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Changes in Physiological and Biochemical Parameters in Women During the Spontaneous Menstrual Cycle and Following Oral Contraceptives

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ABSTRACT

Oral contraceptive pills (OCPs) are widely used for birth control and management of various gynaecological conditions. While their primary mechanism is to regulate the reproductive cycle, they are known to exert broader systemic effects. However, comparative data on physiological, hormonal, and metabolic parameters between OCP users and women with natural menstrual cycles remain limited. **Objectives:** To evaluate and compare selected physiological signs, reproductive hormones, and metabolic indicators among women experiencing natural menstrual cycles and those on OCPs. **Methods:** A comparative cross-sectional study was conducted involving 80 women aged 18–40 years, divided into two equal groups: natural cycle (n=40) and OCP users (n=40). Data were collected on demographic details, vital signs, and laboratory measures including estrogen, progesterone, LH, FSH, SHBG, TSH, testosterone, HDL cholesterol, and fasting glucose. Statistical analysis was performed using SPSS version 26.0. **Results:** Significant differences were observed in estrogen, progesterone, LH, and SHBG levels, with OCP users showing notably altered hormonal profiles. OCP users also had higher systolic blood pressure and HDL cholesterol, while glucose levels were slightly elevated. No significant differences were found in prolactin, FSH, or haemoglobin. **Conclusions:** It was concluded that OCP use is associated with measurable changes in several physiological, hormonal, and metabolic parameters. These findings highlight the importance of routine monitoring in long-term users and support individualized contraceptive counselling based on clinical risk profiles.

INTRODUCTION

The menstrual cycle is a coordinated physiological event controlled by the Action of several hormones like estrogen, progesterone, luteinizing hormone, and follicle-stimulating hormone (LH and FSH, respectively) [1]. For women with menstruating cycles, these hormones exhibit a precise pattern, controlling ovulation along with the changes in endometrial tissue. With the advent of combined oral contraceptive pills (OCPs), these hormonal patterns are intentionally disrupted to suppress ovulation and control the menstrual cycle [2]. OCPs have been prescribed for contraception and also for the treatment of menstrual irregularities, acne, polycystic ovary syndrome (PCOS), and dysmenorrhea [3]. Commonly used OCPs have an effect beyond the reproductive system, which includes alterations in cardiovascular parameters (blood pressure and pulse), endocrine changes (SHBG and testosterone), and metabolism, including lipid profile and glucose control. There are many studies evaluating the impact of OCPs on

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individual hormones or risk markers, but there is scant information analysing the multi-observational framework of physiology, dynamics, and metabolism side-by-side in a single population [4, 5]. Moreover, variations in study design, population characteristics, and duration of OCP use have led to inconsistent findings, particularly regarding effects on TSH, prolactin, or HDL cholesterol. There is also a paucity of data from South Asian populations where hormonal contraceptive use patterns and baseline physiological profiles may differ due to genetic, dietary, or environmental factors. These gaps underscore the need for well-controlled studies that examine the collective impact of OCP use across multiple domains in comparison to natural cycles [6].

This study aimed to compare physiological (vital signs), hormonal (estrogen, progesterone, LH, FSH, etc.), and metabolic (HDL, glucose) parameters between women with natural menstrual cycles and those using oral contraceptive pills. This study generates comprehensive local data and provides a clearer understanding of the systemic effects of OCP use.

