Pharmacotherapy and Neoteric Dietary Approaches for Polycystic Ovary Syndrome: A Systematic Review

Polikistik Ovary Sendromu İçin Farmakoterapi ve Neoterik Diyet Yaklaşımları: Sistematik Bir Derlemesi

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Abstract
Polycystic ovary syndrome (PCOS) is an ovarian disorder secondary to the dysregulated hypothalamic-pituitary-adrenal axis leading to androgen excess. Numerous studies have documented that insulin resistance is the key pathophysiological element for the development of PCOS. Insulin acts synergistically with luteinizing hormone (LH) to increase androgen production in the theca of the follicles. PCOS is the most malignant endocrine disorder affecting females (7%; from adolescence to menopause). PCOS results in multi-organ derangements categorized by raised androgen levels, irregular menses, and infertility with microcysts formation. The manifestation of PCOS can be specified as polycystic ovaries (morphological) and hyperandrogenemia & hyperlipidemia (metabolic derangements). Clinical hallmarks in PCOS are dyslipidemia, impaired glucose tolerance, hyperandrogenism, microcysts in ovaries, menstrual irregularities, anovulation, and obesity. During clinical examination, a woman’s identity is markedly threatened due to hirsutism, acne, alopecia, obesity, irregular menses, and infertility symptoms. Diagnosis is based on European Society for Human Reproduction and Embryology/The American Society for Reproductive Medicine or Rotterdam consensus criteria. In this article, we present a precise and comprehensible glimpse of updated and efficient patient management via pharmacotherapy and diet therapy with the most practicable type of diets and their positive outcomes. Nutrients (inositol, isoflavonoids, omega-3) and their dose regimens are discussed. A calorie deficit of 500-1,000 kcal based on the patient profile has proven effective in re-vamping biochemical values and weight loss.

Keywords: PCOS; metformin; clomiphene; genistein; dyslipidemia; androgen

Anahtar kelimeler: PKOS; metformin; klomifen; genistein; dislipidemi; androjen

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Introduction

Polycystic ovary syndrome (PCOS) is the most malignant endocrine disorder affecting women (7% from adolescence to menopause) (1). PCOS results in multi-organ derangements categorized by raised androgen levels, irregular menses, and infertility with microcysts formation. The manifestation of PCOS can be specified as polycystic ovaries (morphological), hyperlipidemia (metabolic derangements), and hyperandrogenemia (2). Clinical hallmarks in PCOS are dyslipidemia, impaired glucose tolerance, hyperandrogenism, microcysts in ovaries, menstrual irregularities, anovulation, and obesity. During clinical examination, a woman's identity is markedly threatened due to hirsutism, acne, alopecia, obesity, irregular menses, and infertility symptoms (3). Diagnosis is based on the European Society for Human Reproduction and Embryology/The American Society for Reproductive Medicine (ESHRE/ASRM) or the 2003 Rotterdam consensus criteria. In this article, our objective is to present a precise and comprehensible glimpse of updated and efficient patient management via pharmacotherapy and diet therapy with the most feasible types of diets and their positive outcomes. Nutrients (inositol, isoflavonoids, omega-3) are discussed along with their dose regimen. A calorie deficit of 500-1,000 kcal based on the patient profile is effective in revamping biochemical values and weight loss (4).

Methodology

We conducted a joint literature search using PubMed, Elsevier, and Google Scholar for the period 2000 to 2020. Keywords used were PCOS, infertility, metformin, omega-3, nutraceuticals, insulin resistance, and diet therapy. Papers in the English language alone were considered. Initially, over 100 articles were reviewed, but only 23 research papers were shortlisted based on their acceptability and our set criteria. PRISMA flow chart diagram describes the selection of studies (Figure 1). A literature review aimed to highlight the importance of potential nutrients and types of diets with the most positive outcomes in the early management of PCOS. The ability of nutraceuticals was found to significantly ameliorate complications of PCOS and the prognosis of medical nutrition therapy.

