A Prospective Follow up of Metabolic Changes among Obese Women using two Different Regimens of Ethinylestradiol/ Drospirenone Containing Contraceptive Pills

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Abstract

Objectives: To assess metabolic changes among obese women using 21/7 regimen Ethinylestradiol (EE) 30 ug/ Drospirenone (DRSP) 3mg compared to 24/4 regimen EE 20 ug/ DRSP 3mg over 24 months of use.

Methods: Obese women (Body mass index ≥ 30) who desired Combined oral contraceptive pills (COCs) were designated for two groups; group 1(n=94): 21/7 regimen Ethinylestradiol (EE) 30 ug/ Drospirenone (DRSP) 3mg one tablet daily for 21 days with 7 days off and group 2 (n=92): 24/4 regimen EE 20 ug/ DRSP 3mg one tablet daily for 24 days followed by a 4-day placebo period. Metabolic changes after 12 and 24 cycles of use was the main outcome measure.

Results: There was no significant difference between the two groups regarding body weight, waist circumference, blood pressure, fasting blood glucose, triglycerides and LDL cholesterol with significant decline in total cholesterol levels after 12 cycles (p<0.05) and 24 cycles (p<0.001) from baseline levels in both groups. Also, HDL cholesterol was significantly increased after 12 cycles (p<0.05) and 24 cycles (p<0.001) from baseline levels in both groups.

Conclusion: DRSP containing COCs do not induce detrimental metabolic changes and have favorable lipid profile among obese women when used for 12-24 cycles.

Keywords: Ethinylestradiol/drospirenone, blood lipids, obese women.

1. INTRODUCTION

Combined oral contraceptives (COC) are a well-established method of contraception with proven safety and efficacy for many decades [1]. New low-dose oral contraceptives containing - drospirenone have few health risks and many health benefits as drospirenone has an anti-mineralocorticoid and a slightly anti-androgenic action [2, 3].

The aim of this study was to assess metabolic changes among obese women using 21/7 regimen Ethinylestradiol (EE) 30 ug/ Drospirenone (DRSP) 3mg compared to 24/4 regimen EE 20 ug/ DRSP 3mg over 24 months of use.

2. MATERIALS AND METHODS

This prospective comparative study was conducted at departments of Obstetrics & Gynecology, in Menoufia University hospital, Menoufia governorate, Egypt; between the beginnings of August 2017 and September 2019. Before initiating the study, the local ethical review board approved the study protocol with all included participants signed the informed consent form, after thorough explanation of the study objectives.

Based on previous publication [4], 90 women in each group were needed in each group to detect a 10% significant change of metabolic criteria over 12 cycles of use according to 20% type II error with power set at 80%.

Healthy obese women with body mass index above 30 Kg/m² between the ages of 20 and 35 who requested oral contraceptive therapy, who had no medical contraindication to COCs therapy were invited to participate.

All included women neither were smokers, having criteria used for diagnosing the metabolic syndrome [5] nor, had used herbal remedies or blood lipid-lowering agents for weight reduction during the whole duration of the study. Participants were divided into two
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groups based on their choices regarding COCs regimen:

**Group 1 (n=94):** 21/7 regimen Ethinylestradiol 30 µg/ Drospirenone 3mg (Yasmin, Bayer Pharma AG, Berlin, Germany). One tablet daily for 21 days with 7 days off

**Group 2 (n=92):** 24/4 regimen Ethinylestradiol 20 µg/ Drospirenone 3mg (Yaz, Bayer Healthcare Pharmaceuticals Inc. Berlin, Germany).

Each treatment cycle consisted of 24 consecutive days of active treatment followed by a 4-day placebo period.

All women included in the study underwent:
- Clinical examination: body weight, height, waist circumference (WC) and blood pressure measurements. WC was taken midway between the lowest rib margin and the iliac crest.
- Laboratory testing: following overnight fast, baseline investigations in the form of fasting blood glucose (FBG) and fasting blood lipid profile (Triglycerides, total cholesterol, high density lipoprotein (HDL) cholesterol and low-density lipoprotein (LDL) cholesterol) were measured.
- Follow up in the outpatient clinic monthly during the first 6 months of use then bi-monthly for the next 18 months.
- Clinical examination and laboratory testing were repeated at 12 and 24 cycles.

![Figure 1. Flow diagram of recruitment and retention of participants in the study](image)

**3. OUTCOME MEASURES**

- The primary outcome was to measure metabolic changes.
- The secondary outcomes included adverse effects and women acceptability.

Adverse effects were recorded during follow up visits as participants were asked to do so while women acceptability was assessed via questionnaire at the end of 24 cycles of treatment (in terms of overall discomfort, overall satisfaction and advisability of the method to other women).

**4. STATISTICAL ANALYSIS**

Statistical analysis was performed using Statistical Package for the Social Sciences Version 20 (IBM Corp., Armonk, NY, USA).

Chi square test and Student’s t-test were used as appropriate. P<0.05 was considered to be significant.

