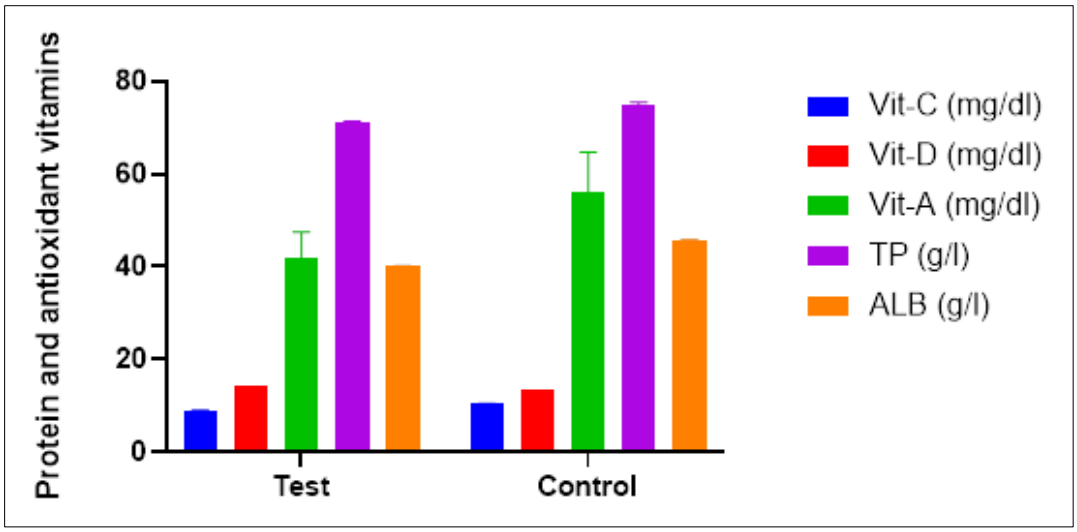

Figure 1 Effect of intra-uterine contraceptive device (iucd) on physiological proteins and antioxidant vitamins in women of reproductive age

Values were expressed as mean ± standard error of mean of three (3) determinants. Vit C=Vitamin C, Vit E=Vitamin E, Vit A= Vitamin A, TP = Total protein, ALB = Albumin. Test subject. =Women usingintra-uterine contraceptive device (IUCD) contraceptive method. Control subjects = Women who were not using any contraceptive method. n=number of subjects.

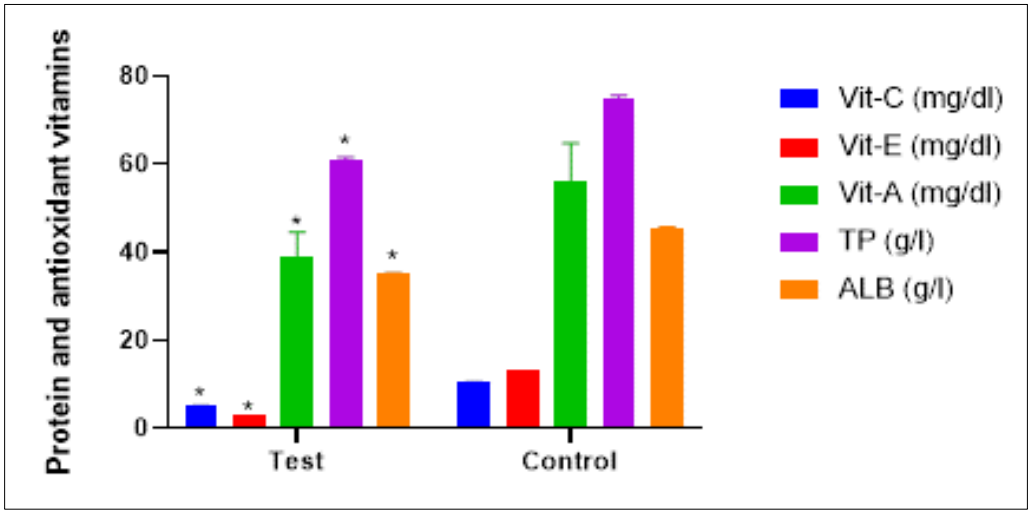

Figure 2 Effect of implant contraceptive method on physiological proteins and antioxidant vitamins in women of reproductive age

Values were expressed as mean ± standard error of mean of three (3) determinants. Vit C=Vitamin C, Vit E=Vitamin E, Vit A= Vitamin A, TP = Total protein, ALB = Albumin. Test subject. =Women using Implant contraceptive method. Control subjects = Women who were not using any contraceptive method. n=number of subjects. Figures with * are significantly different at ($p<0.05$) compared with control.

