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ORIGINAL ARTICLE

Efficacy of Combined Cabergoline and Metformin Compared to Metformin Alone on Cycle Regularity in Patients with Polycystic Ovarian Disease with Hyperprolactinemia: A Randomized Clinical Trial

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Abstract

Purpose Polycystic ovarian syndrome (PCOS) is a common reproductive disorder. Increasing serum prolactin in these patients could be detected in both follicular and luteal phase of the normal and stimulated cycles. Hyperprolactinemia affects the hypothalamic–pituitary–ovarian axis causing anovulation and abnormal uterine bleeding. In this study, the efficacy of combined cabergoline and metformin therapy was compared to metformin therapy alone in patients with PCOS on the body mass index, androgen profile and menstrual cycle regulation.

Methods Two hundred and fifty patients with polycystic ovarian syndrome (PCOS) with increased serum prolactin were randomly allocated into two groups: group (1) received oral metformin tablet 1000 mg per day and cabergoline 0.5 g tablet weekly for 3 months as a case group, and group (2) received oral metformin tablet 1000 mg per day and a placebo tablet weekly for 3 months as the control group ($n = 123$). Body mass index (BMI), menstrual cycle regularity, serum testosterone, serum prolactin and dehydroepiandrosterone sulfate (DHEAS) level were compared before and after treatment in both groups.

Results There was significant decrease in body mass index and improvement of androgenic profile in both groups after treatment. In group (1), there was significant improvement in cycle regularity and significant decrease in serum prolactin level post-treatment.

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Conclusions The use of cabergoline in addition to metformin had more favorable effect on cycle regularity and prolactin level in patients with polycystic ovarian syndrome with hyperprolactinemia than the use of metformin alone.

Keywords Randomized clinical trial · Cabergoline · Metformin · Polycystic ovarian disease · Hyperprolactinemia

Introduction

Polycystic ovarian syndrome (PCOS) is a common reproductive disorder and is considered the most common cause of an ovulatory infertility. According to the Rotterdam criteria, PCOS is characterized by a combination of oligo/amenorrhea, clinical or endocrine signs of hyperandrogenemia and polycystic ovaries [1].

In fact, menstrual irregularity exists in approximately all obese and 72% of thin PCOS patients. Thirty percent of patients with PCOS show also a modest rise in prolactin level. Increasing serum prolactin in these patients could be detected in both follicular and luteal phase of the normal and stimulated cycles [2].

Dopamine released from the hypothalamus inhibits prolactin secretion, and it also affects the secretion of gonadotropins. When this inhibitory effect of dopamine is reduced, prolactin secretion will increase in addition to abnormalities in gonadotropins including luteinizing hormone (LH) [3].

Prevalence of hyperprolactinemia is not rare in young women with menstruation-related problems; its prevalence varies according to age and manifestations. It varies from 0.4% in the normal adults or 2.9% in of women with adult-onset amenorrhea or up to 75% in women with both amenorrhea and galactorrhea [4].

Hyperprolactinemia affects the hypothalamic–pituitary–ovarian axis causing anovulation and abnormal uterine bleeding (AUB). Mild hyperprolactinemia (20–50 ng/mL) may cause only a short luteal phase, resulting from poor preovulatory follicle development. Moderate hyperprolactinemia (50–100 ng/mL) usually leads to oligomenorrhea or amenorrhea; higher prolactin levels (>100 ng/mL) typically present with hypogonadism [5].

Metformin is the most frequently used therapy to control the steroid-related disorder in PCOS women [6]. Some researchers proved that cabergoline which is a dopamine receptor agonist, with higher affinity to dopamine D2 receptors and has the serum half-life of 43-h limit had improved uterine perfusion and achieved a better ovulatory response in PCOS patients [7]. Other researchers concluded that cabergoline use could normalize androgen level and improve the menstrual irregularity in women with PCOS [8].

So we assumed that the use cabergoline could normalize prolactin level and could also be effective in the treatment of menstrual cycle irregularities in PCOS patients.

In this study, we will investigate the effects of combined cabergoline and metformin therapy in PCOS patients on androgen profile and menstrual cycle regulation in comparison with metformin alone.