Presentation

National Institute of Health (NIH), in 1990, proposed a list of internationally accepted diagnostic criteria. According to these criteria, both hyperandrogenemia and oligo-anovulation, are mandatory to diagnose PCOS (5). However, NIH criteria were revisited by the ESHRE and ASRM in 2003. NIH 2012 and Androgen Excess Society 2006 guidelines are listed in Table 1. The revised criteria, internationally known as Rotterdam consensus criteria, are now widely used in the diagnosis and requires a minimum of two of the following three features to confirm PCOS:

(i) Clinical or biochemical hyperandrogenism, (ii) anovulation/oligomenorrhea, and (iii) polycystic ovaries on ultrasound, with the exclusion of conditions having similar presentation (6). Polycystic and ovarian volume >10 mL in the absence of a dominant follicle or ovaries on ultrasound was defined as 12 or more follicles measuring 2-9 mm in at least one ovary. Nevertheless, as PCOS remains a diagnosis of exclusion, other endocrinopathies with similar presentation to PCOS should always be considered.

PCOS is an ovarian disorder secondary to the dysregulated hypothalamic-pituitary-ovarian axis leading to androgen excess (9). Numerous studies have also specified that insulin resistance is the key pathophysiological element for the development of PCOS. Insulin acts synergistically with luteinizing hormone (LH) to increase androgen release in the theca cells of the ovarian follicles (10). Raised levels of LH pulse frequency and an elevated ratio of LH to the follicle-stimulating hormone (FSH) in many women are reported. This abnormality of gonadotrophins is responsible for many of the ovarian features of PCOS, including increased androgen synthesis (11). Hyperandrogenism characteristically varies with race and ethnicity, but the most common manifestations include menstrual irregularities (predominantly oligomenorrhea), hirsutism, central obesity, and even frontal alopecia (12-15). Furthermore, pregnant women with PCOS carry a greater risk of de-
Developing complications such as hypertensive disorders, gestational diabetes, premature delivery, and congenital abnormalities in their neonates (16). Due to underlying metabolic and hormonal disturbances associated with PCOS, women are more susceptible to cardiovascular diseases, particularly hypertension (HTN) (17,18). Wild et al. documented in a cohort study an increased prevalence of HTN in subjects with PCOS (19). Nevertheless, the association between hypertension and PCOS remains inconclusive as few studies have reported a counter link between systolic arterial pressure and insulin sensitivity in the subjects with PCOS (20).

**Treatment**

As the primary source of PCOS remains elusive, medication is usually directed at symptoms, such as menstrual irregularities, hirsutism, infertility, and psychological issues. The first step in management for PCOS is lifestyle modification, including diet and exercise, to reduce weight. Weight loss not only helps to decrease levels of androgen, LH, and insulin but also aids in regulating ovulation, thereby improving the chances of pregnancy (21). The treatment plan should be customized to individual patients. Bariatric surgery may be considered in obese patients and cases requiring lifestyle modifications.

**Induction of Ovulation in PCOS**

PCOS is the principal cause of 70% of all anovulatory-related types of infertility (22). Hart et al. reported that infertility was ten times more common among women with PCOS in comparison to healthy controls.
For women without any plans for children, long term control can be achieved with oral contraceptive pills (OCPs). In individuals with reproductive desires, ovulation can be induced by several methods. Recently, clomiphene citrate (CC) has been universally acknowledged as the first-choice drug for inducing ovulation in PCOS individuals. After binding to estrogen receptors on the hypothalamus, the CC makes an antiestrogenic effect and stimulates a gonadotropin-releasing hormone pulse that induces gonadotropin secretion from the anterior pituitary gland. Although up to 15-40% of patients with PCOS show resistance to CC; anovulation persists despite treatment for three successive months, and such patients are considered to be “clomiphene-resistant”

Interestingly, a recent study has documented an alternative therapy of gonadotrophins as standard second-line treatment. The study formulated a new CC treatment protocol, named “intermittent CC treatment (ICT)” for non-responders to standard CC therapy. Under the protocol, the non-responders for five days were given 100 mg/day of CC for 1-3 months depending on follicular growth (size >10 mm), observed after completion of each phase of CC treatment. When the diameter of the follicle reached >18 mm, ovulation was induced by injecting 10,000 IU of human chorionic gonadotropin (hCG). Overall, ICT was effective in around 80% of the CC-resistant PCOS patients. However, gonadotrophins, letrozole, and laparoscopic ovarian diathermy therapies are also recommended in “clomiphene-resistant” subjects.

