ORIGINAL ARTICLE

Comparison of the effects of metformin, flutamide plus oral contraceptives, and simvastatin on the metabolic consequences of polycystic ovary syndrome

Ferdous Mehrabian, Hatav Ghasemi-Tehrani, Mahboobe Mohamadkhani, Maryam Moeinoddini[1], Pooya Karimzadeh[1]
Departments of Obstetrics and Gynecology, [1]Internal Medicine, School of Medicine, Isfahan University of Medical Sciences, Isfahan, Iran

Background: Polycystic ovary syndrome (PCOS) is one of the common endocrine disorders in women of reproductive ages. It is associated with a range of disorders, such as dyslipidemia, hypertension, insulin resistance (IR), compensatory hyperinsulinemia, gestational, and type 2 diabetes, and increased risk of cardiovascular morbidity. There are different treatments available for PCOS. The purpose of this study was to determine and compare the effects of metformin, flutamide plus oral contraceptives (OCs), and simvastatin on the metabolic consequences of PCOS. **Materials and Methods:** This study was a single-blind clinical trial. The subjects were selected from a group of patient with PCOS and metabolic syndrome, who were referred to the midwifery clinic of Al-Zahra Hospital and Beheshti Hospital, Isfahan, Iran. A total of 111 subjects were randomly assigned to three groups: metformin, flutamide plus OCs, and simvastatin groups. The measurements were performed at baseline and after 6 months of therapy. Paired *t*-test, analysis of variance (ANOVA), and chi-square test were applied in this study. **Results:** A total of 102 subjects were analyzed in this study, 34 subjects were allotted in each group. The prevalence of IR was statistically different between three groups (*P*-value = 0.001). After a 6-month course, metformin showed larger reduction in fasting blood sugar (FBS) level (*P*-value < 0.001). However, except for metformin, two other treatments reduced C-reactive protein (CRP) level significantly (both *P*-values < 0.001). The level of triglycerides (TGs) decreased considerably in all groups (all *P*-values < 0.001). Both metformin and simvastatin decreased BMI significantly (both *P*-values < 0.001). None of the treatments changed high-density lipoprotein (HDL) level (all *P*-values > 0.05). **Conclusion:** Metformin performed better in FBS reduction. Simvastatin had better performance in terms of reducing TG level and waist circumference.

Key words: Flutamide, metformin, oral contraceptives (OCs), polycystic ovary syndrome (PCOS), simvastatin

How to cite this article: Mehrabian F, Ghasemi-Tehrani H, Mohamadkhani M, Moeinoddini M, Karimzadeh P. Comparison of the effects of metformin, flutamide plus oral contraceptives, and simvastatin on the metabolic consequences of polycystic ovary syndrome. J Res Med Sci 2016;21:11.

INTRODUCTION

Polycystic ovary syndrome (PCOS), which is associated with hyperandrogenism and cardiovascular risks, is one of the most common endocrine disorders in women. This may affect upto 10% of women of reproductive ages in different countries,[1-3] although the large number of studies in different countries has estimated its prevalence at 5-7% in diverse population,[4-6] depending on the definition, it can affect up to 25% of women of reproductive age.[7]

Access this article online	
Quick Response Code:	Website: www.jmsjournal.net
	DOI: ****

It seems that PCOS can be caused by complicated relationships between behavioral, environmental, and genetics factors.[8,9] PCOS is associated with a broad range of disorders, such as dyslipidemia, hypertension, insulin resistance (IR), compensatory hyperinsulinemia, gestational and type 2 diabetes, and ultimately increased risk of cardiovascular morbidity. Cardiovascular risk factors also include measures of systemic inflammation and endothelial dysfunction and increases in women with PCOS.[4,6,10,11] It seems that PCOS and obesity may act together and cause insulin sensitivity.[3]