Methods

This randomized clinical trial was done on 250 patients with polycystic ovarian disease (PCO) women with increased serum prolactin concentration >29.5 ng/mL. The study protocol was approved by the ethics committee of Hai Jamma hospital. All participants were counseled and informed about the trial protocol, and a written informed consent according to Declaration of Helsinki was signed.

Two hundred and fifty women were recruited from the gynecology outpatient clinics; all of them met the selection criteria and were enrolled in the study. No patient was lost during the follow-up.

Selection criteria:

- Inclusion criteria: patients with polycystic ovarian disease (PCO) with serum prolactin concentration >29.5 ng/mL.
- Exclusion criteria: other causes of increased prolactin levels such as hypothyroidism, pituitary tumors, patients who had history of cardiovascular disease, history of using prolactin increasing drugs, women who wanted to be pregnant, and who could not tolerate cabergoline.

Demographic characteristics including age, body mass index (BMI), drug history and menstrual history were obtained. Also serum testosterone, prolactin and dehydroepiandrosterone sulfate (DHEAS) level were measured using ELISA (enzyme-linked immunosorbent assay) method before the trial for all participants.

They were randomly allocated by a computer-generated numbering system into two groups:

1. Group (1) received oral metformin tablet 1000 mg per day and cabergoline 0.5 g tablet weekly for 3 months as case group ($n = 127$), and
2. Group (2) received oral metformin tablet 1000 mg per day and a placebo tablet weekly for 3 months as the control group ($n = 123$).

The patients and laboratory technicians did not know to which group the patient was assigned.

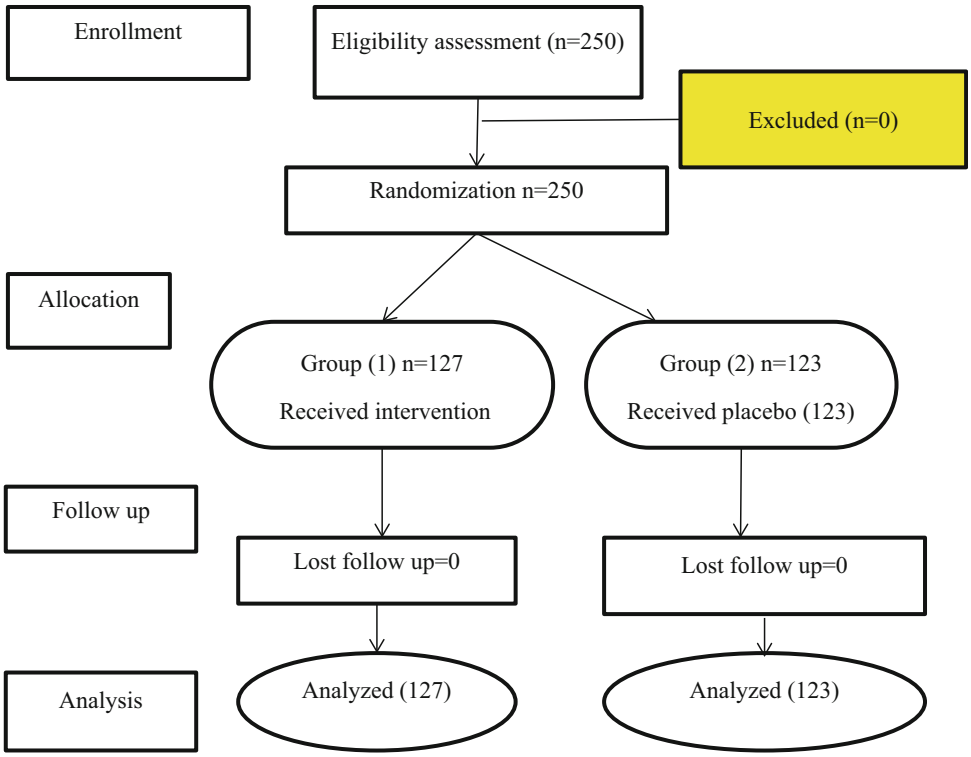

Fig. 1 Consort flow diagram

Testosterone, prolactin, body mass index and DHEAS level were again measured 3 months after intervention in the two studied groups. Also, menstrual cycle history was obtained again and recorded.