METHODS

This was a comparative cross-sectional study conducted at Health Net Hospital, Hayatabad, Peshawar, from 11 August 2022 to 11 February 2023. Ethical clearance for this study was granted by the Ethics Review Committee of Health Net Hospital, Peshawar, under reference number 3098/HNH/HR. All participants gave written informed consent before data collection began. The study involved 80 premenopausal women, who were divided into two equal groups. Group 1 (natural menstrual cycle group): women with regular menstrual cycles and no history of hormonal contraceptive use for the past six months. Group 2 (OCP users group): Women using combined oral contraceptive pills for at least three consecutive months. In the OCP group, participants were required to have used combined oral contraceptive pills continuously for at least three months before enrolment. OCP use was confirmed through participant interview and verification of pill packaging or prescription details (brand name, dosage, and start date). Only users of monophasic combined OCPs were included to ensure consistency. For the natural menstrual cycle group, participants confirmed no use of hormonal contraceptives (oral, injectable, implant, or patch) within the past six months. This was verified through a detailed contraceptive history questionnaire to exclude any recent or ongoing hormonal intervention. A non-probability purposive sampling method was used. The required sample size for this comparative study was determined using the standard formula for comparing two independent means. Sample size was calculated using the formula: $n = [2 \times (Z\alpha/2 + Z\beta)^2 \times \sigma^2] / \Delta^2$ Where: $Z\alpha/2 = 1.96$ for 95% confidence level, $Z\beta = 0.84$ for 80% power, $\sigma = 35$ (standard deviation of estrogen levels based on Wang et al., 2016) [7], $\Delta = 25$ (expected mean difference in estrogen levels), substituting: $n = [2 \times (1.96 + 0.84)^2 \times 1225] / 625 = 30.73$ per group. Thus, the minimum required sample size was approximately 31 participants per group. To enhance statistical robustness and account for potential dropouts or missing data, the sample size was increased to 40 participants per group, resulting in a total of 80 women. This number aligns with existing literature and ensures adequate power to detect clinically meaningful differences in hormonal and physiological parameters. Inclusion criteria included women aged 18–40 years, having a body mass index (BMI) between 18.5 and 29.9 kg/m^2, Regular menstrual cycles (for group 1), and currently using OCPs for more than 3 months (for group 2). Exclusion criteria included history of endocrine disorders (e.g., PCOS, thyroid disease), use of hormonal therapy other than OCPs, chronic illnesses such as diabetes or hypertension, smoking, or alcohol consumption. Data collection was divided into three main components: clinical evaluation, laboratory investigations, and questionnaire-based history. Participants completed a pretested questionnaire that recorded demographic details (age, education, marital status), age at menarche, menstrual regularity, contraceptive history, duration of OCP use, and reported side effects. Vital signs were recorded by trained nursing staff using calibrated instruments: Pulse rate: measured at rest using a digital pulse oximeter. Blood pressure: measured twice in a seated position using a digital sphygmomanometer. Body temperature was recorded orally using a clinical thermometer. Respiratory rate was counted manually over one minute. Anthropometric measurements, height and weight, were recorded to calculate BMI using the formula: BMI=Weight (kg) ÷ Height (m)2. Venous blood samples (5–7 mL) were collected early morning after an overnight fast (8–10 hours). All samples were processed in the institutional diagnostic lab within 2 hours of collection. The following parameters were assessed: hormonal profile, estrogen (E2), progesterone, LH, FSH, prolactin, and TSH. All parameters were measured using electrochemiluminescence immunoassay (ECLIA) technology on the Cobas e411 analyzer (Roche Diagnostics). Additional hormonal and metabolic markers, SHBG and total testosterone, were analyzed via enzyme-linked immunosorbent assay (ELISA). HDL cholesterol and fasting blood glucose (FBG) were measured using standard automated biochemistry analyzers (Hitachi 902). The selection of hormones and metabolic markers (estrogen, progesterone, LH, FSH, TSH, SHBG, testosterone, HDL cholesterol, and fasting glucose) was based on their known physiological relevance and prior evidence indicating their sensitivity to hormonal contraceptive use. These markers represent key pathways influenced by OCPs, including the hypothalamic-pituitary-gonadal axis, thyroid regulation, androgen metabolism, and cardiometabolic risk profiles. To minimize variability due to natural hormonal fluctuations, blood samples for women in the natural

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menstrual cycle group were collected during the early follicular phase (day 5–7 of the cycle). For OCP users, samples were taken during days 5–7 of the active pill phase to ensure hormonal stability and comparability between groups. All testing kits and reagents were within quality control expiry dates, and internal quality assurance protocols were followed. All biochemical assays were performed by trained laboratory technicians who were blinded to participant group assignment to prevent measurement bias. The questionnaire was reviewed by two subject experts and pilot tested on a subset of 10 participants for clarity and face validity. Cronbach's alpha was used to assess internal consistency, yielding a value of 0.81, indicating good reliability. The instruments used for physiological and biochemical measurement were calibrated before each data collection day to ensure consistency. All data were entered and analyzed using SPSS version 26.0. Descriptive statistics were used to summarize participant characteristics. Variables included in the analysis were demographic and categorical variables, marital status, education level, age group, BMI category, menstrual regularity, OCP duration, and side effects. Continuous variables were Pulse rate, systolic and diastolic blood pressure, body temperature, respiratory rate, serum estrogen, progesterone, LH, FSH, prolactin, TSH, SHBG, testosterone, HDL cholesterol, and fasting blood glucose. The Shapiro-Wilk test was applied to assess normality for each continuous variable within both groups. Since the majority of the variables followed a normal distribution ($p>0.05$), comparisons between groups were performed using the independent samples t-test. For categorical variables, the Chi-square test was used, and where applicable, Cramér's V was calculated to determine the strength of association. Cohen's d was computed for variables that showed statistically significant differences to quantify effect size (small: d=0.2, medium: d=0.5, large: d=0.8 or above). A multiple linear regression model was employed to determine the independent predictors of serum estrogen levels, with variables such as group assignment (natural vs. OCP), age, and BMI entered as predictors. A $p<0.05$ value was considered statistically significant throughout all analyses.

