ORIGINAL ARTICLE

INTERNATIONAL JOURNAL OF RESEARCH IN PHARMACEUTICAL SCIENCES

Published by JK Welfare & Pharmascope Foundation Journal Home Page: https://ijrps.com

# The added effect of cabergoline to metformin on serum hormones and rate and regularity of menstruation in women with Polycystic ovary syndrome

Rana Hatem Matrood* and Alaq Saeed Abdulhussain

Department of Obstetrics & Gynecology, College of Medicine, University of Al Qadisiyah, Iraq

*Article History:*

Received on: 06.01.2018
Revised on: 22.02.2018
Accepted on: 27.02.2018

*Keywords:*

Cabergoline
PCOS
Metformin
Menstruation

ABSTRACT

Polycystic ovary syndrome (PCOS) is an important cause of menstrual irregularities and infertility in women. Management approaches are variable and share in common the objectives of improving menstrual irregularities, hormonal disturbances, associated clinical features, and fertility. Cabergoline has been suggested to be effective in reducing some adverse effect associated with PCOS; however, sufficient controversy existed that permitted the conduction of the current study. This study was aimed to evaluate the effect of adding Cabergoline to the standard mode of treatment (metformin) in a cohort of women with PCOS, on serum hormone levels, BMI, and menstrual irregularities. The present case-control study included 100 women diagnosed as having a polycystic ovarian syndrome (PCOS) according to clinical, ultrasonic and hormonal bases. They were divided into two groups; the first group included 50 PCOS women received metformin treatment for 4 months' duration and served as control group whereas the second group included 50 PCOS women who were given cabergoline in addition to metformin for 4 months' duration and served as a study group. Both types of treatment, with or without cabergoline, resulted in highly significant reduction in mean weight in both groups (P<0.001), highly significant reduction in mean serum prolactin in both groups (P<0.001), highly significant reduction in mean serum testosterone in both groups (P<0.001) and highly significant reduction in mean serum DHEAS in both groups (P<0.001); however cabergoline was more effective in reducing mean serum prolactin, 10.20 ±1.92 ng/ml versus 32.20 ±1.79 ng/ml (P<0.001) and improved menstrual irregularities more efficiently. Addition of cabergoline lowers serum prolactin more significantly than metformin alone has improved menstrual irregularity more significantly.

* Corresponding Author

Name: Rana Hatem Matrood
Phone: +9647800722078
Email: ranahatem_80@yahoo.com

ISSN: 0975-7538
DOI: https://doi.org/10.26452/ijrps.v9i1.1255

Production and Hosted by

IJRPS | https://ijrps.com


## INTRODUCTION

The first appearance of Polycystic ovary syndrome (PCOS) in modern medical reports is dated back to the observation made by Stein and Leventhal in 1935, who identified 7 women having in common the following abnormalities: "amenorrhea, hirsutism, and enlarged ovaries with multiple cysts" (Stein, I.F. & Leventhal, 1935).

The disease is now identified as a frequent, heterogeneous, heritable disease targeting females during their lifetime. PCOS is distinguished by polycystic ovaries, ovulatory dysfunction, and hyperandrogenism. (Sirmans and Pate, 2013). Females having PCOS usually require care for menstrual abnormalities, clinical features of hyperandrogenism, and subfertility. Menstrual abnormalities usually seen in PCOS are in the form amenorrhea, oligomenorrhea, and unpredicted menstrual bleeding

of the prolonged period (Farquhar, 2007). Nevertheless, approximately one-third of PCOS women will possess normal menstruation (Balen et al., 1995).

Majority of females having clinical features of high androgen are diagnosed with PCOS. (Azziz et al., 2004). One of the frequent manifestations of hyperandrogenism in PCOS women is hirsutism, affecting up to 70 percent of females with PCOS (Fauser et al., 2012). More than 90 percent of naturally menstruating females with hirsutism are diagnosed via ultrasound examination to possess "polycystic ovaries" (Adams et al., 1986). Moreover, PCOS happens in 50% of females with a little amount of unpleasant hair distribution (Souter et al., 2004). Acne may also be an indicator of hyperandrogenism; however, it is less frequent in PCOS and of inferior value as a diagnostic criterion when compared with hirsutism. Out of the population of PCOS women, about 15 to 30 percent seek medical advice because of acne (Zhao and Qiao, 2013). The rate of PCOS diagnoses in women with severe acne approaches 40 percent (Eden, 1991).