The laboratory technicians were blind about the study, and samples were sending in the context of outpatient work out.

The data of the 250 patients were analyzed as shown in Fig. 1. Qualitative data were described using number and percent and were compared using Chi-square test or Fisher exact test, while normally quantitative data were expressed in mean ± SD and were compared using Student's *t* test or paired *t* test. Statistical significance at $p \leq 0.05$.

Results

Two hundred and fifty patients were enrolled in the study, and they were divided into two groups: a case group ($n = 127$) and a control group ($n = 123$). Analysis of data of both groups before treatment showed no statistical difference as regards the age, the mean ± SD for group (1) was 25.4 ± 4.7 years, while in group (2), it was 25.4 ± 4.8 years with $p = 0.947$. As regards the body mass index (BMI), there was no statistical difference between the two groups for group (1), the mean ± SD was 29.6 ± 2.7 kg/m^2, while in group (2), it was 29.4 ± 2.7 kg/m^2 with $P = 0.559$.

Before treatment, the mean ± SD of testosterone level in group (1) was 1.0 ± 0.3 nmol/L, and in group (2), it was 0.97 ± 0.3 nmol/L with $P = 0.430$ which indicated insignificant difference between the two groups. There was also insignificant difference between the two groups as regards DHEAS and serum prolactin level with $P = 0.704$ and 0.215, respectively. All patients in both groups had irregular cycles as shown in Table 1.

The patients in group (1) received metformin 1000 mg daily plus cabergoline 0.5 gm weekly for three months. Analysis of the results revealed significant differences in the mean level of prolactin, which was 46 ± 4 IU/L before treatment and became 7.1 ± 5.2 IU/L after treatment with $P < 0.001$. Also the 59.8% of patients in group (1) became regularly menstruating which indicated significant difference before and after treatment with $P < 0.001$. As regards the mean ± SD of DHEAS level, it was 401.7 ± 212.4 µmol/L before treatment and 231.7 ± 121.5 µmol/L after treatment with $P < 0.001$. Also there was significant reduction in the body mass index of patients in group (1) before and after treatment, mean ± SD was 29.6 ± 2.7 kg/m^2 before treatment, and it became 25.1 ± 3.4 kg/m^2 after treatment with $P < 0.001$. There was also significant reduction in testosterone level before and after treatment of patients in group (1), the mean ± SD was 1.0 ± 0.3 nmol/L before treatment, and it became 0.9 ± 0.17 nmol/L after treatment with $P < 0.001$ as shown in Table 2.

Table 1 Baseline characteristics in the two studied groups before treatment

Variables	Group (1) ($n = 127$)	Group (2) ($n = 123$)	*P*
Age (year)	25.4 ± 4.7	25.4 ± 4.8	0.947
BMI (kg/m^2)[a]	29.6 ± 2.7	29.4 ± 2.7	0.559
Testosterone (nmol/L)	1.0 ± 0.3	0.97 ± 0.3	0.430
DHEAS (μmol/L)[b]	401.7 ± 212.4	409.3 ± 65.4	0.704
Prolactin (IU/L)	46 ± 4	46.8 ± 6	0.215
Menstrual cycles			
Regular	0 (0.0%)	0 (0.0%)	–
Irregular	127 (100.0%)	123 (100.0%)	

Qualitative data were described using number and percent and were compared using Chi-square test or Fisher exact test, while normally quantitative data were expressed in mean ± SD and were compared using Student's *t* test

[a] *BMI* body mass index

[b] *DHEAS* dehydroepiandrosterone sulfate

Table 2 Comparison of prolactin, DHEAS, weight and testosterone group (1) before and after treatment

Variables	Before treatment	After treatment	*P*
BMI (kg/m^2)[a]	29.6 ± 2.7	25.1 ± 3.4	<0.001*
DHEAS (μmol/L)[b]	401.7 ± 212.4	231.7 ± 121.5	<0.001*
Testosterone (nmol/L)	1.0 ± 0.3	0.9 ± 0.17	0.001*
Prolactin (IU/L)	46 ± 4	7.1 ± 5.2	<0.001*
Menstrual cycles			
Regular	0 (0.0%)	76 (59.8%)	<0.001*
Irregular	127 (100.0%)	51 (40.2%)	

