CLINICAL THERAPEUTICS

Metformin for the Treatment of the Polycystic Ovary Syndrome

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This Journal *feature begins with a case vignette that includes a therapeutic recommendation. A discussion of the clinical problem and the mechanism of benefit of this form of therapy follows. Major clinical studies, the clinical use of this therapy, and potential adverse effects are reviewed. Relevant formal guidelines, if they exist, are presented. The article ends with the author's clinical recommendations.*

A 23-year-old woman with known polycystic ovary syndrome visits her family physician. She has taken oral contraceptive pills in the past but did not tolerate them and is not currently receiving any treatment. She has three or four menstrual periods per year and is not interested in becoming pregnant now, but she will be getting married in a year. She has heard that the polycystic ovary syndrome is associated with diabetes and is concerned because both her mother and father have type 2 diabetes. Her body-mass index (the weight in kilograms divided by the square of the height in meters) is 32, her waist circumference is 38 in. (96.5 cm), her serum total testosterone level is elevated at 0.9 ng per milliliter (90 ng per deciliter, or 2.9 nmol per liter), her plasma high-density lipoprotein cholesterol level is 35 mg per deciliter (0.9 mmol per liter), and her triglyceride level is 190 mg per deciliter (2.1 mmol per liter). Her serum glucose level 2 hours after the ingestion of 75 g of dextrose is 138 mg per deciliter (7.7 mmol per liter). The physician wonders whether treatment with metformin would be beneficial and refers the patient to an endocrinologist.

THE CLINICAL PROBLEM

The polycystic ovary syndrome is a clinical diagnosis characterized by the presence of two or more of the following features: chronic oligo-ovulation or anovulation, androgen excess, and polycystic ovaries.[1] It affects 5 to 10% of women of childbearing age[2,3] and is the most common cause of anovulatory infertility in developed countries. Common clinical manifestations include menstrual irregularities and signs of androgen excess such as hirsutism, acne, and alopecia.

The polycystic ovary syndrome is associated with important metabolic derangements. The prevalence of type 2 diabetes in the United States is 10 times as high among young women with the polycystic ovary syndrome as among normal women,[4,5] and impaired glucose tolerance or overt type 2 diabetes develops by the age of 30 years in 30 to 50% of obese women with the polycystic ovary syndrome.[4-6] The prevalence of the metabolic syndrome is two to three times as high among women with the polycystic ovary syndrome as among normal women matched for age and body-mass index, and 20% of women with the polycystic ovary syndrome who are younger than 20 years of age have the metabolic syndrome.[7] Although outcome data specifically for women with the polycystic ovary syndrome are lacking, the risk of fatal myocardial infarction is twice as high among women with severe oligomenorrhea, most of whom would be expected to have the polycystic ovary syndrome, as among women with eumenorrhea.[8]

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N Engl J Med 2008;358:47-54.

PATHOPHYSIOLOGY AND EFFECT OF THERAPY

The pathophysiological characteristics of the polycystic ovary syndrome are not fully understood but are known to involve complex interactions between the actions of gonadotropins, the ovaries, androgens, and insulin (Fig. 1). An important element of this syndrome is insulin resistance. The majority of women with the polycystic ovary syndrome, regardless of weight, have a form of insulin resistance that is intrinsic to the syndrome and is poorly understood.[9-11] Obese women with the polycystic ovary syndrome have an added burden of insulin resistance related to their adiposity.[11]

The insulin resistance that is characteristic of the polycystic ovary syndrome appears to be responsible for the association of the disorder with type 2 diabetes.[12] Insulin resistance may also underlie the association of the polycystic ovary syndrome with recognized cardiovascular risk factors such as dyslipidemia and hypertension,[13] as well as with anatomical[14-17] and functional[16,18,19] cardiovascular derangements.