"Infertility" is observed in 40 percent of females having PCOS https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3872139/ - b14-clep-6-001(Teede et al., 2010). PCOS stands as the most frequent cause of infertility with anovulation. The rate of PCOS in women with anovulatory type infertility in infertility clinics approaches 95%. Females with PCOS possess a normal count of "primordial follicles"; however, the count of "primary and secondary follicles" is significantly high. Follicular growth stops when follicles become 4–8 mm in diameter, because of alteration in factors enrolled in the natural development of follicles. For that reason, "a dominant follicle does not develop" and ovulation is not going to happen (Brassard et al., 2008). Moreover, the rate of spontaneous abortion is more frequent in PCOS (Glueck et al., 2001).

The high rate of PCOS is accompanied by some situations. Increase in weight frequently precedes the acquisition of the PCOS clinical manifestations, and when diet and exercise is followed, weight reduction happen, abdominal fat is going to be abolished, testosterone is going to drop down, insulin resistance is going to be markedly improved, hirsutism will be less prominent in females with PCOS (Moran et al., 2011). The rate of PCOS in women seeking medical advice for the problem of obesity reaches about 28.3% (Alvarez-Blasco et al., 2006). Despite that, population-based studies show lack of significant association between obesity and PCOS (Yildiz et al., 2008). A modest rise in prolactin levels is seen 30% of patients with PCOS show (Işik et al., 1997). Both follicular and luteal phase of the normal and stimulated cycles are accompanied by increased of serum prolactin in these patients (Broekmans et al., 2006). Prolactin hormone is produced by lactotrophs of the anterior part of the "pituitary gland". Features associated with prolactin over-production are galactorrhea, subfertility, and amenorrhea (Kasper et al., 2015). It has been reported that the increased prolactin is accompanied by reduced frequency of ovulation as well as the count of ovarian follicles. These manifestations are the direct results of the luteolytic action of this hormone, however, the mechanism behind that is not obvious (Oh and Aghi, 2011). In human, prolactin secretion is under the inhibitory effect of dopamine (Falaschi et al., 1986). Despite the significant controversy, some studies have reported that "central dopaminergic mechanisms" are also involved in common in the regulation of the gonadotropins secretion. When dopamine control is reduced there will be abnormal secretion of prolactin and LH (Moran et al., 2003). In the present time clinical practice, metformin is indicated to regulate steroid associated disorders and reduce the menstrual irregularity and enhance infertility in women with PCOS (Casanueva et al., 2006). "Cabergoline is a dopamine receptor agonist that its formula is C26H37N5O2". Cabergoline has been shown to be more efficient in women with hyperprolactinemia when compared to bromocriptine (Alhusaynei et al., 2008). Cabergoline possesses better affinity than dopamine to D2 receptors and possesses longer serum half-life, making it better in controlling hyperprolactinemia (Papaleo et al., 2001). Some studies have been carried out utilizing long-acting dopamine agonists (cabergoline) in women with PCOS (Gómez et al., 2011). Some improvement in clinical features, hormonal abnormalities, and fertility parameters has been reported by a number of studies in PCOS women following cabergoline administration (Gómez et al., 2011; Papaleo et al., 2001).

Enough controversy about the benefit of cabergoline use in PCOS exists in published articles to justify carrying out this study in Iraq on women with PCOS.