Role of Antiandrogens in the Treatment of Hirsutism

Hirsutism, a common manifestation in women with PCOS, is defined as an unnecessary growth of terminal hair at androgen-dependent areas in females analogous to male pattern. It can be managed in several ways, including by spironolactone, flutamide, finasteride, oral contraceptive pills, and laser beam. Souter et al. reported a diagnosis of PCOS on further evaluation in approximately 50% of women, who complained of unwanted excess facial hairs. Androgen excess is predominantly responsible for hirsutism, and thus, antiandrogens offer an excellent choice to counter hyperandrogenism effects. Competitive in-
of androgen-binding receptors or 5-alpha-reductase inhibitors decreases androgen production.

Spironolactone is the most commonly used antiandrogen drug (standard dose, 25-100 mg/day), generally well-tolerated, and has shown more efficacy on hirsutism than by use of OCPs (27). Flutamide 250 mg/day and finasteride 5 mg/day are other antiandrogens but are inferior to spironolactone in terms of efficacy (28). Contraception is recommended when patients use antiandrogens for the treatment of PCOS as these drugs pose a risk to the developing male fetus (opposing genital formation). Hirsutic women usually show clinical improvement approximately six months after treatment with OCPs and also present an enhanced clinical effect when OCPs are combined with antiandrogens. Ezeh et al. found that combined treatment with OCP and spironolactone showed greater improvements than with either drug individually (29).

**Role of Metformin in PCOS**

To date, numerous studies have reported on the vital role of hyperinsulinemia in the development of metabolic abnormalities in PCOS, regardless of body weight index (30,31). Metformin, a biguanide, acts to improve insulin sensitivity and thus lowers free circulating insulin as well as androgens in the bloodstream, resulting in improvement of the clinical sequelae of PCOS (32). However, despite a well-established role in the management of PCOS, conflicting results regarding its efficacy are found in the literature.

Wahab et al. conducted a study (33) on 35 female patients with established PCOS, age 20-35 years. They were given metformin (850 mg twice a day). In order to improve compliance, at every follow-up visit, patients were educated properly regarding the use of metformin. A final assessment was completed two years later with repetition of the transvaginal scan and reevaluation of all laboratory values (random blood glucose, serum insulin, LH/FSH, testosterone, prolactin, etc.). Metformin therapy for two years has shown improvements in the laboratory values. Furthermore, metformin is an effective drug to improve menstrual irregularities, LH, FSH, and testosterone, as indicated in this study (33). Similarly, numerous studies have reported that insulin-sensitizing drugs and dietary/lifestyle modifications improve not only hyperandrogenism but also menstrual irregularities, rate of ovulation, fertility, hirsutism, and weight in patients suffering from PCOS (34-36); these findings are confirmed in the current study. However, two recently published meta-analyses and systematic reviews (in which metformin efficacy was evaluated in improving reproductive outcomes for women with PCOS) concluded no significant evidence of improved rates of live births and clinical pregnancy with metformin alone or in combination with clomiphene (37,38).

In summary, metformin is an appropriate choice and plays a positive role in improving menstrual irregularities and weight reduction in females with PCOS, but current findings do not suggest its use as a first-line drug for ovulation induction. For medical practitioners, we outlined a schematic representation of an efficient clinical approach for PCOS patients in Figure 2. This provides quick insight into the management of PCOS assessment and treatment protocols.