**5. RESULTS**

The study was started with 96 participants in each group but 2 participants in group 1 and 4 participants in group 2 did not complete the 24 cycles of treatment and not included in the final analysis of data Participants’ age in years was (26.4±6.3 vs 26.6±6.1) and body mass index in Kg/m² was (33.3±2.1 vs 33.2±2.1) respectively.

There was no significant difference between the two groups regarding baseline body weight (BW, Kg), BW after 12 cycles, BW after 24 cycles, baseline Waist circumference (WC, cm), WC after 12 cycles, WC after 24 cycles, baseline systolic blood pressure (SBP, mmHg), SBP after
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12 cycles, SBP after 24 cycles, baseline diastolic cycles and DBP after 24 cycles as shown in blood pressure (DBP, mmHg), DBP after 12

Table1. Changes in body weight, waist circumference and arterial blood pressure after 12 and 24 cycles in comparison to baseline characteristics

| Body weight (Kg)                  | Group-1 (n=94) | Group-2 (n=92) | Student t-test | P-value |
|-----------------------------------|---------------|---------------|----------------|---------|
| -Basal                            | 88.8±7.2      | 88.2±7.9      | 0.54           | >0.05   |
| After 12 cycles                   | 88.3±7.3      | 88.1±7.6      | 0.18           | >0.05   |
| (compared to basal)               | (P>0.05)      | (P>0.05)      |                |         |
| -After 24 cycles                  | 88.1±7.2      | 88.1±7.5      | 0.99           | >0.05   |
| (compared to basal)               | (P>0.05)      | (P>0.05)      |                |         |

| Waist circumference (cm)          |               |               |                |         |
|-----------------------------------|---------------|---------------|----------------|---------|
| -Basal                            | 77.1±5.3      | 77.3±5.1      | 0.26           | >0.05   |
| After 12 cycles                   | 76.9±5.3      | 77.1±5.2      | 0.27           | >0.05   |
| (compared to basal)               | (P>0.05)      | (P>0.05)      |                |         |
| -After 24 cycles                  | 76.6±5.1      | 76.9±5.1      | 0.40           | >0.05   |
| (compared to basal)               | (P>0.05)      | (P>0.05)      |                |         |

| Arterial blood pressure (mmHg)    |               |               |                |         |
|-----------------------------------|---------------|---------------|----------------|---------|
| -Basal systolic                   | 118.5±6.5     | 117.9±5.9     | 0.21           | >0.05   |
| After 12 cycles                   | 117.8±5.3     | 117.4±6.1     | 0.57           | >0.05   |
| (compared to basal)               | (P>0.05)      | (P>0.05)      |                |         |
| -After 24 cycles                  | 118.3±6.7     | 117.9±5.1     | 0.13           | >0.05   |
| (compared to basal)               | (P>0.05)      | (P>0.05)      |                |         |

No significant change was observed between the two groups (p>0.05) or from baseline values (p>0.05) regarding fasting blood glucose, triglycerides and LDL cholesterol with significant decline in total cholesterol levels after 12 cycles (p<0.05) and 24 cycles (p<0.001) from baseline levels in both groups.

Also, HDL cholesterol was significantly increased after 12 cycles (p<0.05) and 24 cycles (p<0.001) from baseline levels in both groups as depicted in table 2

Table2. Changes in fasting blood glucose and fasting blood lipids after 12 and 24 cycles in comparison to baseline characteristics

| Fasting blood glucose (mg/dl)      | Group-1 (n=94) | Group-2 (n=92) | Student t-test | P-value |
|-----------------------------------|---------------|---------------|----------------|---------|
| -Basal                            | 85.8±6.4      | 86.2±6.2      | 0.43           | >0.05   |
| After 12 cycles                   | 85.9±6.3      | 85.8±6.4      | 0.11           | >0.05   |
| (compared to basal)               | (P>0.05)      | (P>0.05)      |                |         |
| -After 24 cycles                  | 85.7±6.2      | 85.6±6.3      | 0.11           | >0.05   |
| (compared to basal)               | (P>0.05)      | (P>0.05)      |                |         |

| Fasting blood lipids              |               |               |                |         |
|-----------------------------------|---------------|---------------|----------------|---------|
| -Triglycerides (mg/dl)            |               |               |                |         |
| -Basal                            | 138.2±3.1     | 137.9±3.6     | 0.61           | >0.05   |
| After 12 cycles                   | 139.1±2.9     | 139.2±2.8     | 0.24           | >0.05   |
| (compared to basal)               | (P>0.05)      | (P>0.05)      |                |         |
| -After 24 cycles                  | 138.8±2.9     | 138.9±2.8     | 2.24           | >0.05   |
| (compared to basal)               | (P>0.05)      | (P>0.05)      |                |         |

| -Total cholesterol (mg/dl)        |               |               |                |         |
|-----------------------------------|---------------|---------------|----------------|---------|
| -Basal                            | 184.6±2.4     | 184.2±2.8     | 1.05           | >0.05   |
| After 12 cycles                   | 184.5±2.5     | 184.7±2.3     | 0.59           | >0.05   |
| (compared to basal)               | (P>0.05)      | (P>0.05)      |                |         |
| -After 24 cycles                  | 182.3±2.2     | 182.1±2.4     | 0.59           | >0.05   |
| (compared to basal)               | (P<0.001)     | (P<0.001)     |                |         |
| -LDL cholesterol (mg/dl)          |               |               |                |         |
| -Basal                            |               |               | 0.40           |         |
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There was no significant difference between the two groups regarding reported adverse effects and patients’ acceptability at 24 cycles of use (p>0.05) as revealed in table 3.