## PATIENTS AND METHODS

This study was conducted as a case-control study carried out between 1st of July 2017 and 28 of February 2018. The present study included 100 women diagnosed as having a polycystic ovarian syndrome (PCOS) according to clinical, ultrasonic and hormonal bases. They were divided into two groups; the first group included 50 PCOS women received metformin treatment for 4 months' duration and served as control group whereas the second group included 50 PCOS women who were given cabergoline in addition to metformin for 4

**Table 1: Characteristics of the study and control groups before treatment**

| Characteristic | Control n = 50 | Study group n = 50 | P * |
|---|---|---|---|
| Age (years) | 24.44 ±2.94 | 24.60 ±3.13 | 0.793 |
| BMI (kg/m$^2$) | 26.31 ±2.20 | 26.49 ±2.48 | 0.699 |
| Weight (kg) | 70.03 ±9.72 | 72.34 ±12.08 | 0.295 |
| Prolactin (ng/ml) | 40.39 ±1.99 | 40.18 ±2.19 | 0.613 |
| Testesterone (ng/ml) | 2.54 ±3.85 | 2.13 ±0.67 | 0.451 |
| DHEAS (ng/ml) | 323.86 ±75.89 | 347.76 ±62.97 | 0.090 |

Variables are expressed as mean ±standard deviation; *Independent samples t-test; n: number of cases; BMI: body mass index

**Table 2: Mean weight and serum hormone levels following treatment in both groups**

| Characteristic Group | Weight (kg) | | Prolactin (ng/ml) | | Testosterone (ng/ml) | | DHEAS (ng/ml) | |
|---|---|---|---|---|---|---|---|---|
| | Control | Study | Control | Study | Control | Study | Control | Study |
| Before treatment | 70.03± 9.72 | 72.34 ± 12.08 | 40.39 ± 1.99 | 40.18 ± 2.19 | 2.54 ± 3.85 | 2.13 ± 0.67 | 323.86 ± 75.89 | 347.76 ± 62.97 |
| After treatment | 68.83± 9.75 | 71.49 ± 11.93 | 32.20 ± 1.79 | 10.20 ± 1.92 | 1.06 ± 0.28 | 0.97 ± 0.34 | 246.96 ± 51.48 | 241.42 ± 44.44 |
| P-value * | <0.001 | <0.001 | <0.001 | <0.001 | 0.008 | <0.001 | <0.001 | <0.001 |

Variables are expressed as mean ±standard deviation; *paired samples t-test; n: number of cases

months duration and served as a study group. Age of women, weight, body mass index (BMI), serum prolactin, testosterone, and DHEAS were the main variables included in the present study.

### Statistical analysis

Statistical analysis was carried out using statistical package for social sciences (SPSS) version 23.0. Variables were expressed as mean, standard deviation, number, and percentage.

Paired t-test was used to compare mean difference before and after treatment, while independent samples t-test was used to compare mean difference between study and control groups. Chi-square test was used to compare the difference in the rate of menstrual irregularities after treatment between study and control groups. The level of significance was chosen at $P \leq 0.05$.

## RESULTS

Table 1 summarizes the characteristics of study and control groups before starting the treatment. Mean age of study and control groups was 24.60 ±3.13 years and 24.44 ±2.94 years, respectively and there was no significant difference in mean age between the two groups (P=0.793). There was also no significant difference in the mean body mass index (BMI) between study and control groups, 26.49 ±2.48 kg/m$^2$ versus 26.31 ±2.20 kg/m$^2$, respectively (P=0.699). In addition, no significant difference in mean weight was observed between the two groups, 72.34 ±12.08 kg versus 70.03 ±9.72 kg, respectively (P=0.295). Mean serum prolactin in study and control groups was 40.18 ±2.19 ng/ml versus 40.39 ±1.99 ng/ml, respectively and the difference was not significant (P=0.613), also mean serum testosterone in both groups showed no significant difference, 2.13 ±0.67 ng/ml versus 2.54 ±3.85 ng/ml, respectively (P= 0.451), moreover, mean serum DHEAS show no significant difference in both groups, 347.76 ±62.97 ng/ml versus 323.86 ±75.89 ng/ml, respectively (P=0.090), as shown in table 1. Both types of treatment, with or without cabergoline, resulted in highly significant reduction in mean weight in both groups (P<0.001), highly significant reduction in mean serum prolactin in both groups (P<0.001), highly significant reduction in mean serum testosterone in both groups (P<0.001) and highly significant reduction in mean serum DHEAS in both groups (P<0.001), as shown in table 2.