Address for correspondence: Dr. Hatav Ghasemi-Tehrani, Department of Obstetrics and Gynecology, School of Medicine, Isfahan University of Medical Sciences, Isfahan, Iran. E-mail: Tehrani@med.mui.ac.ir
Received: 02-06-2015; **Revised:** 02-01-2016; **Accepted:** 14-12-2015

Metabolic syndrome in reproductive ages is more common in women with PCOS. The prevalence of metabolic syndrome in women with PCOS is reported in 33-45% cases, whereas the prevalence in none PCOS is between 6-15%.[12] Increasing the blood cells and C-reactive protein (CRP) is also reported in women with PCOS.[13] In women with PCOS, IR is associated with reproductive abnormalities.[14]

Some common symptoms of PCOS are amenorrhea, uterine bleeding, obesity, and lack of ovulation.[10,15,16] Cosmetic issues, such as hirsutism, androgenic alopecia, and acne, are also reported in the patients with PCOS.[7] Reproductive and cardiometabolic abnormalities coexist, and their interactions have created a need for a modified therapy in women with PCOS.[17] An effective treatment of PCOS would be the combination of reducing cardiovascular risk and improving the ovary function.[16]

There are different treatments for PCOS such as oral contraceptives (OC), antiandrogen therapy, and insulin-lowering drugs.[14] Metformin is one of the insulin sensitizers[17,18] that has been increasingly used as a standard treatment for PCOS.[19] It can improve IR, increase serum sex hormone binding globulin (SHBG), decrease glucose and free serum testosterone, improve lipid profile, and improve frequency of ovulation in women with PCOS.[3,5,8,12,19] Among the other treatment options, flutamide is a nonsteroidal antiandrogen that improves androgenic clinical and biochemical symptoms.[8,20]

Using statins is a more recent treatment for PCOS. Statins can decrease cardiovascular morbidity and mortality,[16] reduce serum androgen levels,[14] and improve lipid profiles and endothelial function. They also have proper effects on cardiovascular protection as an anti-inflammatory and antioxidant.[4,8]

According to different aspects of PCOS, researchers have studied various drugs, alone or in combination with other drugs, in order to treat PCOS. However, available treatments of PCOS are not able to manage metabolic aberrations in PCOS.[8] The purpose of this study was to determine and compare the effects of metformin, flutamide, and simvastatin on metabolic consequences of PCOS.

MATERIALS AND METHODS

This study was a single-blind clinical trial. It was approved by the Ethical Committee of the Isfahan University of Medical Sciences (project number: 394074). It was approved by the Iranian Registry of Clinical Trial (IRCT201405217513N10).

The purpose of the protocol was explained to each subject, and then written informed consent was obtained from each participant.

Subjects

The subjects were selected from a group of patients with PCOS and metabolic syndrome, who were referred to Ob& Gyn clinic of Al-Zahra and Beheshti hospitals, Isfahan, Iran, during April 2013 to November 2014.

The diagnosis of PCOS was made using the National Institutes of Health (NIH) criteria, which is having at least two of the followings:

1. Ovulatory dysfunction as oligo- and/or anovulation,
2. Biochemical or clinical evidence of hyperandrogenism, and
3. Polycystic ovaries as viewed by transvaginal ultrasound.

The patients who were selected had no evidence of congenital adrenal hyperplasia, Cushing's syndrome, or androgen-secreting tumors.[1,4,8,18]

Metabolic syndrome definition criteria

Waist circumference >88 cm with simultaneously presence of at least two of the followings:

1. Triglyceride (TG) level ≥150 mg/dL or under TG medication,
2. High-density lipoprotein-cholesterol (HDL-C) level <50 mg/dL for women, or under therapy,
3. Blood pressure (BP) ≥130/85 mmHg or under medication,
4. Glucose level ≥100 mg/dL or overt diabetes.[21,22]

Inclusion criteria

The patients who match the following criteria were included in the study:

1. Age ≥18 years;
2. Single;
3. Having no evidence of thyroid dysfunction, Cushing's syndrome, and hyperprolactinemia;
4. Symptoms of normal kidney function, bilirubin level, and serum aminotransferases;
5. Non—smoker;
6. Not having breast cancer;
7. Not using any drug that probably affects the ovarian function, insulin sensitivity, and lipid profile;
8. No contraindication to use drugs.