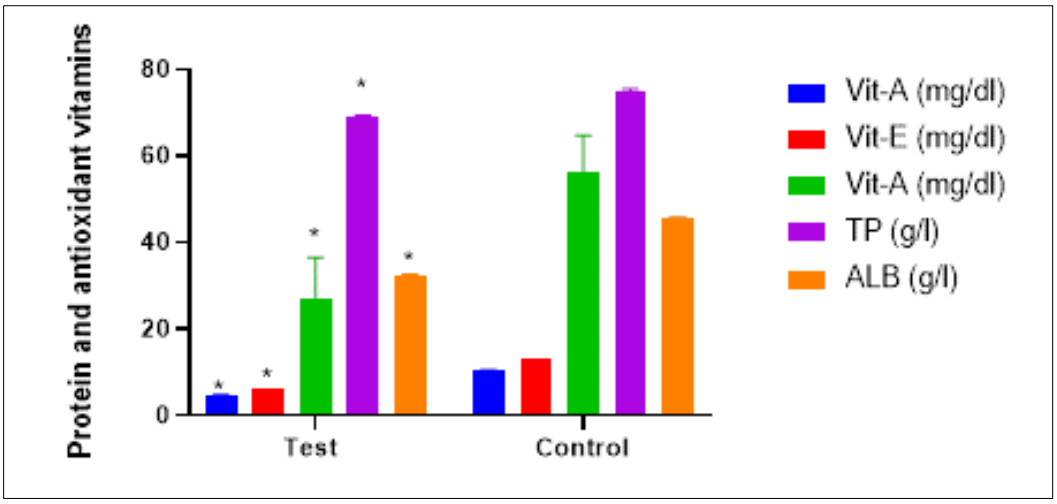

Figure 3 Effect of injectable contraceptive method on physiological proteins and antioxidant vitamins in women of reproductive age

Values were expressed as mean ± standard error of mean of three (3) determinants. Vit C=Vitamin C, Vit E=Vitamin E, Vit A= Vitamin A, TP = Total protein, ALB = Albumin. Test subject. =Women using Implant contraceptive method. Control subjects = Women who were not using any contraceptive method. n=number of subjects. Figures with * are significantly different at ($p<0.05$) compared with control.

Table 1 Showing the effect of IUCD contraceptive method on plasma levels of lipid peroxidation and enzymatic antioxidants in women of reproductive age

Parameters	SOD(Unit/L)	CAT(Unit/L)	MDA (mol/L)	GSH (mol/L)	GPX(Unit/L)
Test subjects (n=50	0.670±0.045[a]	0.020±0.001[a]	2.866±0.291[a]	0.128±0.013	0.870±0.500[a]
Control Subjects(n=50)	1.368±0.056	0.025±0.011	1.652±.321	0.145±0.024	0.860±0.437

Values were expressed as mean ± standard error of mean of three (3) determinants. Test subject =Women using IUCD contraceptive method. Control subjects = Women who were not using any contraceptive method. N = number of subjects. MDA = Malonaldehyde, SOD = Superoxide dismutase, CAT = Catalase, GSH = Reduced glutathione, GPX = Glutathione peroxidase. Values with superscript are significantly different: a=$p<0.05$(compared with control)

Table 2 Showing the effect of injectable contraceptive method on plasma levels of lipid peroxidation and enzymatic antioxidants in women of reproductive age

Parameters	SOD (Unit/L)	CAT (Unit/L)	MDA (mol/L)	GSH (mol/L)	GPX (Unit/L)
TestSubject(n=50)	0.503±0.048[a]	0.023±0.007[a]	2.032±0.363[a]	0.102±0.012	0.869±0.326[a]
Control Subjects (n= 50)	1.368±0.056	0.025±0.011	1.652±.321	0.145±0.024	0.860±0.437

Values were expressed as mean ± standard error of mean of three (3) determinants. Test subject =Women using injectable contraceptive method. Control subjects = Women who were not using any contraceptive method. N = number of subjects. MDA = Malonaldehyde, SOD = Superoxide dismutase, CAT = Catalase, GSH = Reduced glutathione, GPX = Glutathione peroxidase. Values with superscript are significantly different: a=$p<0.05$(compared with control)

