



# POLYCYSTIC OVARY SYNDROME: PREVENTIVE MANAGEMENT WITH LIFE STYLE MODIFICATION

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## ABSTRACT

polycystic ovary syndrome is one of the most common endocrine disorders that affect approximately 6- 20% of women of childbearing age.

It is characterized by hyperandrogenism and ovarian dysfunction along with metabolic disorders. Anovulation, hirsutism, obesity, insulin resistance and dyslipidemia may appear as clinical symptoms of polycystic ovary syndrome. There is increased risk of type 2 diabetes and cardiometabolic risk particularly in presence of obesity.

Women with polycystic ovary syndrome are at high risk of obesity which further leads to metabolic, psychological and reproductive changes.

Drugs like metformin, combined oral contraceptive pills, Spironolactone, play a key role in polycystic ovary syndrome.

Polycystic ovary syndrome is not curable, but symptoms can be managed, hence lifestyle modification including proper diet, exercise and behavioral management remain the primary and most effective prevention strategy for polycystic ovary syndrome management.

**KEYWORDS:** Polycystic ovary syndrome, hyperandrogenism, anovulation, life style modification, exercise, diet plan.

## INTRODUCTION

polycystic ovary syndrome is a heterogeneous disorder characterized by androgen excess and chronic anovulation with the clinical features of oligomenorrhea, subfertility, hirsutism and acne. Increased androgen synthesis, disrupted folliculogenesis and insulin resistance plays an important role in pathophysiology.

Polycystic ovary syndrome is universally recognized most common endocrine disorder. Women with polycystic ovary syndrome may suffer from prolonged or infrequent menstrual period or excess male hormone androgen levels.

The high amount of androgen interferes with egg development and release.

Instead of an egg being released during ovulation normal period, the cysts build up in the ovaries and polycystic ovaries become enlarged.

Management aims to subside the symptoms, lower body weight and insulin levels, restore fertility, restore regular menstruation, treat hirsutism, acne and prevent the complications.

Recent studies shows that polycystic ovary syndrome has strongly correlation with obesity, insulin resistance, hyperandrogenism, and the severity of polycystic ovary syndrome can be improved and the symptoms can be subsided through lifestyle modification like proper diet, physical exercise, behavioral changes and certain medications are also helpful such as metformin, combined oral contraceptive pills, Spironolactone or bariatric surgery.

lifestyle modification has the positive impact on the clinical improvement in fertility, menstrual function, pregnancy outcome and endocrine parameters.