Exclusion criteria

The patients who match the following criteria were excluded from the study:

1. Unwillingness to continue the study,
2. Married,
3. With emerging side effect of drugs or contraindication, and
4. No to compliance with the study protocol.

Study design

The study was a single-blind clinical trial. Similar diet and physical activities were presented to all the subjects, though they did not control during this study. The participants were evaluated at baseline during the follicular phase of a natural cycle or after

the administration of medroxyprogesterone and before starting the intervention. The evaluation included determinations of fasting insulin [enzyme-linked immunosorbent assay (ELISA) method], fasting blood sugar (FBS), lipid profile (HDL-TG), C- CRP, BP, waist circumference, height, and weight. BMI was calculated for each subject. All blood samples were obtained between 7 a.m. and 8 a.m., after an overnight fast.

All examinations were carried out by a single physician. BMI was measured by the formula: weight (kg)/[height (m)]^2. Fasting blood glucose was measured by:

Homeostasis model assessment (HOMA)-IR = [fasting serum insulin (micro U/mL) × fasting plasma glucose (mg/dL)/22.5. HOMA-IR ≥ 2.5 was considered as insulin resistance.[22]

The patients took the treatment after 6 months. After this period, all the examinations and clinical assessments were reevaluated at baseline.

A total of 111 subjects were randomly assigned to three therapeutic groups: Group A (1000 mg meformin per day), group B [62.5 mg flutamide plus low dose OCs (levonorgestrel 0.15 mg plus ethinyl estradiol 0.03 mg) per day], and group C (20 mg simvastatin per day).

The consort table of this study is implied in Figure 1.

Randomization

In order to randomly allocate the subjects into three groups, 111 cards were prepared each containing a number. The numbers had one, two, or three digits. Therefore, there were 37 cards with one digit, 37 cards with two digits, and 37 with three digits. Each subject had been randomly given a card by the acceptance nurse. After referring to a physician, according to the subject's card, the physician had given them a sealed envelope, with one of the letter A, B, or C on it. Each letter contained a different treatment and contained enough pills for study duration (6 month). The physician was not informed of sealed envelopes' contents.

Statistical analysis

In this study, paired *t*-test, analysis of variance (ANOVA), and chi-square test were performed by using Statistical Package for the Social Sciences (SPSS) version 20 (SPSS-Inc., California, USA). For normally distributed variables, paired *t*-tests were applied to evaluate changes between measurements at baseline and after 6 months of treatment, separately in each group. ANOVA method was applied to compare differences between three treatment groups. IR and BP were analyzed by percentage calculations and χ^2 tests.

For all analyses, *P*-value < 0.05 is considered statistically significant. Descriptive statistics are reported as mean ± standard deviation (SD).

RESULTS

A total of 102 patients were analyzed in this study; 34 subjects were allotted to each study group. Patients were aged between 18 years and 43 years. None of the patients in the three treatment groups experienced significant

