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EFFECT OF DIFFERENT FORMULATIONS OF ORAL CONTRACEPTIVE AGENTS ON LIPIDS AND CARBOHYDRATES METABOLISM IN NORMAL WOMEN AND WOMEN WITH PCOS

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ABSTRACT

Background

Oral contraceptive pills (OCPs) are frequently prescribed for menstrual cycle regulation and birth control, especially for women suffering from polycystic ovary syndrome (PCOS). While OCPs are effective in managing reproductive symptoms, the type of progestin used alters metabolic health in varying degrees. Because PCOS is characterized by an insulin resistant state along with lipid abnormality, it is important to study the metabolic implications of various contraceptive options in this population. In this study when comparing the two formulations ethinylestradiol and drospirenone versus ethinylestradiol and levonorgestrel, focus will be on lipid and carbohydrate metabolism on normal and PCOS women.

Methods

This study was conducted at Kuwait Teaching Hospital, Peshawar, in January 2024 as a comparative cross-sectional study. Out of the total 93 women, 93 were enrolled and grouped based on OCP type and clinical status. Blood samples were collected after fasting for lipid profile, glucose, insulin, HbA1c, and HOMA-IR. Data analysis was performed using SPSS version 25 and significance was set at $p < 0.05$.

Results
Among the groups, women with PCOS using levonorgestrel contraceptive OCPs exhibited the most pronounced increase in total cholesterol, LDL levels, fasting insulin, and HOMA-IR. Androgens' effect on lipids was more favorable. Insulin resistance increased the least with drospirenone. Normal women on drospirenone had the least amount of metabolic changes relative to the other women.
Conclusion
OCPs containing drospirenone appears to affect metabolic parameters more positively compared to those containing levonorgestrel, particularly in patients suffering from PCOS. This emphasizes the need to tailor contraceptive methods to women's specific needs and profile combining both endocrinology and metabolism.

Keywords
Polycystic ovary syndrome, oral contraceptive pills, levonorgestrel, drospirenone, insulin resistance, lipid metabolism, HOMA-IR

INTRODUCTION

Women's healthcare providers often prescribe oral contraceptive pills (OCPs) for managing menstruation, preventing pregnancy, acne, and, in some cases, even hormonal therapy. One of the common conditions that is managed with OCPs is Polycystic Ovary Syndrome (PCOS). 'PCOS is a prevalent and complex endocrine disease that affects a large number of women worldwide'. It usually presents with menses irregularity, clinical signs of hyperandrogenism, and polycystic ovaries on ultrasound. 'Reproductive features aside, PCOS has a stronger association with other systemic metabolic features like insulin resistance, dyslipidemia, or increased cholesterol levels, and greater risk of cardiovascular disease'[1, 2].

Combined Oral Contraceptives (COCs) play a significant role in managing the symptoms of PCOS, a condition that affects many women. They work by lowering androgen levels, regulating menstrual cycles, and easing the symptoms associated with the disorder. 'However, there are still concerns about how COCs impact a patient's metabolic health, which is an area that requires more research'. It's important to note that different progestins in oral contraceptive formulations can influence glucose metabolism, insulin sensitivity, and lipid metabolism in various ways. 'Levonorgestrel, a second-generation progestin, is known for its strong androgenic activity, which can lead to increased insulin resistance and unfavorable lipid profiles'. In contrast, Sprintec, which contains drospirenone, is thought to have a neutral or less detrimental effect on metabolic disturbances due to its anti-androgenic and anti-mineralocorticoid properties, making it a newer option worth considering [3-5].

The choice of formulation of OCPs is rarely tailored to the patient's metabolic risk profile. This imbalance is more concerning for PCOS patients who likely already have some metabolic derangement due to the disorder. Understanding the differential impacts of OCPs on metabolism in women with PCOS, as well as those without the condition, is essential for optimizing therapeutic outcomes and mitigating risks[6-8].

The aim of the study was to analyze and assess how two widely utilized contraceptive formulations: ethinylestradiol and levonorgestrel, and ethinylestradiol and drospirenone influence lipid and carbohydrate metabolism in normotensive women and those with PCOS. The results are expected to support better individualized contraceptive selection on the basis of reproductive and metabolic profile.