Insulin resistance and compensatory hyperinsulinemia also play an important role in other aspects of the polycystic ovary syndrome, including androgen excess and anovulation (Fig. 1). Insulin stimulates the ovarian production of androgen by activating its homologous receptor,[20,21] and the ovaries of women with the polycystic ovary syndrome appear to remain sensitive to insulin,[22] or perhaps hypersensitive to it,[23-25] even when classic target tissues such as muscle and fat manifest resistance to insulin action. In addition, hyperinsulinemia inhibits the hepatic production of sex hormone–binding globulin,[26] further increasing circulating free testosterone levels. Finally, insulin impedes ovulation, either by directly affecting follicular development or by indirectly increasing intraovarian androgen levels or altering gonadotropin secretion.[27] Further evidence of the influence of insulin resistance in the polycystic ovary syndrome is that multiple diverse interventions, which are related to one another only in that they lower circulating insulin levels, result in increased frequency of ovulation or menses, reduced serum testosterone levels, or both. These interventions include the inhibition of insulin release (with the use of diazoxide[20] or octreotide[28]), improvement of insulin sensitivity (with the use of diet-induced weight loss,[29] metformin,[30,31] troglitazone,[32] rosiglitazone,[23,33] or pioglitazone[34]), or the reduction of carbohydrate absorption (with the use of acarbose[35]).

Metformin, a biguanide, is the most widely used drug for the treatment of type 2 diabetes worldwide. Its primary action is to inhibit hepatic glucose production, but it also increases the sensitivity of peripheral tissues to insulin.[36] The increase in insulin sensitivity, which contributes to the efficacy of metformin in the treatment of diabetes, has also been shown in nondiabetic women with the polycystic ovary syndrome.[37] In women with the syndrome, long-term treatment with metformin may increase ovulation, improve menstrual cyclicity, and reduce serum androgen levels[30,31]; the use of metformin may also improve hirsutism.[38] If published data on the effects of metformin in the prevention of diabetes can be extrapolated to women with the polycystic ovary syndrome, then the drug may actually retard progression to glucose intolerance in affected women, as reported in a small, retrospective study.[39]

CLINICAL EVIDENCE

In 1996, it was reported that the administration of metformin to women with the polycystic ovary syndrome reduced circulating insulin levels and was associated with decreases in ovarian 17,20-lyase activity and ovarian secretion of androgens.[40] Most, but not all, subsequent studies confirmed the ability of metformin to lower fasting serum insulin[30] and androgen[31] levels in women with the polycystic ovary syndrome. However, studies specifically assessing the effects of metformin on clinical signs of androgen excess (e.g., hirsutism, acne, and androgenetic alopecia) are limited.[38]

With regard to ovulation, in results of a randomized clinical trial reported in 1998, pretreatment with metformin, as compared with placebo, increased the incidence of ovulation after subsequent treatment with clomiphene.[41] Subsequently, several studies compared metformin with placebo, metformin with no treatment, metformin plus clomiphene with clomiphene alone, or metformin plus clomiphene with placebo. The most rigorous of these studies were included in a meta-analysis by Lord et al. in 2003.[30] The meta-analysis included data from 13 trials and 543