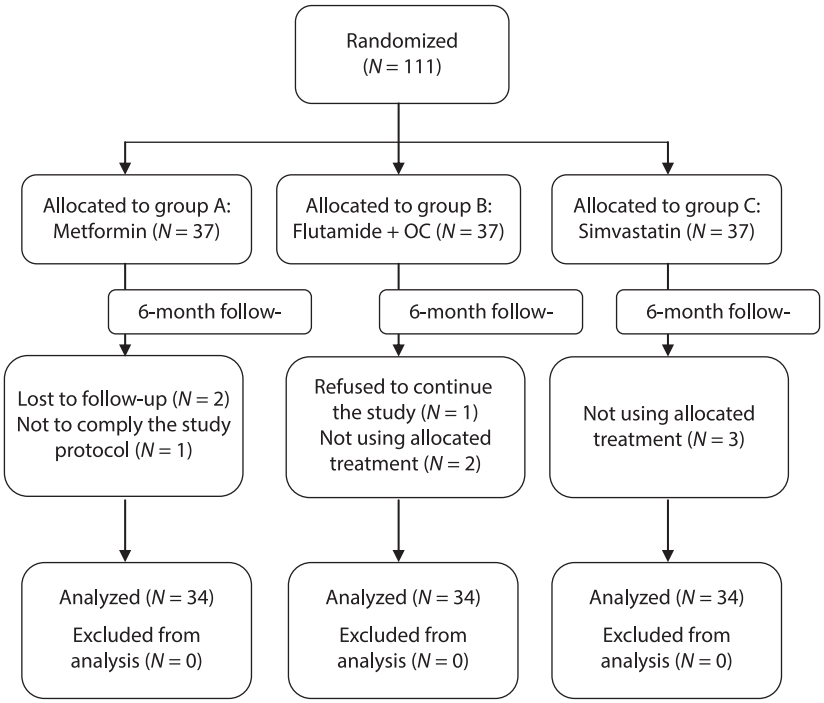

Figure 1: Flow diagram of the trial

side effects. Table 1 summarizes baseline characteristics of subjects in each group. As it is shown in Table 1, the patients in three groups had same characteristics, except for waist circumference, in which waist circumference in patients in Simvastatin group, was significantly smaller than patients in two other groups. However, the difference between metformin and flutamide plus OC groups was not statistically significant.

HOMA-IR ≥ 2.5 was considered as IR. IR was observed in 70.6% of the subjects (24 out of 34 subjects) in each group at baseline. According to Pearson's chi-square test, the proportion of IR was completely the same in three groups (*P*-value = 1).

BP > 130/85 mmHg was considered as hypertension, and was denoted by BP here. Ten patients (29.4%) in the metformin group, 10 patients (29.4%) in the flutamide plus OC, and 11 patients (32.4%) in the simvstatin group had BP at baseline. The proportion of BP was statistically the same in three groups (Pearson's chi-square *P*-value = 0.955).

All the measurements were repeated, after a 6-month follow-up. The results are shown in Table 2. As it can be seen in Table 2, FBS was significantly different in three groups. The mean FBS in the metformin group was smaller than that in two other groups. The mean CRP in the metformin group was significantly higher than that in the flutamide plus OC group (*P*-value = 0.044). Also waist circumference differed in three groups. The subjects in the simvastatin group had significantly smaller waist circumference compared with the subjects in the two other groups. However, this relationship has been observed at baseline. TG, HDL, and BMI did not differ significantly between the three groups.

After 6 months, 33 patients (97.1%) in the metformin group, 26 patients (76.5%) in the flutamide plus OC group, and 34 patients (100%) in the simvastatin group were observed insulin resistant. According to Pearson's chi-square test, the prevalence of IR was statistically different in three groups (*P*-value = 0.001).

Eight patients (23.5%) in the metformin group, 9 patients (26.5%) in the flutamide plus OC group, and 10 patients (29.4%) in the simvstatin group had BP. The proportion of BP was statistically the same in three groups (Pearson's chi-square *P*-value = 0.860).

The main purpose of this study was comparison between changes in three treatments, during the 6-month follow-up. Differences between baseline and after 6 months, for each measurement, are reported in Table 3. According to the results, for waist circumference, the mean difference was 1.15 cm in the metformin group. Which positive