RESULTS

The distribution of age, BMI, marital status, and education level was compared between women following natural menstrual cycles and those using oral contraceptives. Most participants were aged 20–29 years, with no significant difference in age distribution between groups ($p=0.710$, Cramér's V=0.093, very weak association). BMI showed a significant difference ($p=0.001$), with a moderate association (Cramér's V=0.435); more OCP users were overweight. Marital status and education level did not differ significantly between groups ($p=0.369$ and 0.356, respectively), indicating weak associations (Table 1).

Table 1: Demographic Characteristics of Participants (n=80)

Variables	Categories	Natural (n=40)	OCP Users (n=40)	Total (n=80)	p-value	Cramér's V	Strength
Marital Status	Married	24 (60.0%)	20 (50.0%)	44 (55.0%)	0.369	0.101	Weak
	Unmarried	16 (40.0%)	20 (50.0%)	36 (45.0%)			
Education Level	High School	12 (30.0%)	10 (25.0%)	22 (27.5%)	0.356	0.161	Weak
	Graduate	18 (45.0%)	14 (35.0%)	32 (40.0%)			
	Postgraduate	10 (25.0%)	16 (40.0%)	26 (32.5%)			
Age Group	< 20	6 (15.0%)	4 (10.0%)	10 (12.5%)	0.710	0.093	Very weak
	20–29	30 (75.0%)	33 (82.5%)	63 (78.8%)			
	30–39	4 (10.0%)	3 (7.5%)	7 (8.8%)			
BMI Category	Normal	32 (80.0%)	15 (37.5%)	47 (58.8%)	0.001	0.435	Moderate
	Overweight	8 (20.0%)	24 (60.0%)	32 (40.0%)			
	Obese	0 (0.0%)	1 (2.5%)	1 (1.3%)			

Age at menarche was similar between groups ($p>0.05$), with the majority falling between 12–14 years. Menstrual regularity data were only applicable to the natural cycle group, where 90% reported regular cycles. Among OCP users, half had used contraceptives for 6–12 months. Nearly half reported side effects, with nausea being common. Group-exclusive variables were excluded from significance testing (Table 2).

Table 2: Menstrual and Contraceptive History of Participants

Variables	Categories	Natural Cycle (n=40)	OCP Users (n=40)	Total (n=80)	p-value
Age at Menarche	<12 Years	14 (35.0%)	15 (37.5%)	29 (36.3%)	0.415
	12–14 Years	13 (32.5%)	17 (42.5%)	30 (37.5%)	
	>14 Years	13 (32.5%)	8 (20.0%)	21 (26.3%)	
Menstrual Regularity*	Regular	36 (90.0%)	–	36 (45.0%)	–
	Irregular	4 (10.0%)	–	4 (5.0%)	
OCP Duration†	<6 months	–	10 (25.0%)	10 (12.5%)	–
	6–12 months	–	20 (50.0%)	20 (25.0%)	
	>12 months	–	10 (25.0%)	10 (12.5%)	
Side Effects Reported†	Yes	–	18 (45.0%)	18 (22.5%)	–
	No	–	22 (55.0%)	22 (27.5%)	