Qualitative data were described using number and percent and were compared using Chi-square test or Fisher exact test, while normally quantitative data were expressed in mean ± SD and were compared using for paired *t* test

* Statistically significant at $P \leq 0.05$

[a] *BMI* body mass index

[b] *DHEAS* dehydroepiandrosterone sulfate

In group (2), the patients received metformin 1000 mg daily plus placebo tablet weekly for three months. Analysis of the results of those patients showed that the mean of the body mass index decreased significantly after treatment, it was 29.4 ± 2.7 kg/m^2 before treatment, and it became 24 ± 1.2 kg/m^2 after treatment with $P < 0.001$. Also the mean level of DHEAS was reduced significantly from 409.3 ± 65.4 μmol/L before treatment to 251.3 ± 109.4 μmol/L after treatment with $P < 0.001$. The mean of testosterone level also showed significant reduction, it was 0.97 ± 0.3 nmol/L before treatment and 0.9 ± 0.2 nmol/L after treatment with $P = 0.003$. On the other hand, the mean of prolactin level did not show significant difference before and after treatment $P = 0.204$, as shown in Table 3.

Comparison between the results of the two studied groups after treatment showed no statistically significant differences between the two groups as regards the mean of body mass index, it was 25.1 ± 13.4 kg/m^2 in group (1), while in group (2) it was 24 ± 11.2 kg/m^2 with $P = 0.483$. There was no significant difference between the two studied groups as regards the mean level of DHEAS, it was 231.68 ± 121.4 μmol/L in group (1) and 251.29 ± 109.42 μmol/L in group (2) with $P = 0.182$. The changes of the mean level of testosterone were not statistically significant between the two groups, and it was 0.9 ± 0.72 nmol/L in group (1) and 0.87 ± 0.22 nmol/L in group (2) with $P = 0.658$. The changes of the mean level of prolactin were significantly different, in group (1) it was 7.11 ± 5.24 IU/L, while in group (2) it was 42.8 ± 32.6 with $P < 0.001$ as shown in Table 4.

All patients in both studied groups had irregular menstrual cycles; there was significant difference in both groups as regards cycle regulation, 59.8% of patients in group (1) became regularly menstruating in comparison with 29.3% of patients in group (2) with $P < 0.001$. Such

Table 3 Comparison of prolactin, DHEAS, weight and testosterone group (2) before and after treatment

Variables	Before treatment	After treatment	*P*
BMI (kg/m^2)[a]	29.4 ± 2.7	24 ± 1.2	<0.001*
DHEAS (μmol/L)[b]	409.3 ± 65.4	251.3 ± 109.4	<0.001*
Testosterone (nmol/L)	0.97 ± 0.3	0.9 ± 0.2	0.003*
Prolactin (IU/L)	46.8 ± 26.2	42.8 ± 32.6	0.204
Menstrual cycles			
Regular	0 (0.0%)	36 (29.3%)	<0.001*
Irregular	123 (100.0%)	87 (70.7%)	

Qualitative data were described using number and percent and were compared using Chi-square test or Fisher exact test, while normally quantitative data were expressed in mean ± SD and were compared using for paired *t* test

* Statistically significant at $P \leq 0.05$

[a] *BMI* body mass index

[b] *DHEAS* dehydroepiandrosterone sulfate

Table 4 Comparison of prolactin, DHEAS, weight and testosterone in the two studied groups after treatment

Variables	Group (1) ($n = 127$)	Group (2) ($n = 123$)	*P*
BMI (kg/m^2)[a]	25.1 ± 13.4	24 ± 11.2	0.483
DHEAS (μmol/L)[b]	231.68 ± 121.49	251.29 ± 109.42	0.182
Testosterone (nmol/L)	0.9 ± 0.72	0.87 ± 0.22	0.658
Prolactin (IU/L)	7.11 ± 5.24	42.8 ± 32.6	<0.001*
Menstrual cycles			
Regular	76 (59.8%)	36 (29.3%)	<0.001*
Irregular	51 (40.2%)	87 (70.7%)	

Qualitative data were described using number and percent and were compared using Chi-square test or Fisher exact test, while normally quantitative data were expressed in mean ± SD and were compared using Student's *t* test

* Statistically significant at $P \leq 0.05$

[a] *BMI* body mass index

[b] *DHEAS* dehydroepiandrosterone sulfate

an observation raised the possibility of the use of cabergoline in cases of cycle irregularity.