Table 1: Baseline parameters in individual groups

Variable	Metformin (M)	Flutamide + OC (F)	Simvastatin (S)	Comparison between groups *P*-value, (pair-wise comparisons*)
Age (year)	29.18±8.288	29.00±7.663	29.15±8.261	0.995
Waist (cm)	96.50±5.889	96.323±5.798	88.12±12.732	<0.001 (M vs S, *P*<0.001) (F vs S, *P*=0.001)
TG (mg/dL)	200.29±53.277	199.82±53.152	200.68±53.752	0.998
FBS (mg/dL)	92.15±13.944	91.79±13.746	92.59±13.828	0.972
CRP(mg/L)	1.49±0.430	1.48±0.434	1.48±0.430	0.996
HDL (mg/dL)	42.82±7.217	42.53±6.981	42.41±7.050	0.970
BMI (kg/m^2)	29.83±4.146	29.83±4.159	29.93±4.145	0.993

Each value represents mean ± SD; *Tukey HSD method was applied for pair-wise comparisons

Table 2: Parameters in individual groups after 6 months

Variable	Metformin (M)	Flutamide + OC (F)	Simvastatin (S)	Comparison between groups *P*-value, (pair-wise comparisons*)
Waist (cm)	95.35±5.704	95.44±5.727	85.32±12.162	<0.001 (M vs S, *P*<0.001) (F vs S, *P*<0.001)
TG (mg/dL)	193.18±53.899	187.44±52.012	175.50±48.663	0.357
FBS (mg/dL)	78.32±15.526	91.00±13.334	85.59±7.374	<0.001 (M vs F, *P*<0.001) (M vs S, *P*=0.049)
CRP (mg/L)	1.45±0.470	1.22±0.289	1.27±0.368	0.044 (M vs F, *P*=0.044)
HDL (mg/dL)	42.50±6.716	42.23±6.845	41.97±6.312	0.947
BMI (kg/m^2)	29.54±4.184	29.75±4.014	28.80±3.999	0.603

Each value represents mean ± SD; *Tukey HSD method was applied for pair-wise comparisons

Table 3: Change of parameters after 6 months of treatment in comparison to baseline values

Variable	Metformin (M)		Flutamide + OC (F)		Simvastatin (S)		*P*-value*
	Mean diff.	*P*-value	Mean diff.	*P*-value	Mean diff.	*P*-value	
Waist(1)-Waist(2)	1.15±0.784	<0.001	0.88±0.640	<0.001	2.79±1.610	<0.001	<0.001 M vs S, *P*<0.001 F vs S, *P*<0.001
TG(1)-TG(2)	7.12±9.834	<0.001	12.38±4.445	<0.001	25.18±26.831	<0.001	<0.001 M vs S, *P*<0.001 F vs S, *P*=0.006
FBS(1)-FBS(2)	13.82±16.609	<0.001	0.79±2.728	<0.001	7.00±7.984	<0.001	<0.001 M vs F, *P*<0.001 M vs S, *P*=0.028
CRP(1)-CRP(2)	0.04±0.152	0.135	0.26±0.349	<0.001	0.21±0.267	<0.001	0.003 M vs F, *P*=0.003 M vs S, *P*=0.036
HDL(1)-HDL(2)	0.32±2.056	0.365	0.29±1.382	0.223	0.44±1.580	.113	0.931
BMI(1)-BMI(2)	0.29±0.356	<0.001	0.08±0.345	0.172	1.13±0.391	<0.001	<0.001 M vs S, *P*<0.001 F vs S, *P*<0.001

(1): Baseline measurement; (2): After 6 month measurement; *Overall test among three groups (calculated by ANOVA method)

value means that waist circumference at baseline was higher than the parameter 6 month later. This difference was statistically significant (*P*-value < 0.001). This result is true for the flutamide plus OC and simvastatin groups. Additionally, according to the ANOVA test, the reduction was significantly larger in the simvastatin groups than that in the two other groups (*P*-value < 0.001).

Test results for TG was completely the same as waist circumference; simvastatin showed the larger reduction, rather than two other groups (*P*-value < 0.001).

In three treatment groups, FBS was significantly smaller after 6 months. Analysis of variance showed a significant difference between mean changes in three groups. According to ANOVA results, Metformin caused a significantly larger reduction in comparison with Flutamide plus OC and Simvastatin.

