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Assessing the Effect of Hormonal Contraceptives on Oxidative Stress and Lipid Metabolism in Reproductive Age Women

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ABSTRACT

Women of reproductive age frequently use hormonal contraceptives for family planning and regulating menstrual cycles. There is growing apprehension, however, regarding the potential long-term metabolic and cardiovascular effects of these contraceptives due to their impact on oxidative stress and lipid metabolism. **Objective:** To assess the impact of hormonal contraceptive use on oxidative stress markers and lipid profile parameters in reproductive-age women. **Methods:** This comparative cross-sectional study encompassed 150 women aged 18 to 40 years, evenly split into users and non-users of hormonal contraceptives. From each participant, blood samples were drawn to assess oxidative stress Markers Malondialdehyde (MDA), Total Antioxidant Capacity (TAC), Superoxide Dismutase (SOD), catalase, Glutathione Peroxidase (GPx), as well as lipid profile parameters such as total cholesterol, triglycerides, LDL-C, HDL-C, and the LDL/HDL ratio. For the analysis, appropriate parametric and non-parametric tests were applied for the statistical comparisons. **Results:** Hormonal contraceptive users had significantly higher MDA levels and reduced TAC, SOD, GPx, and catalase activity, indicating elevated oxidative stress and impaired antioxidant defenses ($p < 0.001$). Lipid profile analysis revealed significantly increased total cholesterol, triglycerides, and LDL-C, along with reduced HDL-C and elevated LDL/HDL ratios among users compared to non-users ($p < 0.001$). **Conclusions:** Hormonal contraceptive use in reproductive-age women is associated with increased oxidative stress and an unfavorable lipid profile. These biochemical alterations may raise the risk of cardiovascular complications with long-term use. Regular monitoring and preventive strategies, including lifestyle counseling and antioxidant support, may help mitigate these risks.

INTRODUCTION

Hormonal contraceptives are an effective family planning method and regulatory tool in reproductive health used globally [1]. These agents, which mainly contain synthetic estrogens and progestins, influence the female reproductive system by suppressing ovulation, changing the secretion from the cervix, and altering the endometrium [2]. While the mitigative role they play in reducing unintentional pregnancies and managing menstruation cycles is well documented, emerging studies indicate that these synthetic hormones may have wider physiological impacts [3]. The possible effects of hormonal contraceptives on the balance of oxidative stress within the body as an emerging concern is noteworthy [4]. Within the context of medicine, oxidative stress is defined as an imbalance between the Reactive Oxygen Species (ROS) production and an organism's ability to neutralize these harmful byproducts using various antioxidant defenses. Estrogens, which have a unique mix of both pro- and antioxidant effects, may metabolically produce Reactive Oxygen Species (ROS) in hepatic and peripheral tissues [5,

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6]. This increased oxidant stress can lead to damage of lipids and proteins as well as DNA injury which contributes to and/or exacerbates many pathological states. For this reason, the use of hormonal contraceptives may increase women's risk of developing condition associated with chronic oxidative stress, especially with long-term use [7]. At the same time, contraceptive hormones are known to affect lipid metabolism [8]. Lipid changes associated with the use estrogen-containing contraceptives include increased hepatic lipoprotein synthesis resulting in total cholesterol, LDL-C, and triglyceride increases and reduction of HDL-C [9, 10]. Such changes, particularly when combined with other metabolic or lifestyle factors, might increase the risk of cardiovascular events in women over the long term. Nevertheless, the degree and reliability of these changes are different for specific formulations, populations, and individual health conditions which underscores the importance of investigating biochemical consequences in different demographic settings [11]. Although oxidative stress and lipid changes have been studied separately, limited research explores their combined effects in women using hormonal contraception [12]. Given the rising use of these contraceptives in developing countries like Pakistanwhere dietary habits and antioxidant status vary there was a pressing need to examine their interconnected impact in this population. Thus, this study aimed to evaluate the influence of hormonal contraceptives on oxidative stress markers and lipid profile parameters among women of reproductive age. By comparing hormonal contraceptive users with non-users, we aimed to provide a more comprehensive understanding of the biochemical changes associated with contraceptive use and to identify potential early indicators of cardiovascular or metabolic risk.