**Role of Diet Therapy in PCOS**

Though PCOS is associated with overweight, central obesity with insulin resistance is markedly prevalent. In this article, we focused on how macronutrients and micronutrients strongly influence PCOS management. We also highlight the relationship of the type of diet with PCOS and the importance of calorie deficit for the treatment of PCOS. Besides nutritional management and pharmacotherapy, genetics, lifestyle, and ethnicity have a strong influence on the outcomes. Increased insulin resistance causes the overproduction of androgens in response to LH in ovaries. Previous studies confirm the significant role of short term calorie deficit therapy in correcting LH levels and menstrual irregularities. Levels of leptin (energy expenditure hormone) and ghrelin (ligand-increase appetite) levels get deranged in PCOS and can be corrected via calorie deficit therapy (39). Nutritional assessment and biochemical lab findings, along with physical assessment conducted by registered dietitian/nutritionist (RDN), calculates patient BMI and BMR according to
Harris-Benedict Equation. Based on the patient profile, the Dietitian (RDN) recommends a daily calorie deficit of 500-1,000 kcal.

**Inositol** present in whole grains, seeds, and fruits has two isomers D-chiro-inositol and Myo-inositol. Myo-inositol, a nutrient, belongs to the vitamin B complex. Studies have indicated the beneficial role of Myo-inositol in correcting hormonal profile, oxidative stress, and metabolic factors among PCOS patients. The dose of 4 g/d Myo-inositol along with 400 mcg/d folic acid has shown proven effects in diminishing serum androgen levels and improving glucose tolerance (40). Administration of 2-3 g/d myo-inositol plus 200 mcg/d folic acid has a beneficial role in the amelioration of plasma LH (41). D-chiro-inositol improves glucose levels and enhances uptake via post-receptor mediation of inositol phosphoglycans (IPGs), a mediator of insulin signaling pathways (42). Administration of 600-1,200 mg/dL D-chiro-inositol (DCI) for a period of 6 to 12 weeks in PCOS patients has shown positive outcomes with improving insulin resistance, serum androgen levels (43). **Isoflavonoids** (genistein and daidzein) found in soybean, chickpeas have promising effects on LDL-c levels. Administration of 18 mg genistein (twice a day) for three months significantly lowers LDL-c profile. Isoflavonoids also have

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Figure 2. Schematic representation of an efficient and multipronged clinical approach for PCOS patients.

GI: Glycemic index; LGI: Low glycemic index; HGI: High glycemic index; FA: Fatty acid; FSH: Follicle stimulating hormone; IR: Insulin resistance; LH: Leutinizing hormone; BD: (bis in die in Latin) twice daily.
a positive impact on reproductive hormones \((44)\). Mohammadi et al. conducted an 8-week study on 61 subjects of PCOS (overweight/obese) and administered omega-3 mcg/d in one group and compared placebo therapy in another group \((45)\). A significant increase was reported in HDL. TC and LDL-c levels decreased, and insulin, glucose, and HOMA returned to optimum levels. Type of diets with the most feasible and positive outcomes are summarized in Table 2. However, the type of diet to be prescribed is based on individual nutritional assessments and biochemical lab reports. We strongly recommend calorie deficit therapy (500-1,000 kcal) for PCOS patients with monitoring at regular intervals. Calories from carbohydrates should range from 40-45%, the protein starts with 15% and may increase as per patient profile. Fats should not exceed 30% of total calories. Moderate to an intense exercise of 30 min or more is effective. Exercises such as brisk walk, swimming, arm exercise while seated in a chair for 10 min have been shown to improve glycemic control.

### Conclusion

There is an urgent need to conduct extensive research at a genomic and molecular level to understand the pathophysiology of PCOS and the development of metabolic and cardiovascular outcomes in women suffering from the disorder. PCOS is a complex disorder, and the pharmacological approach is limited to the presentation and concern of the patient since the etiology of the disorder remains poorly understood. Nutraceuticals have offered new opportunities for PCOS management and show promising results.
(such as omega-3, myo-inositol, folic acid, vitamin-D, and calorie deficit diet therapy); all reduce weight and improve deranged reproductive hormones, insulin resistance, and lipid profile.