## AETIOLOGY:

Obesity

Insulin resistance

Hormonal imbalance

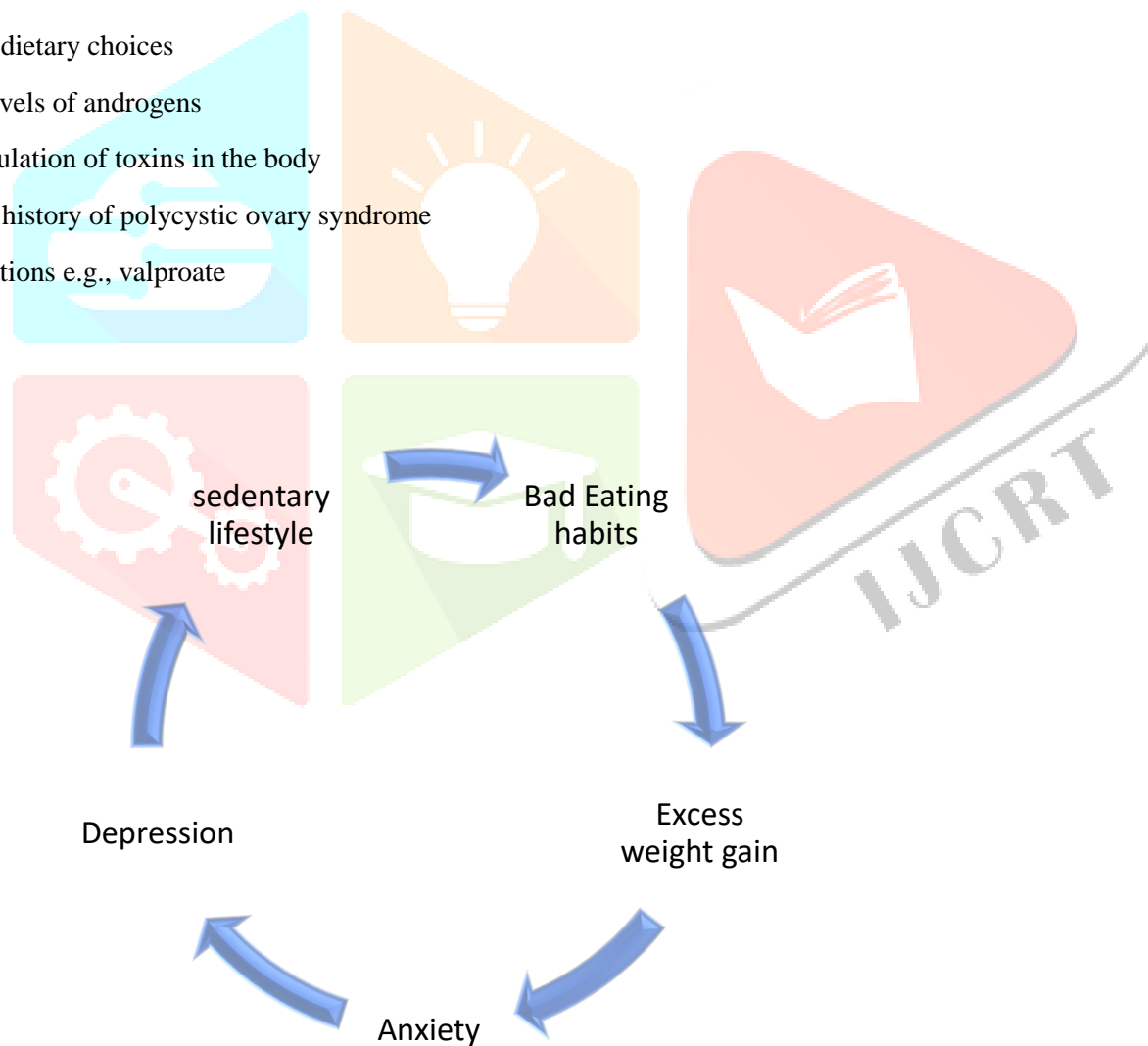
Wrong dietary choices

High levels of androgens

Accumulation of toxins in the body

Family history of polycystic ovary syndrome

Medications e.g., valproate



Some routine habits may leads to polycystic ovary syndrome condition

**CLINICAL MANIFESTATIONS:**

Insulin resistance – gestational diabetes, hyperinsulinemia

Hormonal imbalance – oligomenorrhea /anovulation, menstrual dysfunction

Metabolic syndrome – central obesity, hypertriglycerides

Hyperandrogenism - hirsutism, acne

Psychological problems – anxiety, depression and poor self-esteem.

**DIAGNOSIS:****1.Rotterdam criteria 2003**

presence of 2 out of 3 criteria considered for diagnosis:

**Hyperandrogenism-**

Clinical examination-

androgenetic alopecia, acanthosis nigricans, hirsutism and acne.

Laboratory values-

high circulating levels of androstenedione or testosterone.

**Menstrual irregularity-**

Clinical examination-

Amenorrhea or oligomenorrhea

Laboratory values-

Increased level of luteinizing hormone.