Table 3. Adverse effects and acceptability of the methods used

|                        | Group-1 (n=94) | Group-2 (n=92) | Chi square test | P-value |
|------------------------|---------------|---------------|-----------------|---------|
| Headache               | 12            | 14            | 0.07            | >0.05   |
| Nausea                 | 6             | 8             | 0.10            | >0.05   |
| Menstrual changes      | 14            | 10            | 0.36            | >0.05   |
| Mood changes           | 3             | 3             | 0.15            | >0.05   |
| Vaginal discharge      | 8             | 14            | 1.41            | >0.05   |
| Lower abdominal pain   | 8             | 6             | 0.06            | >0.05   |
| Venous thromboembolism | 0             | 0             | -               | -       |
| Overall discomfort with the method: |                     |               |                 |         |
| -Moderate/High/Extreme | 4             | 90            | 87              | 0.01    | >0.05   |
| -None or slight        | 90            |               |                 |         |
| Overall satisfaction with the method: |                     |               |                 |         |
| -Very or somewhat satisfied | 91           | 3             | 90              | 0.01    | >0.05   |
| -Neutral or somewhat not satisfied | 3             | 2             | 2               |         |
| Would recommend the method to other women: |                     |               |                 |         |
| -Highly or somewhat agree | 92           | 2             | 90              | 0.23    | >0.05   |
| -Neutral or somewhat disagree | 2             | 2             | 2               |         |

6. DISCUSSION

The current study revealed absence of any significant change in the body weight, blood pressure and fasting blood glucose among obese women after 24 cycles of use of two different formulations and two different regimens of EE/DRSP COCs.

Absence of any change in body weight and blood pressure following the use of EE/DRSP COCs was reported by previous studies over 6-36 cycles of use [4, 6,7] even in hypertensive patients [8].

A previous randomized trial including 72 women reported that the EE/DRSP preparation demonstrated a more favorable effect on body mass index (BMI) and blood pressure (BP) with the mean BMI and mean BP remaining lower than baseline mean after 6-12 cycles of use [9].

Drospirenone (DRSP) is 17α-spirolactone derivative, acting as an antagonist of aldosterone receptors with clinically recognized ant androgenic and anti-mineralocorticoid activity in addition to its potent progestogenic activity, may reduce possible water retention in women using COCs which is the main responsible factor in stabilizing or even decreasing the blood pressure among users [10, 11].

In this study, no significant change was observed in triglycerides (TG) levels after 12-24 cycles of use among obese women. Previous studies reported contradictory findings regarding changes in TG levels with the use of EE/DRSP COCs, some reported absence of significant changes at 12 cycles of use [7], increase in TG levels after 6 cycles in hypertensive patients [8], after 13 cycles [6] or after 24-36 cycles of use [4].

However, this increase still lies within the normal range for TG in women in addition to different populations studied. In contrast to endogenous hypertriglyceridemia, there is good evidence that elevated triglycerides secondary to COCs use do not increase the atherosclerotic risk if HDL levels are also high [12,13] and LDL is not increased. In the current study, HDL

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cholergeric effect, and rogestogen have counteracting effects on serum lipids. Progestogens with androgenic activity can shift lipid and lipoprotein metabolism in a potentially unfavorable way [14, 15].

Drospirenone-containing COCs displays a potentially favorable change in lipid profile with increased HDL/LDL ratio which is considered clinically beneficial with respect to cardiovascular disease risk [6].

In the current study, there was no difference between both groups regarding adverse effects particularly bleeding patterns and patients' acceptability as most adverse effects were transient and mild without the need for specific interventions or method withdrawal.

A previous large study conducted on 326 healthy women (received EE 30ug/DRSP 3 mg in 21/7 regimen) compared to 1027 healthy women (received EE 20ug/DRSP 3 mg in 24/4 regimen); found no significant difference in cycle regularity and bleeding disorders between the two regimens of EE/DRSP COCs [16].

The strength of this study resides in being prospective with inclusion of high risk group (obese women) for cardiovascular disease.

Inability to conduct a randomized trial and to include a larger group of women as well as to record diet preferences of participants throughout the follow up period; was unintended limitations of the current study.

Future research should explore the impact of using EE/DRSP COCs on women with different risk factors for cardiovascular diseases as smoking and prior history of hypertension.

7. Conclusion

DRSP containing COCs do not induce detrimental metabolic changes and have favorable lipid profile among obese women when used for 12-24 cycles.

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