To sum up, this paper will be immensely useful for professionals and researchers and would offer a guidepost for future larger, multicentric, studies for the prevention and treatment of PCOS.

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**Conflict of Interest**

No conflicts of interest between the authors and / or family members of the scientific and medical committee members or members of the potential conflicts of interest, counseling, expertise, working conditions, share holding and similar situations in any firm.

**Authorship Contributions**

Idea/Concept: Tayyab Hamid Malik, Hussnain Ali; Design: Tayyab Hamid Malik, Hussnain Ali; Control/Supervision: Tayyab Hamid Malik; Data Collection and/or Processing: Tayyab Hamid Malik, Hussnain Ali, Amina Hassan, Junaid Quayyum, Arfah Naseem; Analysis and/or Interpretation: Tayyab Hamid Malik, Hussnain Ali, Amina Hassan, Junaid Quayyum, Arfah Naseem; Literature Review: Tayyab Hamid Malik, Hussnain Ali, Amina Hassan, Junaid Quayyum, Arfah Naseem; Writing the Article: Tayyab Hamid Malik, Hussnain Ali; Critical Review: Tayyab Hamid Malik, Hussnain Ali.

**References**

1. Centres for Disease Control and Prevention. [Link]
2. Rosenfield RL. The polycystic ovary morphology-polycystic ovary syndrome spectrum. J Pediatr Adolesc Gynecol. 2015;28:412-419.[Crossref] [PubMed] [PMC]
3. Lee H, Oh JY, Sung YA, Chung H, Cho WY. The prevalence and risk factors for glucose intolerance in young Korean women with polycystic ovary syndrome. Endocrine. 2009;36:326-332.[Crossref] [PubMed]
4. Stamets K, Taylor DS, Kunselman A, Demers LM, Pelkman CL, Legro RS. A randomized trial of the effects of two types of short-term hypocaloric diets on weight loss in women with polycystic ovary syndrome. Fertil Steril. 2004;81:630-637.[Crossref] [PubMed]
5. Zawadzki JK, Dunaif A. Diagnostic criteria for polycystic ovary syndrome; towards rational approach. In: Dunaif A, Givens JR, Haseltine F, Merriam G, eds. Polycystic Ovary Syndrome. Boston; Blackwell Scientific; 1992;418:377-384.
6. Rotterdam ESHRE/ASRM-Sponsored PCOS Consensus Workshop Group. Revised 2003 consensus on diagnostic criteria and long-term health risks related to polycystic ovary syndrome. Fertil Steril. 2004;81:19-25.[Crossref] [PubMed]
7. Azziz R, Carmina E, Dewailly D, Diamanti-Kandarakis E, Escobar-Morreale HF, Futterweit W, Janssen OE, Legro RS, Norman RJ, Taylor AE, Witchel SF; Task Force on the Phenotype of the Polycystic Ovary Syndrome of The Androgen Excess and PCOS Society. The Androgen Excess and PCOS Society criteria for the polycystic ovary syndrome: the complete task force report. Fertil Steril. 2009;91:456-488.[Crossref] [PubMed]
8. Fauser BC, Tarlatzis BC, Rebar RW, Legro RS, Balen AH, Lobo R, Carmina E, Chang J, Yildiz BO, Laven JS, Boivin J, Petraglia F, Wijeyeratne CN, Norman RJ, Dunaif A, Franks S, Wild RA, Dumesic D, Barnhart K. Consensus on women’s health aspects of polycystic ovary syndrome (PCOS): the Amsterdam ESHRE/ASRM-Sponsored 3rd PCOS Consensus Workshop Group. Fertil Steril. 2012;97:28-38. e25.[Crossref] [PubMed]
9. Azziz R, Carmina E, Chen Z, Dunaif A, Laven JS, Legro RS, Lizneva D, Natterson-Horowitz B, Teede HJ, Yildiz BO. Polycystic ovary syndrome. Nat Rev Dis Primers. 2016;2:16057.[Crossref] [PubMed]
10. Ehrmann DA. Polycystic ovary syndrome. N Engl J Med. 2005;352:1223-1236.[Crossref] [PubMed]
11. Coyle C, Campbell RE. Pathological pulses in PCOS. Mol Cell Endocrinol. 2019;498:110561.[Crossref] [PubMed]
12. Bates GW Jr, Propt AM. Polycystic ovarian syndrome management options. Obstet Gynecol Clin North Am. 2012;39:495-506.[Crossref] [PubMed]
13. Escobar-Morreale HF, Carmina E, Dewailly D, Gambineri A, Kelestimur F, Moghetti P, Puggeat M, Qiao J, Wijeyeratne CN, Witchel SF, Norman RJ. Epidemiology, diagnosis and management of hirsutism: a consensus statement by the Androgen Excess and Polycystic Ovary Syndrome Society. Hum Reprod Update. 2012;18:146-170. Erratum in: Hum Reprod Update. 2013;19:207.[Crossref] [PubMed]
14. Tsikouras P, Spyros L, Manav B, Zervoudis S, Poiana C, Nikolaos T, Petros P, Dimitraki M, Koukouri C, Galazios G, von Tempelhoff GF. Features of polycystic ovary syndrome in adolescence. J Med Life. 2015;8:291-296.[PubMed] [PMC]
15. Krishnan A, Muthusami S. Hormonal alterations in PCOS and its influence on bone metabolism. J Endocrinol. 2017;232:R99-R113.[Crossref] [PubMed]
16. Joham AE, Palomba S, Hart R. Polycystic ovary syndrome, obesity, and pregnancy. Semin Reprod Med. 2016;34:93-101.[Crossref] [PubMed]