**Polycystic ovaries on ultrasonography-**

Clinical examination-

Presence of 12 or more follicles in either ovary, measuring 2-9 mm

Increased ovarian volume >10 ml

**2.National institutes of health 1990**

Both criteria required

Clinical or biochemical hyperandrogenism, Amenorrhea / oligomenorrhea, anovulation

**3.Androgen excess and polycystic ovary syndrome society 2006**

both criteria required

clinical or biochemical hyperandrogenism

Amenorrhea/ oligomenorrhea, anovulation

Ultrasound appearance of polycystic ovaries

## Differential diagnosis

Hyperprolactinaemia

congenital adrenal hyperplasia (CAH)

Androgen secreting tumors

thyroid dysfunction

Cushing syndrome

## LIFESTYLE MODIFICATION FOR POLYCYSTIC OVARY SYNDROME-

### Dietary approach:

#### Reduce Carbohydrates and sugars:

A diet low in sugar and simple Carbohydrates should be recommended to lower blood sugar level. It is always advisable to focus on the foods that are low in fat and sugar and have a low glycemic index.

low glycemic index food releases insulin slowly and steadily, making it easier for body to utilize food as an energy instead of store it as fat.

The best possible diet comprises of a variety of food sources-

**Healthy Carbohydrates-** Always choose low-glycemic index carbs which takes a long time to digest and cause slow and small rise in insulin and blood glucose levels.

**Low glycemic index foods-** Whole cereals, Chole, lobia, rajma, etc.

**Vegetables and fruits** -prefer fruits that are low in fructose and rich in fiber are good.

Strawberries, lemon, guava, pear, oranges, watermelon, apples, kiwi, tomato, capsicum, onion, broccoli, etc.

**Green leafy vegetables** - Methi, carrot, spinach, bathua, etc.

**Lean protein**-Fish, pulses, chicken, etc.

#### Healthy fats:

Increase amount of healthy fats in daily diet is a significant way to keep body satiated and helps to absorb the vitamins like A, D, E, K. Also help with healthy female hormone levels.

Nuts, almonds, cashews, corn nuts, pistachio, walnuts, black walnuts, soy nuts, sunflower seeds, pumpkin seeds, peanuts, pine nuts, flake seeds, olive oil, mustard oil, etc.

#### Decrease intake of calories:

Studies proves that a calorie restricted diet helps to normalize the hormones, treat infertility and induce ovulation.

It is suggested that to spread the calories in 5-6 small meals throughout the day which keeps metabolism potent and decrease cravings for sweets and starches.

Decrease calorie intake especially in the evening timing.

#### Monounsaturated fats:

The substances found rich in monounsaturated fat helps to fight insulin resistance related with polycystic ovary syndrome.

Olive, peanut, and canola oils, Avocados and Seeds such as pumpkin and sesame seeds. Nuts like almonds, hazelnuts, and pecans are found to contain high concentration of monounsaturated fat.

**Load on the fiber:**

Consuming fiber is to considered as " the traffic controller for a safe journey".

Daily consumption of fiber provides a feeling of fullness and able to control weight.it increases the bulk hence, helpful in delaying glucose absorption which stabilize the insulin levels.

Wheat, bajara, red gram, black gram, ragi, citrus fruits are to be considered as good sources of dietary fiber.

Eat vegetables in raw or cooked form which are low in calories.

Prefer fresh fruits daily instead of drinking fruit juice.

**B Vitamins:**

Sunflower seeds contain high amount of B vitamins which is helpful in treating the symptoms.

Vitamins B2, B3, and B6 are essential for normal thyroid metabolism and functioning thus helps in reducing excess body weight.

Vitamin B2- It converts protein, carbohydrates and dietary fat into energy.

Vitamin B3- keeps blood sugar level in normal

Vitamin B5- Its ability to control fat metabolism is helpful in weight loss

Vitamin B6- It plays an important role in maintaining female hormonal balance and fertility. Also needed for zinc absorption in the intestines.

B vitamins found in high concentrations in

Whole grains - millet, brown rice, barley.

Legumes - beans, lentils

leafy, dark vegetables - broccoli, spinach, etc.

Meat - red meat, poultry, fish.

Seeds and nuts - almonds, sunflower seeds, etc.

Fruits - citrus fruits, bananas, avocados, etc.

**Sufficient intake of vitamin D:**

In the intestine vitamin D promotes calcium absorption.