Table 3 Showing the effect of implant contraceptive method on plasma levels of lipid peroxidation and enzymatic antioxidants in women of reproductive age

Parameters	SOD (Unit/L)	CAT (Unit/L)	MDA (mol/L)	GSH (mol/L)	GPX (Unit/L)
Test subjects (n=50	0.670±0.045[a]	0.020±0.001[a]	2.866±0.291[a]	0.128±0.013	0.870±0.500[a]
Control Subjects(n=50)	1.368±0.056	0.025±0.011	2.866±.321	0.145±0.024	0.860±0.437

Values were expressed as mean ± standard error of mean of three (3) determinants. Test subject =Women using implant contraceptive method. Control subjects = Women who were not using any contraceptive method. N = number of subjects. MDA = Malonaldehyde, SOD = Superoxide dismutase, CAT = Catalase, GSH = Reduced glutathione, GPX = Glutathione peroxidase. Values with superscript are significantly different: a=p<0.05(compared with control)

4. Discussion

This study provides robust evidence that steroidal hormonal contraceptives, such as injectables and implants, significantly disrupt the oxidative balance in reproductive-age women, while the non-hormonal IUCD method does not. Our findings align with a growing body of literature that links exogenous hormones to pro-oxidant states.

4.1. IUCD vs. Hormonal Methods

The absence of significant biochemical changes in the IUCD group is expected, as this method primarily prevents pregnancy through a localized inflammatory response and physical barrier, without systemic hormonal effects.

4.2. Hormonal-Induced Oxidative Stress

The significant increase in MDA levels in hormonal contraceptive users is a key finding, as MDA is a widely accepted marker of lipid peroxidation and cellular membrane damage (Bishay et al., 2021). This is likely a direct result of hormonal-induced oxidative stress, as synthetic hormones can increase the generation of reactive oxygen species (ROS) (Kaur et al., 2022).

4.3. Depletion of Antioxidant Defenses

The observed decrease in SOD, CAT, GSH, and antioxidant vitamins (A, C, E) indicates a compromised antioxidant defense system. This is a critical finding, as it suggests that the body's natural defense against free radical damage is overwhelmed. A recent study found that hormonal contraceptive users had significantly lower levels of total antioxidant capacity, supporting our results (Işik et al., 2021). The significant decrease in SOD, in particular, may be due to the inverse relationship between high estrogen levels and SOD activity (Kumar et al., 2010), leading to an inability to neutralize superoxide anions effectively.

4.4. Increase in GPx Activity

The elevated GPx activity in hormonal contraceptive users is a seemingly paradoxical but explainable finding. GPx is an enzyme that detoxifies hydrogen peroxide and lipid hydroperoxides. Its increased activity could be a compensatory mechanism in response to the heightened oxidative stress, attempting to neutralize the high levels of pro-oxidants and prevent further damage (Fallah et al., 2011).

4.5. Impact on Plasma Proteins

The significant decrease in plasma total protein and albumin levels is also a noteworthy result. Albumin is a major antioxidant in plasma, capable of scavenging free radicals. Its depletion could further contribute to the state of oxidative stress. This decrease may be due to the influence of estrogen on liver protein synthesis or an increased catabolism of these proteins in response to systemic stress (Gleichmann et al., 1973).

Limitations and Future Directions

This study is limited by its cross-sectional design, which does not allow for the evaluation of long-term effects over time. Future longitudinal studies are needed to monitor these biochemical changes throughout the duration of contraceptive use. Furthermore, research into the specific dose-dependent effects of different hormonal formulations and the influence of nutritional status on these parameters would be valuable.

5. Conclusion

This study demonstrates that hormonal contraceptives (injectables and implants) induce a state of oxidative stress in reproductive-age women in Osun State, Nigeria, as evidenced by increased lipid peroxidation and a significant reduction in both enzymatic and non-enzymatic antioxidant defenses. The observed decrease in total protein and albumin further compounds this oxidative imbalance. These findings underscore the importance of integrating biochemical monitoring into the healthcare plan for women on long-term steroidal hormonal contraceptives to mitigate the potential long-term risks of oxidative stress-related diseases.

Compliance with ethical standards

Disclosure of conflict of interest

No conflict-of-interest to be disclosed.

Statement of informed consent

Informed consent was obtained from all individual participants included in the study.

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