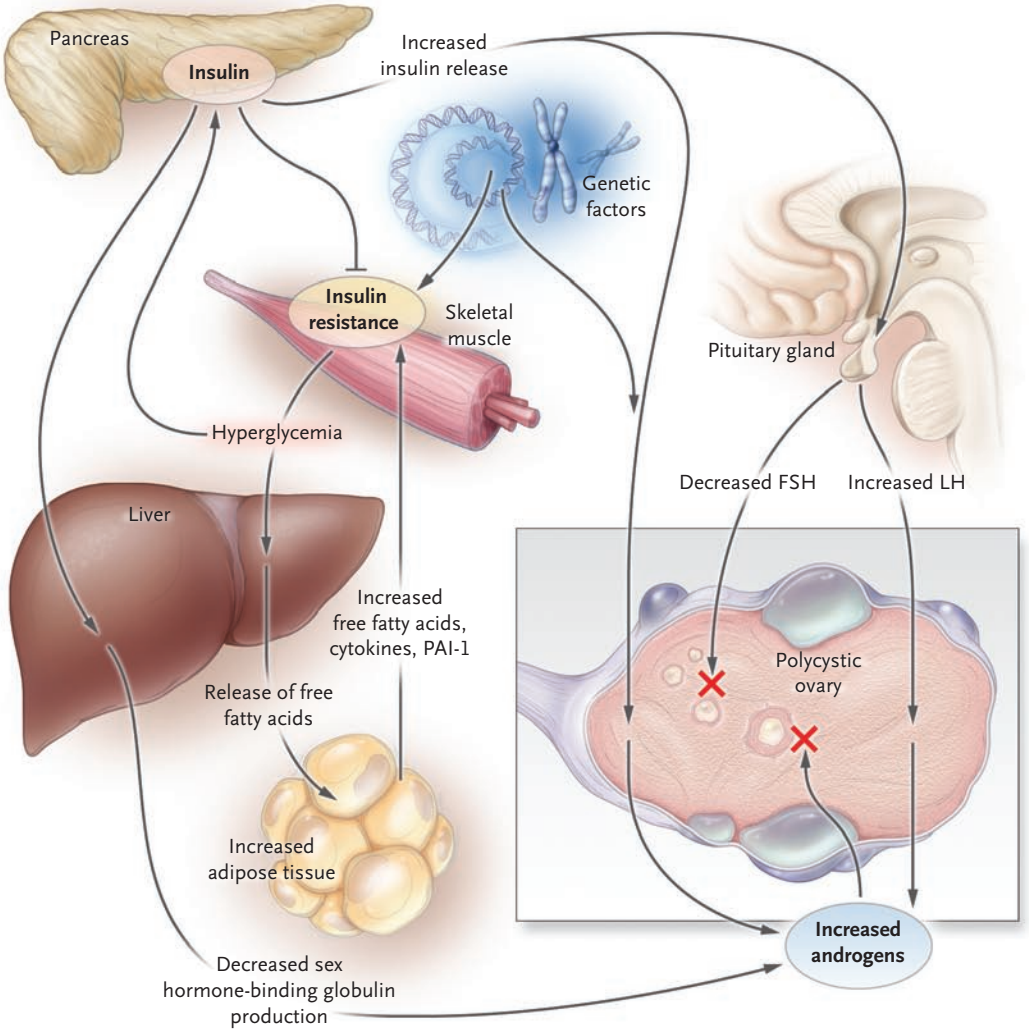

Figure 1. Pathophysiological Characteristics of the Polycystic Ovary Syndrome (PCOS).

Insulin resistance results in a compensatory hyperinsulinemia, which stimulates ovarian androgen production in an ovary genetically predisposed to PCOS. Arrest of follicular development (red "X") and anovulation could be caused by the abnormal secretion of gonadotropins such as follicle-stimulating hormone (FSH) or luteinizing hormone (LH) (perhaps induced by hyperinsulinemia), intraovarian androgen excess, direct effects of insulin, or a combination of these factors. Insulin resistance, in concert with genetic factors, may also lead to hyperglycemia and an adverse profile of cardiovascular risk factors. PAI-1 denotes plasminogen-activator inhibitor type 1.

women with the polycystic ovary syndrome; it was concluded that metformin is effective in increasing the frequency of ovulation (odds ratio, 3.88; 95% confidence interval, 2.25 to 6.69).

Since publication of the meta-analysis, three additional randomized clinical trials have been published.[42-44] They involved head-to-head comparisons of metformin or metformin plus clomiphene with clomiphene for the short-term induction of ovulation in women with the polycystic ovary syndrome who desire pregnancy, and the trials yielded conflicting results. The largest of these trials, the Pregnancy in Polycystic Ovary Syndrome trial,[42] included 626 infertile women with the polycystic ovary syndrome. It confirmed that the addition of metformin to clomiphene therapy increased the cumulative ovulation rate as compared with administration of clomiphene alone (60.4% vs. 49.0%, P=0.003), but the rate of live birth did not differ between the two groups

(26.8% and 22.5%, respectively; P=0.31). In that study, clomiphene was more effective than metformin in inducing ovulation in the short term and producing a live birth.