Low levels of vitamin D creates problems related to polycystic ovary syndrome, contributes to the development of weight gain, insulin resistance, and infertility.

Exposure to dusk and dawn sunlight, traditional diets rich, vitamin D supplements will be beneficial.

Food rich in vitamin D are some dairy products, Beef liver, orange juice, soy milk, cereals, Cheese, fatty fish and Egg yolks.

**Consume food rich in calcium:**

calcium plays a critical role in egg maturation and promoting the development of follicles in the ovaries.

Study shows that calcium has the positive effect on menstrual regularity, weight loss, improvement of hyperandrogenism in the infertile female with polycystic ovary syndrome.

Calcium rich foods are cheese, yogurt, sardines, dark leafy greens such as spinach, kale, turnips, and collard greens.

Fortified cereals like Raisin Bran, Corn Flakes, etc.

Fruits such as apricots, kiwi, berries orange, pineapple, papaya, etc.

Apricot contains high concentration of calcium among all fruits.

### **Eat food that contain Magnesium:**

Some research indicates that there is a strong relation between magnesium deficiency and insulin resistance correlated with polycystic ovary syndrome.

Magnesium seems to be the most common type of micronutrient and found to be depleted in diabetes and insulin resistance patients.

Almond, Spinach, cashews, Pumpkin seeds, Peanuts, Banana, etc. contains magnesium.

### **Ensure a sufficient intake of zinc:**

Zinc supplements can be a beneficial factor in treating the root cause of polycystic ovary syndrome including blood sugar balance, optimizing hormone production and reduces unwanted hair growth or acne.

Meat, Shellfish, legumes, seeds, nuts, eggs, whole grains and legumes such as chickpeas, lentils and beans all contain sufficient amount of zinc.

### **Eat plenty of food that contain chromium:**

Chromium Decreases body weight by controlling Cravings, reduce hunger, and control fat present in blood.

It is a component of the glucose tolerance factor (GTF) which requires for maintaining normal blood glucose levels. Some studies shows that chromium will be fight insulin resistance more linked with pcos.

Dietary sources of chromium are Grape juice, broccoli, tomatoes, whole grains, onions, etc

### **An anti-inflammatory diet:**

Consuming anti-inflammatory diet reduces inflammation that may contribute to polycystic ovary condition as well as helpful for controlling body weight.

Anti-inflammatory foods like, berries, extra virgin olive oil, fatty fish and leafy greens, are helpful in managing inflammation-related symptoms.

Dietary approaches to stop hypertension (DASH)-

Dietary Approaches to Stop Hypertension (DASH) diet is useful to reduce the risk of cardiovascular diseases. Also helps to manage PCOS symptoms. A DASH diet is high in fish, whole grain, low-fat dairy produce, poultry, fruits and vegetables.

Some research indicates that obese women who follows a designed diet for 8 weeks saw a decrease in belly fat and insulin resistance compared to those that did not follow the same diet.

### **Smoking Cessation:**

Quitting smoking is an important part of polycystic ovary syndrome management because that it worsens the metabolic profile in women.

Research indicates that by inhibiting aromatase activity smoking can able to decrease the estrogen level in body, and also increases the androgen levels in reproductive age women.

## **EXERCISE AND YOGA:**

### **EXERCISE:**

Dedicated individualized weight reduction program is considered as a keystone for managing and preventing obesity associated with polycystic ovary syndrome.

Exercises like zumba, aerobics, pilates, jog, yoga, walking, gym and sprint or any other mode of exercise helps to enhances the fitness level, flexibility and posture. Also helps to manage and prevent the excess weight, decreases the risk of heart disease, type 2 diabetes and control the blood pressure.

## **BENEFITS OF YOGA:**

**Yoga relieves stress**- stress produces negative effect on polycystic ovary syndrome high cortisol levels shows itself in the form of testosterone which, in turn promotes weight gain.