CRP mean change during 6 months in the metformin group did not differ significantly from zero. However, in the flutamide plus OC and simvastatin groups, the CRP decreased significantly compared with baseline (both *P*-values < 0.001). As ANOVA showed, the mean changes in the simvastatin and flutamide plus OC groups were statistically larger than that in the metformin group (*P*-value < 0.001).

Except for flutamide plus OC group, in two other groups, BMI decreased significantly after 6 months. BMI reduction in the simvastatin group was significantly larger than that in the two other groups (*P*-value < 0.001).

For HDL, the mean change did not differ from zero in any groups. According to the ANOVA results, the mean changes were equal in three treatment groups (*P*-value = 0.931).

DISCUSSION

PCOS is one of the most common endocrine disorders occurring in women.[1,19] Depending on the definition, it can affect up to 25% of women in reproductive ages.[7] There are different treatments for PCOS.[14] Using statins is a more recent treatment for PCOS.[16] The purpose of this study was to determine and compare the effects of metformin, flutamide plus OC, and simvastatin on the metabolic consequences of PCOS.

In this study, the diagnosis of PCOS was made using the NIH criteria. A total of 102 patients were analyzed after 6 months. The features for the three groups were completely the same at baseline except for the waist circumference.

After a 6-month follow-up, FBS was significantly different between three groups. Metformin indicated considerably larger reduction in comparison with two other treatments. As the results imply, Metformin will be more useful in the patients with high FBS, whereas other studies did not show significant change in fasting glucose in the metformin[1,13] and simvastatin groups.[1] Therefore, the effect of metformin on FBS needs more research.

In our study, metformin did not decline CRP, whereas flutamide plus OC and simvastatin both reduced CRP considerably. However, in a previous study, CRP levels decreased significantly after a 6-month period of metformin treatment in comparison with the baseline values.[13]

In the present study, all treatments decreased TG significantly after 6 months. The effect of Simvastatin on TG reduction was significantly larger than two other treatments, however, in some studies metformin showed a significant effect on TG, whereas simvastanin did not.[1]

In other study, TG decreased significant decrease in statin plus OC compared with OCP alone.[4] Therefore, simvastatin may be an appropriate treatment for the patients with high levels of TG.

After 6 months, the prevalence of IR was statistically different in three groups (*P*-value = 0.001). IR was least prevalent in flutamide plus OC group (76.5% of patients).

In a study on PCOS patients, simvastatin declined IR considerably.[23] The study on another statin (atorvastatin) also indicated a significant reduction in IR by applying statin medication.[24] Other study showed a significant improvement in IR by applying metformin.[25]

The prevalence of BP was the same in three groups (*P*-value = 0.860). Previous study showed a significant improvement on BP using metformin.[26]

For HDL, the mean change did not differ from zero in any group. HDL level was not significantly altered by metformin and simvastatin in other studies.[1] However, metformin showed significant improvement in HDL level in other studies.[12,13]

In our study, BMI decreased significantly in both metformin and simvastatin groups. BMI reduction in Simvastatin group was statistically larger than two other groups. All treatment groups showed a significant decrease of waist circumference (*P*-value < 0.001).

In previous studies, metformin is reported to improve BMI,[12] flutamide-metformin reduced body fat[20] and improved lipid profiles, both together or metformin alone.[4,20] In another study, metformin and simvastatin improved BMI significantly.[1] Therefore, in obese patients either metformin or simvastatin may be more appropriate than flutamide.

CONCLUSION

Simvastatin developed significantly larger reduction in waist circumference and TG. Metformin showed considerably larger reduction in FBS, in comparison with two other groups. Both simvastatin and flutamide plus OC developed a significant reduction in CRP. However, these two groups did not differ significantly. BMI reduced significantly in the metformin and simvastatin groups in comparison with that in the flutamide plus OC group. Additionally, simvastatin had statistically better impact.