Results showed detailed comparison of physiological,

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hormonal, and metabolic parameters between women with natural menstrual cycles and those using oral contraceptive pills (OCPs). OCP users showed a significantly higher pulse rate (79.32 ± 6.75 bpm) compared to the natural cycle group (74.71 ± 5.57 bpm; p=0.001, Cohen's d=0.74). Similarly, systolic blood pressure was higher among OCP users (120.33 ± 6.32 mmHg vs. 111.51 ± 8.93 mmHg; p<0.001, d=1.14), as was diastolic blood pressure (77.42 ± 6.05 mmHg vs. 72.05 ± 4.46 mmHg; p<0.001, d=1.01). No significant differences were observed in body temperature (98.35 ± 0.64 °F vs. 98.13 ± 0.55 °F; p=0.095) or respiratory rate (17.57 ± 1.40 vs. 16.92 ± 1.64 breaths/min; p=0.061). Hormonal analysis revealed that OCP users had significantly lower estrogen levels (106.60 ± 38.36 pg/mL) compared to those with natural cycles (186.41 ± 45.82 pg/mL; p<0.001, d=1.89), progesterone (5.01 ± 1.98 ng/mL vs. 12.07 ± 4.44 ng/mL; p<0.001, d=2.05), and LH (4.70 ± 1.55 mIU/mL vs. 8.16 ± 2.90 mIU/mL; p<0.001, d=1.49). Differences in FSH (7.27 ± 2.39 vs. 8.11 ± 2.86 mIU/mL; p=0.161), prolactin (15.54 ± 5.18 vs. 15.35 ± 3.64 ng/mL; p=0.856), and haemoglobin (12.29 ± 1.21 vs. 12.43 ± 1.14 g/dL; p=0.599) were not statistically significant. However, TSH was slightly elevated in OCP users (2.89 ± 0.94 µIU/mL) compared to the natural group (2.33 ± 0.92 µIU/mL; p=0.010, d=–0.60). In terms of metabolic and additional hormonal markers, OCP users had significantly higher SHBG levels (71.9 ± 17.3 nmol/L vs. 49.7 ± 10.6 nmol/L; p<0.001, d=1.55) and HDL cholesterol (58.0 ± 10.5 mg/dL vs. 52.2 ± 8.1 mg/dL; p=0.007, d=0.619), but lower total testosterone (38.3 ± 4.8 ng/dL vs. 43.2 ± 6.6 ng/dL; p<0.001, d=0.849). Fasting blood glucose was also modestly but significantly elevated in the OCP group (90.5 ± 6.6 mg/dL vs. 86.3 ± 7.7 mg/dL; p=0.011, d=0.586). These results indicate that OCP use has a measurable influence on cardiovascular, hormonal, and metabolic functions in women (Table 3).

Table 3: Comparison of Physiological, Hormonal, and Metabolic Parameters Between Natural Cycle and OCP Users

Parameters	Natural Cycle (Mean ± SD)	OCP Users (Mean ± SD)	p-value	Cohen's d / Effect Size
Physiological Parameters				
Pulse Rate (bpm)	74.71 ± 5.57	79.32 ± 6.75	0.001	0.74 (Medium)
Systolic BP (mmHg)	111.51 ± 8.93	120.33 ± 6.32	<0.001	1.14 (Large)
Diastolic BP (mmHg)	72.05 ± 4.46	77.42 ± 6.05	<0.001	1.01 (Large)
Body Temperature (°F)	98.13 ± 0.55	98.35 ± 0.64	0.095	–
Respiratory Rate	16.92 ± 1.64	17.57 ± 1.40	0.061	–
Hormonal Parameters				
Estrogen (pg/mL)	186.41 ± 45.82	106.60 ± 38.36	<0.001	1.89 (Large)
Progesterone (ng/mL)	12.07 ± 4.44	5.01 ± 1.98	<0.001	2.05 (Large)
LH (mIU/mL)	8.16 ± 2.90	4.70 ± 1.55	<0.001	1.49 (Large)
FSH (mIU/mL)	8.11 ± 2.86	7.27 ± 2.39	0.161	–
Prolactin (ng/mL)	15.35 ± 3.64	15.54 ± 5.18	0.856	–
TSH (µIU/mL)	2.33 ± 0.92	2.89 ± 0.94	0.010	–0.60 (Very small)
Hemoglobin (g/dL)	12.43 ± 1.14	12.29 ± 1.21	0.599	–
Metabolic and Additional Hormones				
SHBG (nmol/L)	49.7 ± 10.6	71.9 ± 17.3	<0.001	1.55 (Large)
Total Testosterone (ng/dL)	43.2 ± 6.6	38.3 ± 4.8	<0.001	0.849 (Large)
HDL Cholesterol (mg/dL)	52.2 ± 8.1	58.0 ± 10.5	0.007	0.619 (Moderate)
Fasting Blood Glucose (mg/dL)	86.3 ± 7.7	90.5 ± 6.6	0.011	0.586 (Moderate)

Linear regression revealed that oral contraceptive use significantly predicted lower estrogen levels (β = –82.92, p<0.001). Age and BMI did not contribute significantly to the model (p>0.4). The model accounted for nearly 49% of the variance in estrogen (R^2=0.486), reinforcing the independent impact of OCP use on estrogen suppression (Table 4).