**Yoga promotes weight loss**-Yoga promotes calories burn in the body by pumping up the metabolism

**Yoga increases fertility**-yoga helps to increase blood supply to the brain which in turn aids to restore hormonal balance

Yoga improves gastrointestinal balance

improves depression

enhance adipose tissue lipolysis

It Decreases dependence on the medications

It improves insulin sensitivity of skeletal muscle.

Reduces body fat mass and percentage.

helps in BMI reduction.

## **DIFFERENT ASANAS THAT ARE USEFUL IN POLYCYSTIC OVARY SYNDROME:**

### **Bhujangasana (Cobra pose):**

This posture applies soothing pressure on the stomach and supports to stimulate the functions of the ovary. It also reduces stress and improves digestion.

### **Badhakonasana or butterfly pose:**

It is a simple and easily doable yoga pose that works good for natural pcos treatment.

This posture aids to open up the pelvic region and promote relaxation which helps to reduce stress and make comfort related to menstruation.

### **Supta badhakonasana (reclining butterfly)**

This posture is extremely relaxing more beneficial for pcos and performed by laying down.

### **Bharadvajasana (Bhardavaja's twist)**

It is a relaxing seated yoga pose which works for spinal column and promotes the overall relaxation by rejuvenating the spine also minimizes the symptoms of polycystic ovary syndrome. This yoga posture helps to maintain blood pressure and normalize the menstrual problems.

### **Naukasana: Boat pose**

This pose helps in reducing belly fat and best for weight loss which ultimately beneficial in polycystic ovary syndrome.

### **Dhanurasana: Bow pose**

This posture stimulates the functions of reproductive organs. regularize and normalized the menstrual cycles and relieves menstrual discomfort.

### **Viparita shalabhasana : Superman pose**

This posture promotes blood circulation to the reproductive organs and works wonderfully for developing toned abdomen and lower back muscles. Also strengthens the chest, arms, and shoulder.

**Padmasana : lotus pose**

Daily practice of this posture helps to stretch the pelvic region and correct the hormonal balance which is beneficial for polycystic ovary syndrome treatment.

This polycystic ovary syndrome eases the childbirth, relax the mind, control the blood pressure and reduces the menstrual discomfort.

**Prasarita padottanasana : Wide legged forward bend**

This pose is for toned abdominal organs

it relieves anxiety and mild depression. This yoga posture works the hips and lower back by making them flexible which in turn increases blood circulation to the ovaries.

**Marjaryasana and Bitilasana: cat and cow pose**

This kind of yoga postures brings a lot of movement in spine and provide relaxation to the shoulder and neck.

It stimulates and massages the reproductive organ and abdominal muscles and increases the functions of central nervous system.

**Balasana: child's pose**

this yoga posture provides relaxation by soothing the central nervous system. It decreases menstrual cramps, releases lower back tension and normalizes the blood flow to the whole body.

**Mill churning pose: chakki chalanasana**

This is a basic yoga pose beneficial in polycystic ovary syndrome.

natural treatment that normalizes the functions of reproductive organs. It massages the reproductive organs, uterus, kidneys, liver and pancreas also modifies the functions of endocrine gland and facilitating the optimum hormonal secretion.

**Diet chart for polycystic ovary syndrome:**

**Early morning:** green tea

4-6 Almonds in soaked form

Drink a glass of warm lemon water/

1 tsp methi dana soaked overnight chew the seeds and drink the water as well

**Breakfast:** veg. poha/upma/ gram flour pancakes/veg. oats dalia/ veg multi grain dalia/omlet with lots of veggies/Chapatti, with curd.

**in between:** 1 seasonal fruit

**Pre lunch:** Take salad half an hour before lunch

**Lunch:** multi grain chapati (2), chole/ rajma/ green leafy veg/ spinach dal/Vegetable raita.

Boiled rice with Daal/ kadi/ choley/ rajma or veg pulao with paneer, raita, and nutrila

**Snacks:** fruit salad/sprouts+ coconut water/lemon water.

**Evening tea:** A cup of green tea/ green coffee with roasted gram.

**Dinner:**Take as early as possible: veg pulav, veg khichari/veg multigrain dalia/ oats porridge/ milk porridge/fruit yogurt/ carrot kheer with jeggary/ lentil salad and have salt free dinner alternate day / lobiya chat with dhaniya chutney.