17. Rocha Gontijo JA, Gui DC, Boer PA, Dos Santos AR, Ferreira-Filho CP, Nery Aguiar AR, Da Silva BB. Evaluation of arterial blood pressure and renal sodium handling in a model of female rats in persistent estrus. Clin Exp Hypertens. 2010;32:385-389.[Crossref] [PubMed]

18. Lenart-Lipińska M, Matyjaszek-Matuszek B, Woźniakowska E, Solski J, Tarach JS, Paszkowski T. Polycystic ovary syndrome: clinical implication in perimenopause. Prz Menopauzalny. 2014;13:348-351.[Crossref] [PubMed] [PMC]

19. Wild RA, Carmina E, Diamanti-Kandarakis E, Dokras A, Escobar-Morreale HF, Futterweit W, Lobo R, Norman RJ, Talbott E, Dumesic DA. Assessment of cardiovascular risk and prevention of cardiovascular disease in women with the polycystic ovary syndrome: a consensus statement by the Androgen Excess and Polycystic Ovary Syndrome (AE-PCOS) Society. J Clin Endocrinol Metab. 2010;95:2038-2049.[Crossref] [PubMed] [PMC]

20. Kargili A, Karakurt F, Kasapoglu B, Derbent A, Koca C, Selcoki Y. Association of polycystic ovary syndrome and a non-dipping blood pressure pattern in young women. Clinics (Sao Paulo). 2010;65:475-479.[Crossref] [PubMed] [PMC]

21. Guzick DS. Polycystic ovary syndrome. Obstet Gynecol. 2004;103:181-193. Erratum in: Obstet Gynecol. 2004;103:799.[Crossref] [PubMed]

22. Teede H, Deeks A, Moran L. Polycystic ovary syndrome: a complex condition with psychological, reproductive and metabolic manifestations that impacts health across the lifespan. BMC Medicine. 2010;8:41.[Crossref] [PubMed] [PMC]

23. Hart R, Doherty DA. The potential implications of a PCOS diagnosis on a woman’s long-term health using data linkage. J Clin Endocrinol Metab. 2015;100:911-919. Erratum in: J Clin Endocrinol Metab. 2015;100:2502.[Crossref] [PubMed]