With regard to diabetes, two major randomized clinical trials, the Indian Diabetes Prevention Programme (IDPP-1)[45] and the U.S. Diabetes Prevention Program (DPP),[46] have shown that the use of metformin decreases the relative risk for progression to type 2 diabetes (by 26% and 31%, respectively) among patients with impaired glucose tolerance at baseline. Whether this effect of metformin truly represented the prevention of progression to diabetes, rather than simply the masking of progression by means of lowering blood glucose levels, remains controversial. However, after the discontinuation of metformin in the DPP, diabetes developed in fewer subjects than would have been expected if masking had been the sole effect.[47] To my knowledge, no randomized clinical trial has assessed the effect of metformin on the progression to type 2 diabetes specifically in patients with the polycystic ovary syndrome. In an uncontrolled, retrospective study of 50 women with the polycystic ovary syndrome treated with metformin for an average of 43 months at an academic medical center, there was no progression to type 2 diabetes, even though 11 women (22.0%) had impaired glucose tolerance at baseline.[39] The annual conversion rate from normal glucose tolerance to impaired glucose tolerance was only 1.4%, as compared with 16 to 19% reported in the literature[4,6] for women with the polycystic ovary syndrome who are not taking metformin.

CLINICAL USE

The approach to the management of the polycystic ovary syndrome depends in part on the patient's and physician's principal therapeutic objectives. For some women, infertility is the principal issue. Such patients are frequently treated in the short term with clomiphene, to induce ovulation. When fertility is not a concern, an estrogen–progestin contraceptive, with or without an antiandrogen such as spironolactone, has been the mainstay of long-term therapy. This approach is effective in achieving the traditional treatment goals in the polycystic ovary syndrome, which include ameliorating the effects of androgen excess (e.g., hirsutism, male pattern baldness, and acne) and restoring regular menses, thereby preventing endometrial hyperplasia.

However, given the metabolic derangements associated with the polycystic ovary syndrome, it seems prudent and appropriate to plan long-term therapy that addresses not only management of the consequences of androgen excess and anovulation but also the new goals of ameliorating insulin resistance and reducing the risks of type 2 diabetes and cardiovascular disease. The effect of estrogen–progestin contraceptive agents on glucose tolerance is controversial. Limited evidence from controlled, short-term studies suggests that the use of oral contraceptives aggravates insulin resistance and worsens glucose tolerance in women with the polycystic ovary syndrome.[48] The use of estrogen–progestin contraceptives is associated with a twofold increase in the relative risk of cardiovascular arterial events in the general female population[49]; the risk among women with the polycystic ovary syndrome in particular is unknown.

Metformin improves insulin sensitivity and, as noted earlier, has been shown to retard or prevent progression to type 2 diabetes in patients with impaired glucose tolerance. Although metformin has not been specifically shown to reduce the risk of cardiovascular events in patients with the polycystic ovary syndrome, the available mechanistic and clinical evidence support the use of metformin as a protective measure against the adverse cardiovascular effects of insulin resistance and insulin excess. In addition, metformin may decrease circulating androgen levels and may improve ovulation and menstrual cyclicity, thus addressing the traditional goals of long-term treatment. For these reasons, although metformin is not approved by the Food and Drug Administration for the treatment of the polycystic ovary syndrome, the drug is commonly used for this purpose.

To minimize side effects, metformin therapy is initiated at a low dose taken with meals, and the dose is then progressively increased. My practice is to have patients take 500 mg of metformin once daily with the largest meal, usually dinner, for 1 week; then increase the dose to 500 mg twice daily, with breakfast and dinner, for 1 week; increase the dose to 500 mg with breakfast and 1000 mg with dinner, for 1 week; and finally,

increase the dose to 1000 mg twice daily, with breakfast and dinner. There is no dose-ranging study of metformin in the polycystic ovary syndrome, but a dose-ranging study of patients with diabetes, using the glycated hemoglobin level as the outcome measure, suggested that a dose of 2000 mg daily is optimal.[50]

Metformin should not be used in women with renal impairment (a serum creatinine level >1.4 mg per deciliter [124 μmol per liter]), hepatic dysfunction, severe congestive heart failure, or a history of alcohol abuse. Given the young age of women with the polycystic ovary syndrome, these contraindications are rarely an issue. Repeat testing during metformin treatment is not indicated unless an illness or condition (e.g., dehydration) that might affect renal or hepatic function develops.