**Bedtime:** take 1 tsp of flaxseeds



## Herbal agents

### Flaxseeds:

Flaxseeds considered as a good source of Dietary fiber, omega 3 fatty acids which helps to improve insulin sensitivity in women with polycystic ovary syndrome. Flaxseed contains phytoestrogens and having an ability to keep hormonal levels in balance.

Research shows that flaxseeds are helpful in improving ovulation, lengthening the luteal phase and significantly reduces excess body weight, BMI and waist circumferences in the women with polycystic ovary syndrome Also helps to regulate the androgen levels in female with polycystic ovary syndrome.

### Cinnamon:

Taking a pinch of cinnamon powder with water in the morning time helps to promotes the glucose metabolism.

Cinnamon has an insulin sensitizing ability which regulates menstrual cycle and improve the both reproductive and metabolic aspects of polycystic ovary syndrome.

Also helpful in reducing weight.

### Fenugreek:

Daily consumption of soaked seeds with water helps to improve the insulin resistance and brings glucose control in women with polycystic ovary syndrome.

Fenugreek reduces body weight, keeps the cholesterol level in control and promotes the heart functioning.

### Carrot juice and carrot seed:

Daily carrot intake helps to regulate the menstrual cycle and minimizes menstrual cramps.

Keep hormones in balance and removes all toxins from body.

### psyllium (isapghol):

psyllium improves the insulin sensitivity and reduces the insulin resistance, hence helpful in managing symptoms. it also control the cholesterol level.

It decreases the digestion and absorption of nutrients which leads to a steady and slow release of glucose in body.

## CONCLUSION:

lifestyle modification including combined nutritional supplements and herbal medicines are very effective and safe for managing and preventing the pcos.

lifestyle interventions remain the first line treatment in improving the insulin resistance, hyperandrogenism, menstrual cycle regulation and reduces the metabolic and cardiac risk factor in women with polycystic ovary syndrome.