However, cabergoline was more effective in reducing mean serum prolactin, 10.20 ±1.92 ng/ml versus 32.20 ±1.79 ng/ml (P<0.001), as shown in table 3. Also, the addition of cabergoline resulted in a significantly better rate of regular menstrual cycles than metformin alone, 605 versus 36% (P=0.016, as shown in table 4.

## DISCUSSION

The present study was conducted primarily to disclose the effect of cabergoline, in women with PCOS, on hormonal levels (mainly prolactin) and on the regularity of menstrual cycle. In comparison with baseline reading, there were significant reductions in mean serum hormonal concentrations, prolactin, testosterone and DHEAS in the control group, as well as in the study group. Ghaneei et al. (2015) also reported reduced serum concentrations of testosterone and DHEAS; however, the difference before and after the intervention was insignificant in control and in study groups. On the

**Table 3: Characteristics of the study and control groups after treatment**

| Characteristic | Control n = 50 | Study group n = 50 | P * |
|---|---|---|---|
| Weight (kg) | 68.83 ±9.75 | 71.49 ±11.93 | 0.226 |
| Prolactin ng/ml) | 32.20 ±1.79 | 10.20 ±1.92 | 0.000 |
| Testosterone (ng/ml) | 1.06 ±0.28 | 0.97 ±0.34 | 0.136 |
| DHEAS (ng/ml) | 246.96 ±51.48 | 241.42 ±44.44 | 0.566 |

Variables are expressed as mean ±standard deviation; *Independent samples t-test; n: number of cases

**Table 4: Menstrual irregularities before and after treatment**

| Menstruation | Control | Study group | P* |
|---|---|---|---|
| Irregular | 32 (64%) | 20 (40%) | |
| Regular | 18 (36 %) | 30 (60%) | 0.016 |
| Total | 50 (100%) | 50 (100%) | |

Variables are expressed as mean ±standard deviation; *paired samples t-test; n: number of cases

other hand, Ghaneei et al. (2015) reported a significant reduction in mean serum prolactin in the study group, but not in control group. Two further studies reported the similar effect of combined use of cabergoline and metformin in reducing, significantly, serum prolactin, yet no significant change was obtained following the use of metformin alone (Prelević et al., 1987). These results, besides the results, obtained in the current study, supported the suggestion that prolactin reduction is the direct effect of cabergoline use. It is postulated that cabergoline, by stimulating dopamine causes this change in prolactin (Ghaneei et al., 2015). The use of dopamine agonists in PCOS is well known in the available literature (Alhusaynei et al., 2008; Pascal-Vigneron et al., 1995). Prelević et al. (1987) proposed that the altered hypothalamic inhibitory effect of dopamine may be a cause for unwanted high LH levels and prolactin in women with PCOS and hyperprolactinemia.

In the current study, adding cabergoline was no effect in further reducing mean of testosterone when compared with metformin alone. Several other studies reported same findings (Ghaneei et al., 2015; Singh et al., 2010). Several other studies documented the role of metformin in reducing mean serum testosterone level in women with PCOS, in accordance with the present study findings (Kazerooni and Dehghan-Kooshkghazi, 2003; Velija-Ašimi, 2013). DHEAS may be in high in half of the patients with PCOS (Ghaneei et al., 2015). Several studies showed that the use of dopamine agonist can significantly reduce DHEAS serum concentrations in women with PCOS (CHAPMAN et al., 1987; Ghaneei et al., 2015; Steingold et al., 1986) and some studies, in contrary to our results, showed that metformin has no significant effect of DHEAS serum concentrations in women with PCOS (Banaszewska et al., 2011, 2009; Otta et al., 2010). indicating that cabergoline may be the preferred mode of a treatment aiming at reducing DHEAS in those patients.