When metformin is prescribed, advice about a weight-loss diet and a scheduled exercise routine should also be given. Such interventions are beneficial in preventing diabetes.[45,46] In addition, weight loss increases the likelihood of resuming ovulation, most likely as a result of improved insulin sensitivity.[29,51]

The patient is asked to maintain a menstrual diary, cautioned that fertility may be rapidly established, and advised to use a barrier method of contraception. Oral contraceptive agents and antiandrogens are not administered at the initial visit, since they might affect menstruation or serum androgen levels and confound the assessment of the efficacy of metformin. Topical eflornithine can be prescribed for the treatment of facial hirsutism.

Follow-up visits are scheduled at 3 and 6 months. Menstrual cyclicity is reviewed and serum total testosterone is determined at each visit. If an improvement in menstrual cyclicity is noted, it is important to document whether the menses are ovulatory. This can be accomplished by measuring the serum progesterone level 7 days before the next onset of menses; a serum progesterone level of more than 4.0 ng per milliliter (12.7 nmol per liter) is consistent with the presence of the luteal phase and ovulation.

After 6 to 9 months of treatment, the efficacy of metformin is assessed. If menstrual cyclicity and ovulation are satisfactorily improved, further treatment is individualized. For some women, treatment with metformin alone might suffice. Women desiring contraception could be given an oral contraceptive agent while continuing to take metformin. In cases in which hirsutism remains troublesome, an oral contraceptive agent, antiandrogen, or both could be added to metformin.

ADVERSE EFFECTS

Lactic acidosis has been reported with the use of metformin, but this complication is rare (0.3 episode per 10,000 patient-years) in otherwise healthy patients and is confined primarily to patients who should not have received the drug, because they had underlying renal or hepatic disease.

The main limiting side effect of metformin, affecting 10 to 25% of patients, is gastrointestinal distress, namely nausea and diarrhea. If the nausea or diarrhea occurs at a given dose, that dose is either maintained or decreased by 500 mg per day for 2 to 4 weeks until the symptoms abate. Fortunately, the gastrointestinal side effects of metformin are usually transient; however, in a minority of cases, gastrointestinal distress may require the discontinuation of metformin.

Metformin can cause malabsorption of vitamin B_{12} in some patients receiving long-term therapy. In one analysis, risk factors for the development of this adverse effect included both the daily dose and duration of metformin therapy as well as age.[52] Although the likelihood of clinical deficiency of vitamin B_{12} appears to be low, patients should be monitored for signs and symptoms.

Metformin is a category B drug, and no teratogenic effects have been found in animal models. It was administered in South Africa to a limited number of women with type 2 diabetes or gestational diabetes, throughout their pregnancies, and no teratogenic effects or adverse fetal outcomes were reported.[31]

AREAS OF UNCERTAINTY

Although metformin is increasingly used to treat patients with the polycystic ovary syndrome, therapy is guided in part by the results of randomized, controlled trials in populations without the polycystic ovary syndrome, which showed that diabetes was prevented. Similar randomized, controlled trials specifically involving patients with the polycystic ovary syndrome are needed. Strategies for long-term metformin therapy in patients

with the polycystic ovary syndrome are evolving, and the identification of predictors of the response to metformin, possibly even through pharmacogenomic approaches, would improve the utility of this agent in the management of the polycystic ovary syndrome. Although long-term treatment with metformin seems likely to be beneficial in many patients with the polycystic ovary syndrome, less clear is when metformin should be used as monotherapy or in combination with antiandrogens or hormonal therapies. The efficacy of metformin in ameliorating the signs of androgen excess, such as hirsutism, has not been critically assessed.

Metformin has been used for many years in patients with type 2 diabetes. However, we do not have data regarding the potential long-term effects of the drug in patients treated for the polycystic ovary syndrome, in whom therapy, if effective, may be continued for many years. If a woman were to become pregnant, it is unclear whether metformin should be continued during pregnancy and, if so, for how long.