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**REFERENCES:**

1. Kiddy DS, Sharp PS, White DM, et al. . Differences in clinical and endocrine features between obese and non-obese subjects with polycystic ovary syndrome: an analysis of 263 consecutive cases. *Clin Endocrinol (Oxf)*. 1990;32:213–220.
2. Knochenhauer ES, Key TJ, Kahsar-Miller M, Waggoner W, Boots LR, Azziz R. Prevalence of the polycystic ovary syndrome in unselected black and white women of the southeastern United States: a prospective study. *J Clin Endocrinol Metab*. 1998;83:3078–3082.
3. Azziz R, Woods KS, Reyna R, Key TJ, Knochenhauer ES, Yildiz BO. The prevalence and features of the polycystic ovary syndrome in an unselected population. *J Clin Endocrinol Metab*. 2004;89:2745–2749.
4. Balen A. Polycystic ovary syndrome and cancer. *Hum Reprod Update*. 2001;7:522–525.
5. Fearnley EJ, Marquart L, Spurdle AB, Weinstein P, Webb PM. Polycystic ovary syndrome increases the risk of endometrial cancer in women aged less than 50 years: an Australian case-control study. *Cancer Causes Control*. 2010;21:2303–2308.
6. Ehrmann DA. Polycystic ovary syndrome. *N Engl J Med*. 2005;352:1223–1236.
7. Dunaif A, Segal KR, Futterweit W, Dobrjansky A. Profound peripheral insulin resistance, independent of obesity, in polycystic ovary syndrome. *Diabetes*. 1989;38:1165–1174.
8. Toprak S, Yönem A, Cakir B, et al. . Insulin resistance in nonobese patients with polycystic ovary syndrome. *Horm Res*. 2001;55:65–70.
9. Kiddy DS, Sharp PS, White DM, et al. . Differences in clinical and endocrine features between obese and non-obese subjects with polycystic ovary syndrome: an analysis of 263 consecutive cases. *Clin Endocrinol (Oxf)*. 1990;32:213–220.
10. Qublan HS, Yannakoula EK, Al-Qudah MA, El-Uri FI. Dietary intervention versus metformin to improve the reproductive outcome in women with polycystic ovary syndrome. A prospective comparative study. *Saudi Med J*. 2007;28:1694–1699.
11. Yildiz BO, Knochenhauer ES, Azziz R. Impact of obesity on the risk for polycystic ovary syndrome. *J Clin Endocrinol Metab*. 2008;93:162–168.
12. Cattrall FR, Healy DL. Long-term metabolic, cardiovascular and neoplastic risks with polycystic ovary syndrome. *Best Pract Res Clin Obstet Gynaecol*. 2004;18:803–812.
13. Moran LJ, Brinkworth G, Noakes M, Norman RJ. Effects of lifestyle modification in polycystic ovarian syndrome. *Reprod Biomed Online*. 2006;12:569–578.
14. Azziz R, Carmina E, Dewailly D, et al. . Positions statement: criteria for defining polycystic ovary syndrome as a predominantly hyperandrogenic syndrome: an Androgen Excess Society guideline. *J Clin Endocrinol Metab*. 2006;91:4237–4245.
15. Kiddy DS, Hamilton-Fairley D, Bush A, et al. . Improvement in endocrine and ovarian function during dietary treatment of obese women with polycystic ovary syndrome. *Clin Endocrinol (Oxf)*. 1992;36:105–111.
16. Karimzadeh MA, Javedani M. An assessment of lifestyle modification versus medical treatment with clomiphene citrate, metformin, and clomiphene citrate-metformin in patients with polycystic ovary syndrome. *Fertil Steril*. 2010;94:216–220.
17. Duncan GE, Perri MG, Theriaque DW, Hutson AD, Eckel RH, Stacpoole PW. Exercise training, without weight loss, increases insulin sensitivity and postheparin plasma lipase activity in previously sedentary adults. *Diabetes Care*. 2003;26:557–562.
18. Gillies CL, Abrams KR, Lambert PC, et al. . Pharmacological and lifestyle interventions to prevent or delay type 2 diabetes in people with impaired glucose tolerance: systematic review and meta-analysis. *BMJ*. 2007;334:299.
19. Yildirim B, Sabir N, Kaleli B. Relation of intra-abdominal fat distribution to metabolic disorders in nonobese patients with polycystic ovary syndrome. *Fertil Steril*. 2003;79:1358–1364.