24. Abu Hashim H, Foda O, Ghayaty E. Combined metformin-clomiphene in clomiphene-resistant polycystic ovary syndrome. J Postgrad Med Inst. 2014;13:105-110.[Crossref] [PubMed] [PMC]

25. Takasaki A, Tamura I, Okada-Hayashi M, Orita T, Tanabe M, Maruyama S, Shimamura K, Morioka H. Usefulness of intermittent clomiphene citrate treatment for women with polycystic ovarian syndrome that is resistant to standard clomiphene citrate treatment. Reprod Med Biol. 2018;17:454-458.[Crossref] [PubMed] [PMC]

26. Souter I, Sanchez LA, Perez M, Bartolucci AA, Aziz R. The prevalence of androgen excess among patients with minimal unwanted hair growth. Am J Obstet Gynecol. 2004;191:1914-1920.[Crossref] [PubMed]

27. Venturoli S, Marescalchi O, Colombo FM, Macrelli S, Ravaoli B, Bagnoli A, Paradisi R, Flamigni C. A prospective randomized trial comparing low dose flutamide, finasteride, ketocazole, and cyproterone acetate-esterogen regimens in the treatment of hirsutism. J Clin Endocrinol Metab. 1999;84:1304-1310.[Crossref] [PubMed]

28. Studen KB, Sebestyén M, Pfeifer M, Prezej J. Influence of spironolactone treatment on endothelial function in non-obese women with polycystic ovary syndrome. Eur J Endocrinol. 2011;164:389-395.[Crossref] [PubMed]

29. Ezeh U, Huang A, Landay M, Aziz R. Long-term response of hirsutism and other hyperandroergic symptoms to combination therapy in polycystic ovary syndrome. J Womens Health (Larchmt). 2018;27:892-902.[Crossref] [PubMed] [PMC]

30. Siklar Z, Berberoğlu M, Çamtosun E, Kocaay P. Diagnostic characteristics and metabolic risk factors of cases with polycystic ovary syndrome during adolescence. J Pediatr Adolesc Gynecol. 2015;28:78-83.[Crossref] [PubMed]

31. Stepto NK, Cassar S, Joham AE, Hutchison SK, Harrison CL, Goldstein RF, Teede HJ. Women with polycystic ovary syndrome have intrinsic insulin resistance on euglycaemic-hyperinsulinaemic clamp. Hum Reprod. 2013;28:777-784.[Crossref] [PubMed]

32. Costello MF, Misso ML, Wong J, Hart R, Rombauts L, Melder A, Norman RJ, Teede HJ. The treatment of infertility in polycystic ovary syndrome: a brief update. Aust N Z J Obstet Gynaecol. 2012;52:400-403.[Crossref] [PubMed]

33. Wahab S, Zahoof F, Karim R. Role of metformin in polycystic ovarian syndrome. J Postgrad Med Inst. 2013;27:179-183.[Link]

34. Diamanti-Kandarakis E, Dunaif A. Insulin resistance and the polycystic ovary syndrome revisited: an update on mechanisms and implications. Endocr Rev. 2012;33:981-1030.[Crossref] [PubMed] [PMC]

35. Janci MM, Smith RC, Odegard PS. Polycystic ovarian syndrome: metformin or thiazolidinediones for cardiovascular risk reduction? Diabetes Spectrum. 2012;25:229-237.[Crossref] [PubMed]

36. Qureshi RT, Rahim F, Haidar G. Polycystic ovarian disease; impact of metformin on fertility in women. Professional Med J. 2016;23:775-779.[Crossref]

37. Kollmann M, Martins WP, Lima ML, Craciunas L, Nasstri CO, Richardson A, Raine-Fenning N. Strategies for improving outcome of assisted reproduction in women with polycystic ovary syndrome: systematic review and meta-analysis. Ultrasound Obstet Gynecol. 2016;48:709-718.[Crossref] [PubMed]