At the beginning of the current study, menstrual irregularities were observed in all women participating in the study, however, a significant number of women developed regular menstruation in both groups, but the rate of the regular cycle was higher in women receiving cabergoline and metformin together. These results are in accordance with the findings of Ghaneei et al. (2015). Lord et al., (2003) reported an improving in the cycle in women with PCOS following metformin use . This is also being the case with the study performed by Kedikova et al. (2012) following the use of metformin. Prelević et al. (1987) found that the use of L DOPA compounds and bromocriptine can cause significant improvement of cycle regularity in women with PCOS and hyperprolactinemia and he linked that to the alteration in LH level with subsequent improvement in ovulation and cycling. From that, one can conclude that the use of cabergoline, as a dopamine agonist, beside metformin in women with PCOS and hyperprolactinemia, is better in achieving cycle regulation and prolactin reduction than metformin alone. Also, Prelević et al. (1987) showed that the compounds of L-DOPA and bromocriptine (dopamine agonist) in PCOS patients with hyperprolactinemia can cause a significant decrease in LH levels in comparison to the normoprolacinemia group. Ajossa et al.(1999) also found that PCOS patients have increased vascular resistance and the use of cabergoline causes a significant increase in uterine blood supply in PCOS patients.

## CONCLUSION

In conclusion, cabergoline proved to be an effective adjuvant therapy that when added to metformin caused more significant improvement in serum prolactin and resulted in higher rate of menstrual regularities and by this way may prove effective in the treatment of fertility disorders in women with PCOS.

**REFERENCES**

Adams, J., Dwpolson, D., Franks, S., 1986. Prevalence of polycystic ovaries in women with anovulation and idiopathic hirsutism. Br. Med. J. (Clin. Res. Ed). 293, 355–359.

Ajossa, S., Paoletti, A.M., Guerriero, S., Floris, S., Mannias, M., Melis, G.B., 1999. Effect of chronic administration of cabergoline on uterine perfusion in women with polycystic ovary syndrome. Fertil. Steril. 71, 314–318.

Alhusaynei, A.J., Mahmood, I.H., Sattam, Z.C.N., 2008. Comparison of the effects of cabergoline and bromocriptine in women with hyperprolactinemic amenorrhea. Middle East Fertil. Soc. J. 13, 33–38.

Alvarez-Blasco, F., Botella-Carretero, J.I., San Millán, J.L., Escobar-Morreale, H.F., 2006. Prevalence and characteristics of the polycystic ovary syndrome in overweight and obese women. Arch. Intern. Med. 166, 2081–6.

Azziz, R., Sanchez, L.A., Knochenhauer, E.S., Moran, C., Lazenby, J., Stephens, K.C., Taylor, K., Boots, L.R., 2004. Androgen Excess in Women: Experience with over 1000 Consecutive Patients. J. Clin. Endocrinol. Metab.

Balen, A.H., Conway, G.S., Kaltsas, G., Techatraisak, K., Manning, P.J., West, C., Jacobs, H.S., 1995. Andrology: Polycystic ovary syndrome: The spectrum of the disorder in 1741 patients. Hum. Reprod. 10, 2107–2111.

Banaszewska, B., Pawelczyk, L., Spaczynski, R.Z., Duleba, A.J., 2009. Comparison of simvastatin and metformin in the treatment of polycystic ovary syndrome: prospective randomized trial. J. Clin. Endocrinol. Metab. 94, 4938–4945.

Banaszewska, B., Pawelczyk, L., Spaczynski, R.Z., Duleba, A.J., 2011. Effects of simvastatin and metformin on polycystic ovary syndrome after six months of treatment. J. Clin. Endocrinol. Metab. 96, 3493–501.

Brassard, M., AinMelk, Y., Baillargeon, J.P., 2008. Basic Infertility Including Polycystic Ovary Syndrome. Med. Clin. North Am.

Broekmans, F.J., Kwee, J., Hendriks, D.J., Mol, B.W., Lambalk, C.B., 2006. A systematic review of tests predicting ovarian reserve and IVF outcome. Hum. Reprod. Update.