20. Lee S, Kuk JL, Davidson LE, et al. . Exercise without weight loss is an effective strategy for obesity reduction in obese individuals with and without type 2 diabetes. *J Appl Physiol*. 2005;99:1220–1225.
21. Galani C, Schneider H. Prevention and treatment of obesity with lifestyle interventions: review and meta-analysis. *Int J Public Health*. 2007;52:348–359.
22. Clark AM, Ledger W, Galletly C, et al. . Weight loss results in significant improvement in pregnancy and ovulation rates in anovulatory obese women. *Hum Reprod*. 1995;10:2705–2712.
23. Moran LJ, Pasquali R, Teede HJ, Hoeger KM, Norman RJ. Treatment of obesity in polycystic ovary syndrome: a position statement of the Androgen Excess and Polycystic Ovary Syndrome Society. *Fertil Steril*. 2009;92:1966–1982.
24. Bianchi C, Miccoli R, Penno G, Del Prato S. Primary prevention of cardiovascular disease in people with dysglycemia. *Diabetes Care*. 2008;31(Suppl 2):S208–S214.
25. Colberg SR, Albright AL, Blissmer BJ, et al. . Exercise and type 2 diabetes: American College of Sports Medicine and the American Diabetes Association: joint position statement. *Exercise and type 2 diabetes*. *Med Sci Sports Exerc*. 2010;42:2282–2303.
26. Escobar-Morreale HF, Botella-Carretero JI, Alvarez-Blasco F, Sancho J, San Millán JL. The polycystic ovary syndrome associated with morbid obesity may resolve after weight loss induced by bariatric surgery. *J Clin Endocrinol Metab*. 2005;90:6364–6369.
27. Pasquali R, Gambineri A, Cavazza C, et al. . Heterogeneity in the responsiveness to long-term lifestyle intervention and predictability in obese women with polycystic ovary syndrome. *Eur J Endocrinol*. 2011;164:53–60.
28. Institute of Medicine. *Clinical Practice Guidelines We Can Trust In*. Washington, DC: National Academies Press; 2011:1–300.
29. Palomba S, Pasquali R, Orio F Jr, Nestler JE. Clomiphene citrate, metformin or both as first-step approach in treating anovulatory infertility in patients with polycystic ovary syndrome (PCOS): a systematic review of head-to-head randomized controlled studies and meta-analysis. *Clin Endocrinol (Oxf)*. 2009;70:311–321.
30. Vause TD, Cheung AP, Sierra S, et al. . Ovulation induction in polycystic ovary syndrome: no. 242, May 2010. *Int J Gynaecol Obstet*. 2010;111:95–100.
31. Higgins JP, Thompson SG, Deeks JJ, Altman DG. Measuring inconsistency in meta-analyses. *BMJ*. 2003;327:557–560.
32. Lau J, Ioannidis JP, Terrin N, Schmid CH, Olkin I. The case of the misleading funnel plot. *BMJ*. 2006;333:597–600.
33. Altman DG, Bland JM. Interaction revisited: the difference between two estimates. *BMJ*. 2003;326:219.
34. Kesaniemi YK, Danforth E Jr, Jensen MD, Kopelman PG, Lefèbvre P, Reeder BA. Dose-response issues concerning physical activity and health: an evidence-based symposium. *Med Sci Sports Exerc*. 2001;33:S351–S358.
35. Hoeger K, Davidson K, Kochman L, Cherry T, Kopin L, Guzick DS. The impact of metformin, oral contraceptives, and lifestyle modification on polycystic ovary syndrome in obese adolescent women in two randomized, placebo-controlled clinical trials. *J Clin Endocrinol Metab*. 2008;93:4299–4306.
36. Brown AJ, Setji TL, Sanders LL, et al. . Effects of exercise on lipoprotein particles in women with polycystic ovary syndrome. *Med Sci Sports Exerc*. 2009;41:497–504.
37. Guzick DS, Wing R, Smith D, Berga SL, Winters SJ. Endocrine consequences of weight loss in obese, hyperandrogenic, anovulatory women. *Fertil Steril*. 1994;61:598–604.
38. Hoeger KM, Kochman L, Wixom N, Craig K, Miller RK, Guzick DS. A randomized, 48-week, placebo-controlled trial of intensive lifestyle modification and/or metformin therapy in overweight women with polycystic ovary syndrome: a pilot study. *Fertil Steril*. 2004;82:421–429.
39. Moran LJ, Hutchison SK, Norman RJ, Teede HJ. Lifestyle changes in women with polycystic ovary syndrome. *Cochrane Database Syst Rev*. 2011:CD007506.

40. Palomba S, Falbo A, Giallauria F, et al. . Six weeks of structured exercise training and hypocaloric diet increases the probability of ovulation after clomiphene citrate in overweight and obese patients with polycystic ovary syndrome: a randomized controlled trial. Hum Reprod. 2010;25:2783–2791.
41. Yamaoka K, Tango T. Efficacy of lifestyle education to prevent type 2 diabetes: a meta-analysis of randomized controlled trials. Diabetes Care. 2005;28:2780–2786.
42. Mozaffarian D, Hao T, Rimm EB, Willett WC, Hu FB. Changes in diet and lifestyle and long-term weight gain in women and men. N Engl J Med. 2011;364:2392–2404.