METHODOLOGY

This research took place at the Department of Obstetrics and Gynecology at Kuwait Teaching Hospital in Peshawar over one month, from January 1 to January 31, 2024. Using a non-probability purposive sampling method, we enrolled 93 women in the study. The main goal was to evaluate and compare how different formulations of oral contraceptives affect lipid and carbohydrate metabolism in women with PCOS as well as in women without the condition.

The Kuwait Teaching Hospital Peshawar's IRB granted approval to conduct this study. All participants were comprehensively briefed about the study's aims and processes and therefore provided an informed consent form. All participants' anonymity and confidentiality were maintained throughout the entire research process.

This study took a 'comparative cross-sectional approach'. The participants were divided into four groups based on their clinical conditions and the type of oral contraceptive they were prescribed. 'Group A consisted of healthy women who were given ethinylestradiol and levonorgestrel, while Group B included healthy women receiving ethinylestradiol and drospirenone'. 'Group C was made up of women diagnosed with PCOS who were prescribed ethinylestradiol and levonorgestrel, and Group D included women with PCOS taking the drospirenone formulation'.

To qualify for the study, women had to be between 18 and 35 years old and must have been on the prescribed oral contraceptive for at least three months. 'Those in the PCOS group were diagnosed using the Rotterdam criteria, which state that at least two of the following must be present: irregular menstrual cycles, signs or lab results showing hyperandrogenism, and polycystic ovarian changes seen on an ultrasound'. Women with known metabolic disorders, thyroid issues, diabetes, or those undergoing treatment for lowering lipids or improving insulin sensitivity were not included. Additionally, the study ruled out women who were pregnant or breastfeeding.

After getting informed consent, we gathered detailed demographic and clinical information using a structured form. This included factors like age, body mass index (BMI), marital status, education level, physical activity, smoking habits, and family history of PCOS. Clinical features such as menstrual regularity, acne, and hirsutism were recorded, and the Ferriman-Gallwey score was used to assess the severity of hirsutism.

Venous blood samples were collected after an overnight fast. Serum lipid profile including total cholesterol, LDL, HDL, triglycerides, and VLDL was measured using standard enzymatic methods. Carbohydrate metabolism was assessed by measuring fasting blood glucose, fasting insulin levels, and glycated hemoglobin (HbA1c). HOMA-IR was calculated using the formula: HOMA-IR = (Fasting insulin μIU/mL × Fasting glucose mg/dL) / 405

All samples were processed in the hospital laboratory using automated analyzers to ensure consistency and reliability of results.

Data were analyzed using SPSS version 25. Continuous variables were presented as mean ± standard deviation and compared using ANOVA or the independent t-test, as appropriate. Categorical variables were expressed as frequencies and percentages and compared using the chi-square test. A p-value of less than 0.05 was considered statistically significant.

RESULT

The demographic data show that the mean age across all four groups was comparable, with no statistically significant difference observed ($p = 0.47$). However, a notable distinction was seen in the BMI values, which were significantly higher in women with PCOS compared to normal participants ($p < 0.001$), indicating the typical association of PCOS with increased body weight. Marital status and educational background did not differ significantly among the groups. A strong family history of PCOS was understandably present only in the PCOS groups and absent in the normal groups, which was statistically significant ($p < 0.001$). While smoking was not prevalent, a significant difference

emerged in physical activity levels, with normal women showing higher rates of regular activity compared to those with PCOS (p = 0.01).