GUIDELINES

The recent position statement of the Androgen Excess Society[53] recommends that women with the polycystic ovary syndrome, regardless of weight, be screened for glucose intolerance with the use of a glucose-tolerance test at the initial presentation and every 2 years thereafter. It notes that the use of metformin to treat or prevent progression to impaired glucose tolerance may be considered but should not be mandated until there have been well-designed randomized, controlled trials demonstrating efficacy. A position statement of the American Association of Clinical Endocrinologists[54] recommends that metformin be considered the initial intervention in most women with the polycystic ovary syndrome, particularly those who are overweight or obese.

RECOMMENDATIONS

The obesity, family history of diabetes, and polycystic ovary syndrome of the patient in the vignette put her at high risk for type 2 diabetes. In addition to obesity, she has several signs of insulin resistance, including a low serum high-density lipoprotein cholesterol level and a high triglyceride level, and her data fulfill the Adult Treatment Panel III criteria of the National Cholesterol Education Program for the metabolic syndrome.[55,56] Although her glucose tolerance is currently normal, treatment with metformin is reasonable, and a weight-loss diet and exercise are also encouraged.

Although fertility is not an immediate concern, it is likely that metformin will increase the frequency of ovulation, thereby improving menstrual cyclicity. Once menstrual cyclicity has improved, I would determine whether ovulation is occurring by measuring the serum progesterone level during the presumed luteal phase. Since the patient does not tolerate oral contraceptives, a barrier method of contraception could be recommended. When and if the patient desires pregnancy, fertility may be improved if the frequency of ovulation increases during metformin therapy. If not, the patient should be evaluated for causes of infertility unrelated to anovulation, and the addition of clomiphene to her regimen should be discussed.

I would see the patient every 3 months during the first year, not only to monitor the efficacy of metformin but also to reinforce lifestyle changes to reduce weight and increase physical activity. Thereafter, she could be seen every 6 to 12 months, depending on the response to treatment. Given that she is at high risk for diabetes, I would repeat the oral glucose-tolerance test every 2 to 3 years, even if metformin therapy is used.

Supported by grants from the National Institutes of Health (R01HD035629, K24D040237, and D43TW007692).

No potential conflict of interest relevant to this article was reported.

REFERENCES

1. The Rotterdam ESHRE/ASRM-Sponsored PCOS Consensus Workshop Group. Revised 2003 consensus on diagnostic criteria and long-term health risks related to polycystic ovary syndrome (PCOS). Hum Reprod 2004;19:41-7.
2. Asunción M, Calvo RM, San Millán JL, Sancho J, Avila S, Escobar-Morreale HF. A prospective study of the prevalence of the polycystic ovary syndrome in unselected Caucasian women from Spain. J Clin Endocrinol Metab 2000;85:2434-8.
3. 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;83:3078-82.
4. Ehrmann DA, Barnes RB, Rosenfield RL, Cavaghan MK, Imperial J. Prevalence of impaired glucose tolerance and diabetes in women with polycystic ovary syndrome. Diabetes Care 1999;22:141-6.