Hormonal contraceptives are widely used by women of reproductive age for family planning and menstrual regulation; however, their potential metabolic and biochemical effects remain a growing concern. Evidence suggests that these contraceptives may influence oxidative stress pathways and alter lipid metabolism, potentially increasing the risk of cardiovascular complications with long-term use. Although several studies have examined oxidative stress or lipid changes independently, limited research has evaluated their combined impact among hormonal contraceptive users. Moreover, there is a scarcity of population-specific data from developing countries such as Pakistan, where lifestyle and nutritional factors may influence oxidative balance and lipid metabolism. The findings could help inform safer prescribing practices and guide the development of targeted preventive strategies, such as antioxidant supplementation or periodic lipid monitoring.

METHODS

This comparative cross-sectional study was conducted to evaluate the effects of hormonal contraceptive use on oxidative stress markers and lipid profile in women of reproductive age. The study was carried out at Health Net Hospital, Peshawar, from May 2023 to October 2024. Pakistani women were selected due to the unique interplay of dietary patterns, environmental exposures (urban pollution, low antioxidant intake), and limited health awareness regarding long-term contraceptive use, all of which may influence oxidative stress and lipid metabolism. Thus, localized data were necessary to tailor clinical recommendations. Ethical approval was granted by the Ethics Review Committee of Health Net Hospital (Ref: 3059/HNH/HR). Written informed consent was obtained, and confidentiality was maintained via coded identifiers. The sample size was calculated using OpenEpi software, based on a previously reported standardized effect size of 0.5 for Malondialdehyde (MDA) levels, with 95% confidence and 80% power, yielding 75 participants per group (total = 150) [13]. A non-probability purposive sampling technique was used to recruit participants from gynecology outpatient clinics. Inclusion criteria were women aged 18–40 years, using hormonal contraceptives for at least 6 months or not using any in the past year, and willing to provide a blood sample. Exclusion criteria were females with diagnosed metabolic, autoimmune, or chronic inflammatory diseases; current infections; and use of antioxidants, corticosteroids, or lipid-lowering drugs. Data were collected over a period of six months. After obtaining consent, participants were interviewed using a structured questionnaire to document demographic data (age, BMI, parity, marital status, education, physical activity, and smoking history) and clinical details, including type of hormonal contraceptive used Combined Oral Contraceptive Pills (COCPs), injectables (depot medroxyprogesterone acetate), or subdermal implants along with duration of use and menstrual regularity. Contraceptive use duration was verified via both self-report and cross-checked with medical prescription records whenever available. Participants were grouped as follows Group 1: Hormonal contraceptive users (n = 75) and Group 2: Non-users (n = 75). After 8–12 hours of overnight fasting, 5 mL of venous blood was collected. Serum was separated for lipid profile testing (total cholesterol, triglycerides, LDL-C, HDL-C, LDL/HDL ratio). Plasma was used for oxidative stress markers MDA via TBARS assay, TAC via FRAP method, SOD via colorimetric assay, Catalase via hydrogen peroxide decomposition and GPx using ELISA-based coupled enzyme reaction kits. Assays followed manufacturer protocols in the hospital biochemistry lab. Laboratory staff were blinded to

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participant group status. All tests were done in duplicate using the same instruments and reagents, with random re-testing of 10% samples (CV <10%) to ensure reliability. Data were analyzed using IBM SPSS version 25.0. Continuous variables were expressed as mean ± SD or median (IQR), and categorical variables as frequencies (%). Normality was assessed with the Shapiro–Wilk test and histograms. Group differences were tested using independent t-tests or Mann–Whitney U tests (for non-parametric data), and Chi-square or Fisher's exact test for categorical variables. Effect sizes were reported with Cramér's V where applicable. Significance was set at p <0.050, with 95% confidence intervals provided where relevant. Complete-case analysis was used for missing data; no imputation was applied as data completeness exceeded 95%.