Casanueva, F.F., Molitch, M.E., Schlechte, J.A., Abs, R., Bonert, V., Bronstein, M.D., Brue, T., Cappabianca, P., Colao, A., Fahlbusch, R., Fideleff, H., Hadani, M., Kelly, P., Kleinberg, D., Laws, E., Marek, J., Scanlon, M., Sobrinho, L.G., Wass, J.A.H., Giustina, A., 2006. Guidelines of the Pituitary Society for the diagnosis and management of prolactinomas. Clin. Endocrinol. (Oxf). 65, 265–273.

CHAPMAN, A.J., WILSON, M.D., OBHRAI, M., SAWERS, R.S., LYNCH, S.S., ROYSTON, J.P., CLAYTON, R.N., 1987. EFFECT OF BROMOCRIPTINE ON LH PULSATILITY IN THE POLYCYSTIC OVARY SYNDROME. Clin. Endocrinol. (Oxf). 27, 571–580.

Eden, J.A., 1991. The polycystic ovary syndrome presenting as resistant acne successfully treated with cyproterone acetate. Med. J. Aust. 155, 677–80.

Falaschi, P., Rocco, A., del Pozo, E., 1986. Inhibitory effect of bromocriptine treatment on luteinizing hormone secretion in polycystic ovary syndrome. J. Clin. Endocrinol. Metab. 62, 348–351.

Farquhar, C., 2007. Introduction and history of polycystic ovary syndrome. In: Polycystic Ovary Syndrome, Second Edition. pp. 4–24.

Fauser, B.C.J.M., Tarlatzis, B.C., Rebar, R.W., Legro, R.S., Balen, A.H., Lobo, R., Carmina, E., Chang, J., Yildiz, B.O., Laven, J.S.E., Boivin, J., Petraglia, F., Wijeyeratne, C.N., Norman, R.J., Dunaif, A., Franks, S., Wild, R.A., Dumesic, D., Barnhart, K., 2012. Consensus on women's health aspects of polycystic ovary syndrome (PCOS): The Amsterdam ESHRE/ASRM-Sponsored 3rd PCOS Consensus Workshop Group. In: Fertility and Sterility.

Ghaneei, A., Jowkar, A., Ghavam, M.R.H., Ghaneei, M.E., 2015. Cabergoline plus metformin therapy effects on menstrual irregularity and androgen system in polycystic ovary syndrome women with hyperprolactinemia. Iran. J. Reprod. Med. 13, 93–100.

Glueck, C.J., Phillips, H., Cameron, D., Sieve-Smith, L., Wang, P., 2001. Continuing metformin throughout pregnancy in women with polycystic ovary syndrome appears to safely reduce first-trimester spontaneous abortion: A pilot study. Fertil. Steril. 75, 46–52.

Gómez, R., Ferrero, H., Delgado-Rosas, F., Gaytan, M., Morales, C., Zimmermann, R.C., Simón, C., Gaytan, F., Pellicer, A., 2011. Evidence for the existence of a low dopaminergic tone in polycystic ovarian syndrome: Implications for OHSS development and treatment. J. Clin. Endocrinol. Metab. 96, 2484–2492.

Işik, A.Z., Gülekli, B., Zorlu, C.G., Ergin, T., Gökmen, O., 1997. Endocrinological and clinical analysis of hyperprolactinemic patients with and without ultrasonically diagnosed polycystic ovarian changes. Gynecol. Obstet. Invest. 43, 183–185.

Kasper, D., Fauci, A., Hauser, S., Longo, D., Jameson, J., Loscalzo, J., 2015. Harrison's Principles of Internal Medicine, Mc GrawHill.

Kazerooni, T., Dehghan-Kooshkghazi, M., 2003. Effects of metformin therapy on hyperandrogenism in women with the polycystic ovarian syndrome. Gynecol. Endocrinol. 17, 51–6.

Kedikova, S., Sirakov, M., Boyadzhieva, M., 2012. [Metformin efficiency for the adolescent PCOS treatment]. Akusherstvo i Ginekol. 51, 6–10.