Table 1: Demographic Characteristics of Study Participants (n = 93)

Variable	Group A (n=23)	Group B (n=21)	Group C (n=25)	Group D (n=24)	*p*-value
Age (years), mean ± SD	27.6 ± 4.2	28.1 ± 3.9	26.8 ± 4.5	27.4 ± 4.0	0.47
BMI (kg/m²), mean ± SD	23.2 ± 2.5	24.0 ± 2.7	28.3 ± 3.2	29.1 ± 3.5	<0.001
Marital Status (Married %)	78.3%	81.0%	88.0%	91.6%	0.38
Education (Graduate %)	60.9%	66.7%	44.0%	50.0%	0.29
Family history of PCOS (%)	0%	0%	36.0%	41.6%	<0.001
Smoking status (Smokers %)	4.3%	0%	8.0%	4.1%	0.55
Physical activity (Active %)	39.1%	33.3%	12.0%	8.3%	0.01

Among the women diagnosed with PCOS, both groups (C and D) exhibited a high prevalence of menstrual irregularities, exceeding 90%, without a significant difference between them. Hirsutism scores were elevated in both groups but slightly higher in those using levonorgestrel-containing contraceptives, although the difference was not statistically meaningful (p = 0.36). Acne was commonly reported across both groups, affecting over half the participants. The average duration of PCOS diagnosis was also similar in both groups (p = 0.42), indicating a well-matched clinical baseline prior to initiating treatment.

Table 2: Clinical Characteristics (PCOS-specific groups only)

Variable	Group C (PCOS + Levonorgestrel)	Group D (PCOS + Drospirenone)	*p*-value
Menstrual irregularity (%)	92.0%	95.8%	0.63
Hirsutism (Ferriman Score, mean)	11.4 ± 2.2	10.8 ± 2.5	0.36
Acne presence (%)	64.0%	58.3%	0.66
Duration of PCOS (months)	14.6 ± 6.7	13.2 ± 5.9	0.42

The lipid profiles showed varying effects across the groups. Women with PCOS who received levonorgestrel-containing OCPs (Group C) experienced the most pronounced increases in total cholesterol and LDL levels post-treatment, with statistically significant changes (p = 0.01 and 0.008, respectively). In contrast, normal women using drospirenone-based pills (Group B) showed a modest and statistically insignificant rise in lipid parameters. Interestingly, HDL cholesterol decreased in the levonorgestrel groups but increased in those using drospirenone, with the overall HDL changes being significant (p < 0.001). Triglyceride levels also showed a rising trend in all groups except Group B, and this increase reached statistical significance (p = 0.02). These findings suggest that drospirenone may have a more favorable or neutral impact on lipid metabolism compared to levonorgestrel, particularly in PCOS patients.

Table 3: Lipid Profile Before and After OCP Use (All Groups)

Variable	Group A (Normal+Levo)	Group B (Normal+Dros)	Group C (PCOS+Levo)	Group D (PCOS+Dros)	*p*-value
Total Cholesterol	↑ 168 → 183 mg/dL	↑ 172 → 177 mg/dL	↑ 181 → 199 mg/dL	↑ 178 → 186 mg/dL	0.01
LDL Cholesterol	↑ 95 → 109 mg/dL	↑ 97 → 102 mg/dL	↑ 104 → 123 mg/dL	↑ 100 → 109 mg/dL	0.008
HDL Cholesterol	↓ 51 → 48 mg/dL	↑ 53 → 57 mg/dL	↓ 48 → 44 mg/dL	↑ 49 → 53 mg/dL	<0.001
Triglycerides	↑ 132 → 145 mg/dL	↔ 130 → 132 mg/dL	↑ 140 → 164 mg/dL	↑ 138 → 150 mg/dL	0.02
VLDL	↑ 26 → 29 mg/dL	↔ 26 → 26.4 mg/dL	↑ 28 → 32.8 mg/dL	↑ 27 → 30 mg/dL	0.03

↑ indicates statistically significant increase; ↓ indicates decrease; ↔ no significant change.

Regarding carbohydrate metabolism, the results highlight a significant increase in fasting insulin and HOMA-IR values in women with PCOS, particularly in those using levonorgestrel-containing contraceptives (Group C). The rise in HOMA-IR from 3.3 to 4.6 in this group was statistically significant ($p < 0.001$), pointing to an exacerbation of insulin resistance. Group D (PCOS + Drospirenone) also showed a rise, though to a lesser extent. Normal women exhibited minimal changes, with only Group A (Normal + Levonorgestrel) showing a slight increase in insulin resistance markers. HbA1c values followed a similar pattern, increasing more noticeably in PCOS groups, with a significant p-value of 0.01. These findings reinforce the known metabolic burden associated with PCOS and suggest that drospirenone may be metabolically safer in terms of insulin sensitivity.