RESULTS

The comparison of demographic and clinical characteristics between groups revealed that the mean age of users was significantly higher than non-users (29.8 ± 5.49 vs. 27.8 ± 5.48 years, p = 0.025), suggesting a possible age-related trend in hormonal contraceptive use. However, there was no statistically significant difference in Body Mass Index (BMI) between the two groups (p = 0.420). Marital status, parity, and education level showed no meaningful differences either, indicating similar socio-demographic backgrounds. Notably, smoking status showed a borderline significant difference (p = 0.050), with a higher proportion of smokers among non-users. Although this association was weak, Cramér's V (0.160) suggests a small effect size. Physical activity levels were also comparable between the groups, with no statistical significance observed (p = 0.596) (Table 1).

Table 1: Comparison of Demographic and Clinical Characteristics between Hormonal Contraceptive Users and Non-Users (n = 150)

Variables	Hormonal Users Mean ± SD / Frequency (%)	Non-Users Mean ± SD / Frequency (%)	p-Value
Age (Years)	29.8 ± 5.49	27.8 ± 5.48	0.025[a]
BMI (Kg/m^2)	24.68 ± 3.40	25.12 ± 3.33	0.420[b]
Marital Status (Married)	69 (92.0)	65 (86.7)	0.290
Parity ≥ 2	46 (61.3)	40 (53.3)	0.322
Education Level ≥ Secondary	42 (56.0)	48 (64.0)	0.381
Smoking (Yes)	2 (2.7)	8 (10.7)	0.050[c]
Physical Activity (Moderate /Active)	40 (53.3)	46 (61.3)	0.596

[a]Mann-Whitney Utest
[b]Independent samples t-test
[c]Chi-square test; Cramér's V = 0.160 (small effect size)

Among the hormonal users, combined oral contraceptive pills (COCPs) were the most commonly used method (40%), followed by injectables (33.3%) and implants (26.7%). The overall rate of menstrual irregularity was 18.7%. No meaningful statistical relationship was found between contraceptive type and menstrual irregularity (p = 0.523) and Cramér's V indicated a negligible effect size (0.131). The mean duration of contraceptive use among these women was 20.6 ± 9.18 months, with a range from 6 to 35 months, indicating diverse long-term exposure among the participants (Table 2).

Table 2: Distribution of Contraceptive Methods, Duration of Use, and Menstrual Irregularity among Hormonal Contraceptive Users Only (n = 75)

Variable	Sub-categories	Frequency (%) / Mean ± SD	p-Value	Cramer's V
Menstrual Irregularity	Yes	14 (18.7)	-	-
	No	61 (81.3)	-	-
Type of Hormonal Contraceptive	COCP	30 (40.0)	0.523	0.131
	Implant	20 (26.7)	-	-
	Injectable	25 (33.3)	-	-
Duration of Use (Months)	Mean ± SD	20.6 ± 9.18	-	-
	Range	6 – 35	-	-

Analysis of oxidative stress biomarkers showed significant differences between hormonal contraceptive users and non-users. Malondialdehyde (MDA), a key marker of lipid peroxidation, was substantially higher in users (4.83 ± 0.34 vs. 3.93 ± 0.32 nmol/mL; p < 0.001), indicating elevated oxidative stress. In contrast, total antioxidant capacity (TAC) was significantly lower in users (1.40 ± 0.19 vs. 1.60 ± 0.20 mmol/L; p <0.001), suggesting reduced systemic antioxidant defenses. Furthermore, enzymatic antioxidants Antioxidant enzymes namely SOD, catalase, and GPx were notably reduced among hormonal contraceptive users, with all differences statistically significant (p <0.001). This suggests a trend toward greater oxidative burden and diminished enzymatic defense in this population (Table 3).

Table 3: Comparison of Oxidative Stress Markers between Groups (n = 150)

Variable	Hormonal User Mean ± SD	Non-User Mean ± SD	p-Value	95% CI of Mean Difference
MDA (nmol/mL)	4.83 ± 0.34	3.93 ± 0.32	<0.001	0.797 – 1.008
TAC (mmol/L)	1.40 ± 0.19	1.60 ± 0.20	<0.001	-0.269 – -0.140
SOD (U/mL)	123.10 ± 8.99	133.81 ± 10.49	<0.001	-13.86 – -7.56
Catalase (U/mL)	30.21 ± 2.62	32.24 ± 3.29	<0.001	-2.99 – -1.06
GPx (U/mL)	52.52 ± 4.94	58.52 ± 3.99	<0.001	-7.44 – -4.55