Financial support and sponsorship

Isfahan University of Medical Sciences.

Conflicts of interest

There are no conflicts of interest.

AUTHOR'S CONTRIBUTION

FM contributed in the conception of the work, conducting the study, interpretation of data for the work, revising the draft, approval of the final version of the manuscript, and agreed for all aspects of the work. HGT contributed in the conception of the work, conducting the study, interpretation of data for the work, revising the draft, approval of the final version of the manuscript, and agreed for all aspects of the work. MM contributed in the conception and design of the work, conducting the study, interpretation of data for the work, revising the draft, approval of the final version of the manuscript, and agreed for all aspects of the work. MM contributed in the design of the work, approval of the final version of the manuscript, and agreed for all aspects of the work. PK contributed in the design of the work, approval of the final version of the manuscript, and agreed for all aspects of the work.

REFERENCES

1. Banaszewska B, Pawelczyk L, Spaczynski RZ, Duleba AJ. Effects of simvastatin and metformin on polycystic ovary syndrome after six months of treatment. J Clin Endocrinol Metab 2011;96:3493-501.
2. Goodarzi MO, Dumesic DA, Chazenbalk G, Azziz R. Polycystic ovary syndrome: Etiology, pathogenesis and diagnosis. Nat Rev Endocrinol 2011;7:219-31.
3. Conway G, Dewailly D, Diamanti-Kandarakis E, Escobar-Morreale HF, Franks S, Gambineri A, *et al.*; ESE PCOS Special Interest Group. The polycystic ovary syndrome: A position statement from the European Society of Endocrinology. Eur J Endocrinol 2014;171: P1-29.
4. Banaszewska B, Pawelczyk L, Spaczynski RZ, Dziura J, Duleba AJ. Effects of simvastatin and oral contraceptive agent on polycystic ovary syndrome: Prospective, randomized, crossover trial. J Clin Endocrinol Metab 2007;92:456-61.
5. Morin-Papunen L, Rantala AS, Unkila-Kallio L, Tiitinen A, Hippeläinen M, Perheentupa A, *et al*. Metformin improves pregnancy and live-birth rates in women with polycystic ovary syndrome (PCOS): A multicenter, double-blind, placebo-controlled randomized trial. J Clin Endocrinol Metab 2012;97:1492-500.
6. Eagleson CA, Gingrich MB, Pastor CL, Arora TK, Burt CM, Evans WS, *et al*. Polycystic ovarian syndrome: Evidence that flutamide restores sensitivity of the gonadotropin-releasing hormone pulse generator to inhibition by estradiol and progesterone 1. J Clin Endocrinol Metab 2000;85:4047-52.
7. Setji TL, Brown AJ. Polycystic ovary syndrome: Update on diagnosis and treatment. Am J Med 2014;127:912-9.
8. Bargiota A, Diamanti-Kandarakis E. The effects of old, new and emerging medicines on metabolic aberrations in PCOS. Ther Adv Endocrinol Metab 2012;3:27-47.
9. Diamanti-Kandarakis E, Christakou C, Marinakis E. Phenotypes and environmental factors: Their influence in PCOS. Curr Pharm Des 2012;18:270-82.
10. Costello M, Shrestha B, Eden J, Sjoblom P, Johnson N. Insulin-sensitising drugs versus the combined oral contraceptive pill for hirsutism, acne and risk of diabetes, cardiovascular disease, and endometrial cancer in polycystic ovary syndrome. Cochrane Database Syst Rev 2007;CD005552.