Table 4: Carbohydrate Metabolism Before and After OCP Use

Variable	Group A	Group B	Group C	Group D	*p*-value
Fasting Glucose	↔ 88 → 90 mg/dL	↔ 86 → 87 mg/dL	↑ 93 → 101 mg/dL	↑ 92 → 95 mg/dL	0.04
Fasting Insulin	↑ 10.2 → 11.8 µIU/mL	↔ 9.8 → 10.1 µIU/mL	↑ 14.1 → 18.6 µIU/mL	↑ 13.5 → 15.3 µIU/mL	0.002
HOMA-IR	↑ 2.2 → 2.6	↔ 2.1 → 2.2	↑ 3.3 → 4.6	↑ 3.1 → 3.9	<0.001
HbA1c (%)	↔ 5.1 → 5.2	↔ 5.0 → 5.0	↑ 5.3 → 5.7	↑ 5.2 → 5.5	0.01

Weight gain was the most commonly reported side effect, especially in the PCOS groups, with nearly half of Group C participants experiencing an increase in body weight ($p = 0.01$). Other side effects such as headache, mood changes, and nausea were reported across all groups but did not differ significantly. While these adverse effects were generally mild, their presence underscores the importance of individualized contraceptive counseling, especially for women already dealing with hormonal imbalances like PCOS.

Table 5: Summary of Side Effects Reported During OCP Use

Side Effect	Group A (%)	Group B (%)	Group C (%)	Group D (%)	*p*-value
Weight gain	21.7%	14.3%	44.0%	33.3%	0.01
Headache	13.0%	9.5%	20.0%	16.7%	0.42
Mood changes	17.4%	14.3%	24.0%	20.8%	0.49
Nausea	8.7%	4.8%	12.0%	8.3%	0.66