Lipid profile analysis revealed marked alterations among hormonal contraceptive users compared to non-users. Median total cholesterol levels were significantly higher in users, as evidenced by the Mann–Whitney U test (p < 0.001), although confidence intervals for the difference could not be calculated due to non-parametric analysis. Triglyceride and LDL-C levels were both significantly elevated in users (163.04 ± 21.73 vs. 142.99 ± 20.78 mg/dL and 129.20 ± 8.24 vs. 114.77 ± 11.14 mg/dL, respectively; p < 0.001 for both), while

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HDL-C was significantly lower in users (43.66 ± 3.45 vs. 48.35 ± 4.21 mg/dL; $p < 0.001$). These differences reflect a more atherogenic lipid profile in hormonal users. Additionally, the LDL/HDL ratio was significantly higher in users (2.93 ± 0.30 vs. 2.30 ± 0.29; $p < 0.001$, Mann–Whitney U), further supporting the potential adverse cardiovascular implications of hormonal contraceptive use (Table 4).

Table 4: Comparison of Lipid Profile Parameters between Hormonal Contraceptive Users and Non-Users (n = 150)

Lipid Parameter	Hormonal User (Mean ± SD)	Non-User (Mean ± SD)	Test Used	p-Value	95% CI of Mean Difference
Total Cholesterol (mg/dL)	209.07 ± 13.99	189.42 ± 16.65	Mann–Whitney U	<0.001	–
Triglycerides (mg/dL)	163.04 ± 21.73	142.99 ± 20.78	Independent t-test	<0.001	13.19 – 26.91
LDL-C (mg/dL)	129.20 ± 8.24	114.77 ± 11.14	Independent t-test	<0.001	11.27 – 17.59
HDL-C (mg/dL)	43.66 ± 3.45	48.35 ± 4.21	Independent t-test	<0.001	-5.93 – -3.45
LDL/HDL Ratio	2.93 ± 0.30	2.30 ± 0.29	Mann–Whitney U	<0.001	–

As depicted in figure 1, the oxidative stress marker MDA was considerably elevated among hormonal contraceptive users (4.83 ± 0.34 nmol/mL) compared to non-users (3.93 ± 0.32 nmol/mL), suggesting heightened lipid peroxidation. Conversely, all antioxidant markers TAC, SOD, Catalase, and GPx were consistently lower in users than in non-users. Specifically, mean TAC was reduced from 1.60 to 1.40 mmol/L, SOD from 133.81 to 123.10 U/mL, Catalase from 32.24 to 30.21 U/mL, and GPx from 58.52 to 52.52 U/mL. These statistically significant differences highlight a shift towards oxidative imbalance in hormonal users, potentially reflecting increased metabolic oxidative burden or decreased enzymatic defense activity. This clustered bar chart illustrates the mean concentrations of oxidative stress (MDA) and antioxidant defense markers (TAC, SOD, Catalase, GPx) in both groups. Hormonal users demonstrated significantly higher levels of MDA, indicating increased oxidative stress, alongside significantly reduced antioxidant levels across all markers measured. These trends support the hypothesis that hormonal contraceptive use may be associated with altered redox balance and compromised antioxidant capacity.

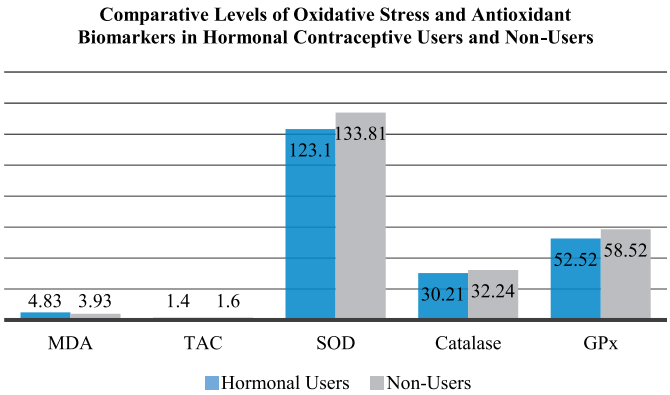

Figure 1: Comparative Levels of Oxidative Stress and Antioxidant Biomarkers in Hormonal Contraceptive Users and Non-Users