Lord, J.M., Flight, I.H.K., Norman, R.J., 2003. Metformin in polycystic ovary syndrome: systematic review and meta-analysis. BMJ 327, 951–3.

Moran, L.J., Hutchison, S.K., Norman, R.J., Teede, H.J., 2011. Lifestyle changes in women with polycystic ovary syndrome. Cochrane Database Syst. Rev. CD007506.

Moran, L.J., Noakes, M., Clifton, P.M., Tomlinson, L., Norman, R.J., 2003. Dietary composition in restoring reproductive and metabolic physiology in overweight women with polycystic ovary syndrome. J. Clin. Endocrinol. Metab. 88, 812–819.

Oh, M.C., Aghi, M.K., 2011. Dopamine agonist–resistant prolactinomas. J. Neurosurg. 114, 1369–1379.

Otta, C.F., Wior, M., Iraqi, G.S., Kaplan, R., Torres, D., Gaido, M.I., Wyse, E.P., 2010. Clinical, metabolic, and endocrine parameters in response to metformin and lifestyle intervention in women with polycystic ovary syndrome: A randomized, double-blind, and placebo control trial. Gynecol. Endocrinol. 26, 173–178.

Papaleo, E., Doldi, N., De Santis, L., Marelli, G., Marsiglio, E., Rofena, S., Ferrari, A., 2001. Cabergoline influences ovarian stimulation in hyperprolactinaemic patients with polycystic ovary syndrome. Hum. Reprod. 16, 2263–2266.

Pascal-Vigneron, V., Weryha, G., Bosc, M., Leclere, J., 1995. [Hyperprolactinemic amenorrhea:treatment with cabergoline versus bromocriptine. Results of a national multicenter randomized double-blind study]. Presse Med. 24, 753–7.

Prelević, G.M., Würzburger, M.I., Perić, L.A., 1987. Acute effects of L-dopa and bromocriptine on serum PRL, LH and FSH levels in patients with hyperprolactinemic and normoprolactinemic polycystic ovary syndrome. J. Endocrinol. Invest. 10, 389–395.

Singh, B., Panda, S., Nanda, R., Pati, S., Mangaraj, M., Sahu, P.K., Mohapatra, P.C., 2010. Effect of metformin on hormonal and biochemical profile in PCOS before and after therapy. Indian J. Clin. Biochem. 25, 367–370.

Sirmans, S.M., Pate, K.A., 2013. Epidemiology, diagnosis, and management of polycystic ovary syndrome. Clin. Epidemiol. 6, 1–13.

Souter, I., Sanchez, L.A., Perez, M., Bartolucci, A.A., Azziz, R., 2004. The prevalence of androgen excess among patients with minimal unwanted hair growth. Am. J. Obstet. Gynecol. 191, 1914–1920.

Stein, I.F. & Leventhal, M.., 1935. Amenorrhoea associated with bilateral polycystic ovaries. Am. J. Obstet. Gynecol. 29, 181–191.

Steingold, K.A., Lobo, R.A., Judd, H.L., Lu, J.K.H., Chang, R.J., 1986. The effect of bromocriptine on gonadotropin and steroid secretion in polycystic ovarian disease. J. Clin. Endocrinol. Metab. 62, 1048–1051.

Teede, H., Deeks, A., Moran, L., 2010. Polycystic ovary syndrome: A complex condition with psychological, reproductive and metabolic manifestations that impacts on health across the lifespan. BMC Med.

Velija-Ašimi, Z., 2013. Evaluation of endocrine changes in women with the polycystic ovary syndrome during metformin treatment. Bosn. J. Basic Med. Sci. 13, 180–5.

Yildiz, B.O., Knochenhauer, E.S., Azziz, R., 2008. Impact of obesity on the risk for polycystic ovary syndrome. J. Clin. Endocrinol. Metab. 93, 162–168.

Zhao, Y., Qiao, J., 2013. Ethnic differences in the phenotypic expression of polycystic ovary syndrome. Steroids.