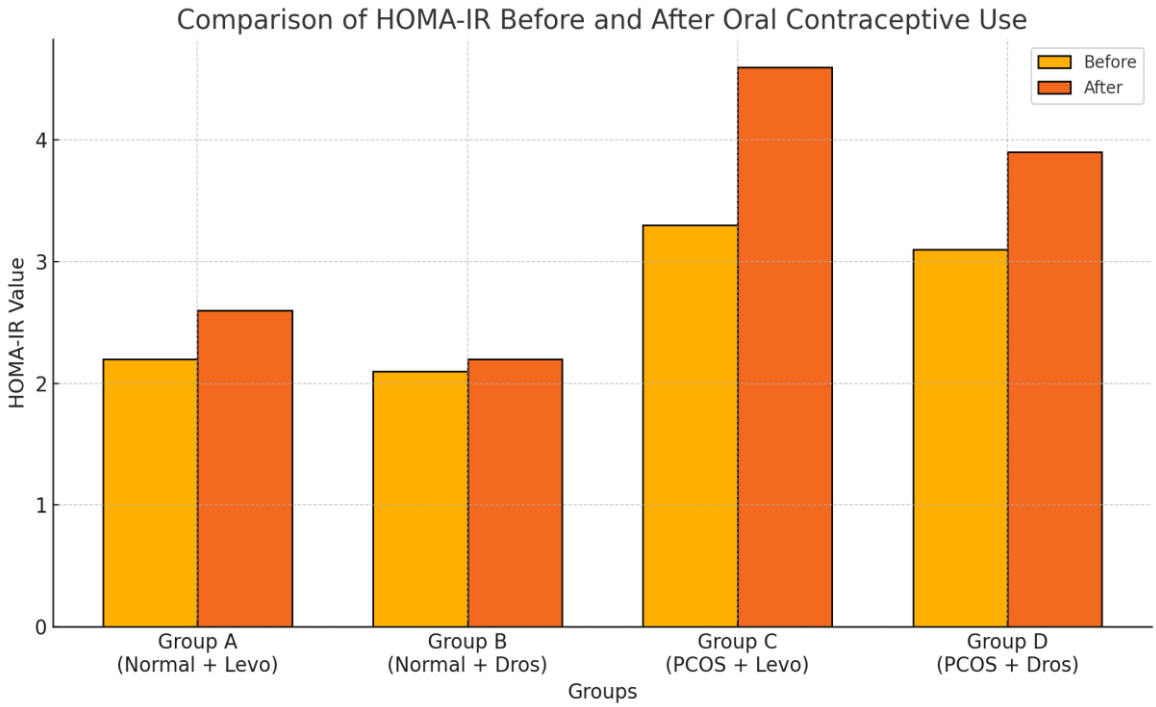

Figure 1

The graph shows that HOMA-IR values increased in all groups after oral contraceptive use, but the rise was most prominent in women with PCOS using levonorgestrel. In contrast, the increase was smaller in the drospirenone group. Normal women showed only slight changes. This suggests that drospirenone may have a lesser impact on insulin resistance compared to levonorgestrel, especially in women with PCOS.

DISCUSSION

The findings of this study highlight significant differences in metabolic responses to oral contraceptives depending on the type of progestin used and the presence of PCOS. Women with PCOS who were treated with levonorgestrel-containing pills experienced more pronounced adverse effects on both lipid and carbohydrate metabolism, compared to those receiving drospirenone. Normal women, in contrast, demonstrated minimal metabolic disturbances, especially when treated with drospirenone-based formulations.

The elevation in LDL and total cholesterol observed in the levonorgestrel groups aligns with earlier research suggesting that second-generation progestins like levonorgestrel have androgenic properties that may negatively impact lipid profiles [9-11]. In contrast, drospirenone, a newer progestin with anti-androgenic and anti-mineralocorticoid activity, was associated with either stable or improved HDL levels and a smaller rise in LDL, consistent with the studies, that reported a more favorable lipid profile in users of drospirenone-based OCPs[12-14].

In terms of carbohydrate metabolism, a significant increase in fasting insulin and HOMA-IR was noted particularly in PCOS patients using levonorgestrel. These results support previous observations that certain OCPs can worsen insulin resistance in women already predisposed due to underlying endocrine dysfunction [15-17]. Women with PCOS inherently have a higher risk of metabolic syndrome, and the type of hormonal contraceptive used can further influence this risk. Drospirenone appeared to be metabolically better tolerated in this group, reflecting the findings of studies, that reported that drospirenone-containing contraceptives caused less deterioration in insulin sensitivity in PCOS women compared to other progestins[18, 19].

Weight gain, a common concern associated with OCPs, was also reported more frequently in the levonorgestrel groups. This may be attributed to the water retention and appetite changes commonly associated with more androgenic progestins[20, 21]. Although mood changes and other minor side effects were recorded, their distribution was relatively even across all groups and not statistically significant, indicating that such effects may be more individual than formulation-dependent.

The results of this study really emphasize the importance of offering personalized contraceptive counseling, particularly for women facing PCOS. Choosing a formulation with a favorable metabolic profile, such as drospirenone, might be essential in lowering the risk of worsening insulin resistance and dyslipidemia in this at-risk group. Additionally, these findings highlight the necessity for regular monitoring of metabolic parameters in women using hormonal contraceptives, especially during long-term use.

The study focused on a one-month timeframe and was conducted at a single location. However, its findings align with global research and offer valuable local insights into the effects of OCPs on women's metabolism in Pakistan. To build on these results, future research should consider longer follow-up periods and involve larger, multicenter groups.

CONCLUSION

This study illustrates how the impact of oral contraceptives on metabolism differs based on type of progestin and the presence of PCOS. Women with PCOS filtered the lipid and carbohydrate metabolism of the body less positively with pills containing levonorgestrel compared to other pills. On the other hand, those using drospirenone-based formulations suffered less from increased insulin resistance and unfavorable lipid levels, demonstrating a safer metabolic profile. These results indicate that women with PCOS seeking contraceptive options may prefer those containing drospirenone. It is critical to select oral contraceptives with care, especially for those who are known to—or already—face risks related to metabolic complications.

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