38. Morley LC, Tang T, Yasmineh E, Norman RJ, Balen AH. Insulin-sensitising drugs (metformin, rosiglitazone, pioglitazone, D-chiro-inositol) for women with polycystic ovary syndrome, oligo amenorrhoea and subfertility. Cochrane Database Syst Rev. 2017;11:CD003053.[Crossref] [PubMed] [PMC]

39. Norman RJ, Noakes M, Wu R, Davies MJ, Moran L, Wang JX. Improving reproductive performance in overweight/obese women with effective weight management. Hum Reprod Update. 2004;10:267-280.[Crossref] [PubMed]

40. Costantino D, Minozzi G, Minozzi E, Guaraldi C. Metabolic and hormonal effects of myo-inositol in women with polycystic ovary syndrome: a double-blind trial. Eur Rev Med Pharmacol Sci. 2009;13:105-110.[PubMed]
41. Genazzani AD, Lanzoni C, Ricchieri F, Jasonni VM. Myo-inositol administration positively affects hyperinsulinemia and hormonal parameters in overweight patients with polycystic ovary syndrome. Gynecol Endocrinol. 2008;24:139-144.[Crossref] [PubMed]

42. Baillargeon JP, Iuorno MJ, Apridonidze T, Nestler JE. Uncoupling between insulin and release of a D-chiro-inositol-containing inositolphosphoglycan mediator of insulin action in obese women with polycystic ovary syndrome. Metab Syndr Relat Disord. 2010;8:127-136.[Crossref] [PubMed] [PMC]

43. Genazzani AD, Santagni S, Rattighieri E, Chierchia E, Despini G, Marini G, Prati A, Simoncini T. Modulatory role of D-chiro-inositol (DCI) on LH and insulin secretion in obese PCOS patients. Gynecol Endocrinol. 2014;30:438-443.[Crossref] [PubMed] [PMC]

44. Khani B, Mehrabian F, Khalesi E, Eshraghi A. Effect of soy phytoestrogen on metabolic and hormonal disturbance of women with polycystic ovary syndrome. J Res Med Sci. 2011;16:297-302.[PubMed] [PMC]

45. Mohammadi E, Rafraf M, Farzadi L, Asghari-Jafarabadi M, Sabour S. Effects of omega-3 fatty acids supplementation on serum adiponectin levels and some metabolic risk factors in women with polycystic ovary syndrome. Asia Pac J Clin Nutr. 2012;21:511-518.[PubMed]

46. Mehrabani HH, Salehpour S, Amiri Z, Farahani SJ, Meyer BJ, Tahbaz F. Beneficial effects of a high-protein, low-glycemic-load hypocaloric diet in overweight and obese women with polycystic ovary syndrome: a randomized controlled intervention study. J Am Coll Nutr. 2012;31:117-125.[Crossref] [PubMed]

47. Marsh KA, Steinbeck KS, Atkinson FS, Petocz P, Brand-Miller JC. Effect of a low glycemic index compared with a conventional healthy diet on polycystic ovary syndrome. Am J Clin Nutr. 2010;92:83-92.[Crossref] [PubMed] [PMC]

48. Sørensen LB, Soe M, Halkier KH, Stigsby B, Astrup A. Effects of increased dietary protein-to-carbohydrate ratios in women with polycystic ovary syndrome. Am J Clin Nutr. 2012;95:39-48.[Crossref] [PubMed] [PMC]

49. Asemi Z, Samimi M, Tabassi Z, Shakeri H, Sabihi SS, Esmaillzadeh A. Effects of DASH diet on lipid profiles and biomarkers of oxidative stress in overweight and obese women with polycystic ovary syndrome: a randomized clinical trial. Nutrition. 2014;30:1287-1293.[Crossref] [PubMed] [PMC]

50. Mavropoulos JC, Yancy WS, Hepburn J, Westman EC. The effects of a low-carbohydrate, ketogenic diet on the polycystic ovary syndrome: a pilot study. Nutr Metab (Lond). 2005;2:35.[Crossref] [PubMed] [PMC]