Discussion

This study aimed to evaluate the effect of adding cabergoline to metformin on PCOS women with hyperprolactinemia.

Prolactin (PRL) is a hormone, mainly secreted by lactotroph cells of the anterior pituitary gland. Recent studies have shown it may also be produced by many extra pituitary cells. Its well-recognized PRL plays an important role in lactation during pregnancy, but it is involved in other biological functions such as angiogenesis, immunoregulation and osmoregulation. Hyperprolactinemia causes reproductive dysfunction in both sexes, resulting in hypogonadism, infertility and galactorrhea [9].

The results of this study showed significant decrease in prolactin level and higher rate of cycle regulation in patients with PCOS after treatment with cabergoline plus metformin which is consistent with those observed by Ghaneei et al. [10] who concluded that cabergoline can be administered safely in PCOS patients with hyperprolactinemia to improve the menstrual cycles.

Although the mechanism is not clear, one of the proposed mechanisms is that cabergoline as a long-acting agonist of dopamine, which has a high affinity to dopamine receptors (type 2), inhibits the vascular endothelial growth factor (VEGF) secretion in luteinized granulosa cells both in vitro and in vivo [11]. Another possible mechanism is that treatment by cabergoline restores ovarian function due to its inhibitory effect on LH secretion and androgen concentration [12].

The results of this study showed significant decrease in the body mass index (BMI) in both groups after treatment,

which is similar to those observed by Pala et al. [13] who concluded that normalization of prolactin (PRL) with dopamine agonists has been found to reverse these abnormalities in body composition and metabolic abnormalities caused by hyperprolactinemia. Our results were also supported by what had been observed by Krysiak et al. [14] who observed that the use of metformin decreased plasma levels of fasting and post-challenge plasma glucose and improved insulin receptor sensitivity, and this effect was more prominent in patients receiving cabergoline.

In this study, combined administration of metformin and cabergoline resulted in better cycle control than metformin alone which was similar to those observed by Mohammadbygi et al. who concluded that PCOS patients had more resistance in uterine blood flow than healthy people; however, cabergoline administration proved to increase uterine blood perfusion and regulate menstruation cycle [15].

In this study, we observed that treatment in both groups resulted in significant improvement in androgenic profile in both groups which was consistent with the results of other researchers who concluded that the administration of cabergoline can normalize androgen levels and improve the menstrual irregularity in women with PCOS [16].

This study was well-designed randomized controlled study and adds to the bulk of evidence in the literature which emphasized on the effectiveness of long-acting dopamine agonist in the control of hyperprolactinemia and restoration of cycle regularity in patient with PCO. The matching of the two groups as regards the demographic data nullified the bias of confounding factors that might affect the strength of the analysis.

This study was limited by the short follow-up period after treatment which was three months only, so longer follow-up period should be considered in further studies to confirm long-term effectiveness of cabergoline administration on cycle regulation. Also the patients who sought for pregnancy were excluded, which limited the study from detecting the effectiveness of the combined therapy of cabergoline and metformin on the restoration of ovulation and pregnancy achievement, but those women were excluded due to the limited data available as regards the safety profile and teratogenicity of cabergoline.

Conclusions

The use of cabergoline in addition to metformin had more favorable effect on cycle regularity and prolactin level reduction in patients with polycystic ovarian syndrome with hyperprolactinemia than the use of metformin alone.

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Compliance with Ethical Standards

Conflicts of interest The author declares that she has no conflict of interest.

Ethical Approval All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Declaration of Helsinki and its later amendments or comparable ethical standards.

Informed Consent The study protocol was approved by the ethics committee of Hai Jamma hospital. All participants were counseled and informed about the trial protocol and a written informed consent according to declaration of Helsinki was signed. A randomized clinical study approved that the use of combined cabergoline and metformin had a better impact on the control of prolactin level and cycle regulation in patients with both PCO and hyperprolactinemia.

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