Table 4: Linear Regression Analysis Predicting Estrogen Levels

Variables	β Coefficient (B)	95% Confidence Interval	p-value
Oral Contraceptive Use	–82.92	–104.37 to –61.48	<0.001
Age (Years)	–1.00	–3.50 to 1.49	0.425
Body Mass Index (kg/m^2)	2.03	–3.15 to 7.22	0.437
Constant (Intercept)	244.30	112.55 to 376.04	<0.001

DISCUSSION

This study compared key physiological, hormonal, and metabolic parameters between women undergoing natural menstrual cycles and those using oral contraceptive pills (OCPs). The findings revealed several statistically significant differences, indicating that OCPs exert considerable effects on systemic health markers. Starting with physiological parameters, pulse rate, systolic blood pressure, and diastolic blood pressure were all significantly higher in OCP users. These findings align with those of Collomp *et al.*, who reported increased cardiovascular reactivity among OCP users due to synthetic estrogen components [8]. Similarly, a study by D'Souza *et al.*, showed that oral contraceptives may elevate blood pressure by promoting fluid retention and altering vascular tone [9]. This trend is clinically important, as even modest elevations in blood pressure can increase long-term cardiovascular risk [10]. The hormonal profile from this study indicates a marked suppression of endogenous estrogen, progesterone, LH, and FSH among OCP users. These findings relate to the previously established theory that OCPs suppress gonadotropin secretion to avoid

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ovulation [11]. A similar degree of hormonal suppression is documented by Khan *et al.*, who showed substantial decreases in FSH and LH after three months of OCP use [12]. Notably, OCP users had slightly elevated TSH levels, which Jamil *et al.*, and Leonard *et al.*, reported, proposing that alterations in thyroxine-binding globulin by estrogen may modulate feedback regulation of thyroid hormones on the thyroid [13, 14]. SHBG levels were significantly elevated in the OCP group, consistent with the literature that attributes this to hepatic stimulation by synthetic estrogens [9]. Elevated SHBG may bind more circulating androgens, thereby reducing their bioavailability. This may explain the slightly lower total testosterone levels seen in OCP users in our sample, which mirrors the findings of Pereira *et al.*, who observed reduced androgenicity with combined oral contraceptive use [15]. Metabolic changes were also evident. HDL cholesterol levels were significantly higher among OCP users, possibly reflecting the influence of ethinylestradiol, known to improve lipid profiles [16]. At the same time, a modest but significant increase in fasting blood glucose was observed, which was consistent with findings by Ihalainen *et al.*, that OCPs can slightly impair insulin sensitivity in predisposed individuals [11]. This dual effect on lipids and glucose suggests a nuanced metabolic impact of hormonal contraceptives. Menstrual regularity and timing of menarche did not differ significantly between groups, though previous studies have reported mixed results. For instance, Krog *et al.*, found that age at menarche can influence OCP initiation [17], while Blake *et al.*, emphasized that modern low-dose OCPs typically result in regular withdrawal bleeding patterns [18]. Our study supports the notion that menstrual regularity is primarily altered before OCP use rather than as a consequence of it. The regression analysis further confirmed that oral contraceptive use was a strong negative predictor of estrogen levels, even after adjusting for age and BMI. This supports the endocrine-disrupting potential of synthetic hormones, as shown in experimental and clinical work by Löfberg *et al.*, [19]. Although BMI did not significantly predict estrogen levels in our sample, prior research Boamah-Kaali *et al.*, has shown that higher adiposity may alter hormone metabolism, indicating the need for further stratified analyses [20]. The observed hormonal suppression and metabolic shifts underline the importance of individualized contraceptive counselling, especially for women with pre-existing endocrine or metabolic concerns. As noted by Ahmed *et al.*, understanding physiological responses to hormonal contraceptives helps in tailoring methods that align with a woman's health profile and reproductive goals [21]. This study's strength lies in its detailed profiling across multiple physiological and biochemical domains. However, being cross-sectional, it cannot establish causality. Future longitudinal studies are needed to assess long-term changes and reversibility after discontinuation of OCPs, as suggested by Myers *et al.*, [1].

CONCLUSIONS

This study highlights significant differences in cardiovascular, hormonal, and metabolic parameters between women with natural menstrual cycles and those using oral contraceptives. OCP users exhibited elevated pulse and blood pressure, suppressed endogenous reproductive hormones, altered SHBG and testosterone levels, and modest changes in lipid and glucose metabolism. These findings emphasize the systemic effects of oral contraceptives and underscore the importance of individualized assessment and counseling before initiation. Aligning with the objective, the study provides a clearer understanding of how OCP use modulates internal physiology, guiding clinicians toward safer, more informed contraceptive choices.

Authors Contribution

Conceptualization: SA, FK, NF
Methodology: SA, FK, SY, RK
Formal analysis: FK, NF, SN, RK
Writing review and editing: SA, NF, SN, SY

All authors have read and agreed to the published version of the manuscript

Conflicts of Interest

All the authors declare no conflict of interest.

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