DISCUSSION

In this study, hormonal contraceptive users exhibited significantly elevated oxidative stress, reflected through higher MDA values and suppressed activities of antioxidant enzymes (SOD, GPx, Catalase, TAC), suggesting a compromised redox balance likely driven by estrogen-induced Reactive Oxygen Species (ROS). Moreover, we found a pronounced dysregulation of lipid metabolism, with increased total cholesterol, triglycerides, LDL-C, and reduced HDL-C levels among users indicating a shift toward an atherogenic lipid profile. These biochemical changes reinforce the hypothesis that hormonal contraceptive use can trigger oxidative imbalance and metabolic alterations that may raise long-term cardiovascular risks. These findings correlate with more established evidence. Sultan et al., in 2025 documented elevated MDA levels and diminished antioxidant enzyme activity in laboratory rodents treated with oral contraceptives [13]. Turki *et al.*, in 2023 reported systematic changes in the markers of oxidative stress with differing classes of hormonal contraceptives, supporting the association of contraceptive hormone use with disruption of the oxidative balance [14]. These results highlight the need to explore antioxidant supplementation strategies for long-term users and conduct mechanistic in vivo studies on protective interventions. On the metabolic side, Cagnacci *et al.*, in 2023 confirmed significant dyslipidemia in OCP users through a meta-analysis, while Quinn *et al.*, 2021 noted elevated total cholesterol levels in users, with variable changes in LDL-C after adjusting for confounders [15]. Counsel users on lifestyle interventions like diet and exercise; tailor contraceptive methods based on individual lipid profiles [16]. Drejza *et al.*, in 2022 further explained how estrogen exposure promotes oxidation of LDL, potentiating atherosclerosis. Co-treatment with antioxidants may reduce vascular damage [17]. Include MDA screening as a routine check in contraceptive health evaluations. Reductions in antioxidant enzymes were

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observed similarly supported by Hashemi *et al.*, in 2023, who demonstrated significant drops in SOD, catalase, and GPx among contraceptive users. Explore nutraceutical or pharmacologic antioxidant support to maintain redox balance [18]. To advance diagnostic precision, Zhang *et al.*, in 2024 proposed novel biomarkers for oxidative stress applicable in inflammation and hormone-related conditions [19]. Evaluate these emerging markers in future contraceptive safety trials. Santander *et al.*, (2024) stressed the need for advanced and standardized oxidative stress quantification techniques in human research [20]. Employ high-fidelity biochemical assays in future studies to enhance accuracy and comparability.

This study has several limitations, including its cross-sectional design, which limits the ability to establish causal relationships between hormonal contraceptive use and biochemical alterations. Additionally, the sample size was relatively small and drawn from a single healthcare facility, which may affect the generalizability of the findings. Variations in the type and duration of contraceptive use were not analyzed in detail, which could influence oxidative and metabolic outcomes. Future longitudinal studies with larger and more diverse populations are recommended to explore long-term biochemical effects and to evaluate potential preventive strategies such as antioxidant supplementation and regular metabolic monitoring.

CONCLUSIONS

This study demonstrated that hormonal contraceptive use in women within the fertility window was significantly linked with increased oxidative stress and adverse lipid profile changes. Users exhibited elevated levels of MDA and reduced antioxidant defenses, including SOD, GPx, Catalase, and TAC. Additionally, unfavourable shifts in lipid parameters such as higher total cholesterol, triglycerides, LDL-C, and lower HDL-C were evident among users compared to non-users. These biochemical alterations suggest a potential increase in long-term cardiovascular and metabolic risks in women using hormonal contraception. Therefore, routine biochemical monitoring, lifestyle counselling, and consideration of antioxidant strategies may be crucial components of safe contraceptive use.

Authors' Contribution

Conceptualization: RIK
Methodology: AH, FS, SA[1]
Formal analysis: AH, FS, SA[1], SA[2]
Writing and Drafting: AM, RIK, SA[1], SA[2]
Review and Editing: AM, FS, RIK, SA[1], SA[2]

All authors approved the final manuscript and take responsibility for the integrity of the work

Conflicts of Interest

All the authors declare no conflict of interest.

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