11. Sirmans SM, Weidman-Evans E, Everton V, Thompson D. Polycystic ovary syndrome and chronic inflammation: Pharmacotherapeutic implications. Ann Pharmacother 2012;46:403-18.
12. Cheang KI, Huszar JM, Best AM, Sharma S, Essah PA, Nestler JE. Long-term effect of metformin on metabolic parameters in the polycystic ovary syndrome. Diab Vasc Dis Res 2009;6:110-9.
13. Orio F, Manguso F, Di Biase S, Falbo A, Giallauria F, Labella D, *et al*. Metformin administration improves leukocyte count in women with polycystic ovary syndrome: A 6-month prospective study. Eur J Endocrinol 2007;157:69-73.
14. Kazerooni T, Shojaei-Baghini A, Dehbashi S, Asadi N, Ghaffarpasand F, Kazerooni Y. Effects of metformin plus simvastatin on polycystic ovary syndrome: A prospective, randomized, double-blind, placebo-controlled study. Fertil Steril 2010;94:2208-13.
15. Nader S, Diamanti-Kandarakis E. Polycystic ovary syndrome, oral contraceptives and metabolic issues: New perspectives and a unifying hypothesis. Hum Reprod 2007;22:317-22.
16. Sathyapalan T, Atkin SL. Evidence for statin therapy in polycystic ovary syndrome. Ther Adv Endocrinol Metab 2010;1:15-22.
17. Diamanti-Kandarakis E, Christakou CD, Kandaraki E, Economou FN. Metformin: An old medication of new fashion: Evolving new molecular mechanisms and clinical implications in polycystic ovary syndrome. Eur J Endocrinol 2010;162:193-212.
18. Legro RS, Arslanian SA, Ehrmann DA, Hoeger KM, Murad MH, Pasquali R, *et al*.; Endocrine Society. Diagnosis and treatment of polycystic ovary syndrome: An endocrine society clinical practice guideline. J Clin Endocrinol Metab 2013;98:4565-92.
19. Lim PS, Wan Abdul Rahim WE, Ng BK, Mohd Yassin MA, Mohd Nor NA, Omar MH. The effect of adding simvastatin or metformin to Yasmin® on the endocrine and metabolic parameters in polycystic ovarian syndrome. J Clin Endocrinol Metab 2015;4:2-11.
20. Ong KK, de Zegher F, López-Bermejo A, Dunger DB, Ibáñez L. Flutamide metformin for post-menarcheal girls with preclinical ovarian androgen excess: Evidence for differential response by androgen receptor genotype. Eur J Endocrinol 2007;157:661-8.
21. Grundy SM, Cleeman JI, Daniels SR, Donato KA, Eckel RH, Franklin BA, *et al*. Diagnosis and management of the metabolic syndrome an American Heart Association/National Heart, Lung, and Blood Institute scientific statement. Circulation 2005;112:2735-52.
22. Mehrabian F, Khani B, Kelishadi R, Kermani N. The prevalence of metabolic syndrome and insulin resistance according to the phenotypic subgroups of polycystic ovary syndrome in a representative sample of Iranian females. J Res Med Sci 2011;16:763-9.
23. Kaya C, Pabuccu R, Cengiz S, Dünder I. Comparison of the effects of atorvastatin and simvastatin in women with polycystic ovary syndrome: A prospective, randomized study. Exp Clin Endocrinol Diabetes 2010;118:161-6.
24. Sathyapalan T, Kilpatrick ES, Coady AM, Atkin SL. The effect of atorvastatin in patients with polycystic ovary syndrome: A randomized double-blind placebo-controlled study. J Clin Endocrinol Metab 2009;94:103-8.
25. Moghetti P, Castello R, Negri C, Tosi F, Perrone F, Caputo M, *et al*. Metformin effects on clinical features, endocrine and metabolic profiles, and insulin sensitivity in polycystic ovary syndrome: A randomized, double-blind, placebo-controlled 6-month trial, followed by open, long-term clinical evaluation 1. J Clin Endocrinol Metab 2000;85:139-46.
26. Velazquez E, Mendoza S, Hamer T, Sosa F, Glueck C. Metformin therapy in polycystic ovary syndrome reduces hyperinsulinemia, insulin resistance, hyperandrogenemia, and systolic blood pressure, while facilitating normal menses and pregnancy. Metabolism 1994;43:647-54.