5. Legro RS, Kunselman AR, Dodson WC, Dunaif A. Prevalence and predictors of risk for type 2 diabetes mellitus and impaired glucose tolerance in polycystic ovary syndrome: a prospective, controlled study in 254 affected women. J Clin Endocrinol Metab 1999;84:165-9.
6. Legro RS, Gnatuk CL, Kunselman AR, Dunaif A. Changes in glucose tolerance over time in women with polycystic ovary syndrome: a controlled study. J Clin Endocrinol Metab 2005;90:3236-42.
7. Apridonidze T, Essah PA, Iuorno MJ, Nestler JE. Prevalence and characteristics of the metabolic syndrome in women with polycystic ovary syndrome. J Clin Endocrinol Metab 2005;90:1929-35.
8. Solomon CG, Hu FB, Dunaif A, et al. Menstrual cycle irregularity and risk for future cardiovascular disease. J Clin Endocrinol Metab 2002;87:2013-7.
9. Chang RJ, Nakamura RM, Judd HL, Kaplan SA. Insulin resistance in nonobese patients with polycystic ovarian disease. J Clin Endocrinol Metab 1983;57:356-9.
10. Dunaif A, Graf M, Mandeli J, Laumas V, Dobrjansky A. Characterization of groups of hyperandrogenic women with acanthosis nigricans, impaired glucose tolerance, and/or hyperinsulinemia. J Clin Endocrinol Metab 1987;65:499-507.
11. Dunaif A, Segal KR, Futterweit W, Dobrjansky A. Profound peripheral insulin resistance, independent of obesity, in polycystic ovary syndrome. Diabetes 1989; 38:1165-74.
12. Lillioja S, Mott DM, Spraul M, et al. Insulin resistance and insulin secretory dysfunction as precursors of non-insulin-dependent diabetes mellitus: prospective studies of Pima Indians. N Engl J Med 1993;329:1988-92.
13. Sharma ST, Nestler JE. Prevention of diabetes and cardiovascular disease in women with PCOS: treatment with insulin sensitizers. Best Pract Res Clin Endocrinol Metab 2006;20:245-60.
14. Talbott EO, Guzick DS, Sutton-Tyrrell K, et al. Evidence for association between polycystic ovary syndrome and premature carotid atherosclerosis in middle-aged women. Arterioscler Thromb Vasc Biol 2000;20:2414-21.
15. Christian RC, Dumesic DA, Behrenbeck T, Oberg AL, Sheedy PF II, Fitzpatrick LA. Prevalence and predictors of coronary artery calcification in women with polycystic ovary syndrome. J Clin Endocrinol Metab 2003;88:2562-8.
16. Orio F Jr, Palomba S, Cascella T, et al. Early impairment of endothelial structure and function in young normal-weight women with polycystic ovary syndrome. J Clin Endocrinol Metab 2004;89:4588-93.
17. Talbott EO, Zborowski JV, Rager JR, Boudreaux MY, Edmundowicz DA, Guzick DS. Evidence for an association between metabolic cardiovascular syndrome and coronary and aortic calcification among women with polycystic ovary syndrome. J Clin Endocrinol Metab 2004;89:5454-61.
18. Paradisi G, Steinberg HO, Hempfling A, et al. Polycystic ovary syndrome is associated with endothelial dysfunction. Circulation 2001;103:1410-5.
19. Kelly CJ, Speirs A, Gould GW, Petrie JR, Lyall H, Connell JM. Altered vascular function in young women with polycystic ovary syndrome. J Clin Endocrinol Metab 2002;87:742-6.
20. Nestler JE, Barlascini CO, Matt DW, et al. Suppression of serum insulin by diazoxide reduces serum testosterone levels in obese women with polycystic ovary syndrome. J Clin Endocrinol Metab 1989; 68:1027-32.
21. Nestler JE, Jakubowicz DJ, de Vargas AF, Brik C, Quintero N, Medina F. Insulin stimulates testosterone biosynthesis by human thecal cells from women with polycystic ovary syndrome by activating its own receptor and using inositolglycan mediators as the signal transduction system. J Clin Endocrinol Metab 1998;83:2001-5.
22. Poretsky L. On the paradox of insulin-induced hyperandrogenism in insulin-resistant states. Endocr Rev 1991;12:3-13.
23. Baillargeon JP, Jakubowicz DJ, Iuorno MJ, Jakubowicz S, Nestler JE. Effects of metformin and rosiglitazone, alone and in combination, in nonobese women with polycystic ovary syndrome and normal indices of insulin sensitivity. Fertil Steril 2004;82:893-902.
24. Baillargeon JP, Nestler JE. Polycystic ovary syndrome: a syndrome of ovarian hypersensitivity to insulin? J Clin Endocrinol Metab 2006;91:22-4.
25. Baillargeon JP, Carpentier A. Role of insulin in the hyperandrogenemia of lean women with polycystic ovary syndrome and normal insulin sensitivity. Fertil Steril 2007;88:886-93.
26. Nestler JE, Powers LP, Matt DW, et al. A direct effect of hyperinsulinemia on serum sex hormone-binding globulin levels in obese women with the polycystic ovary syndrome. J Clin Endocrinol Metab 1991; 72:83-9.
27. Nestler JE. Role of hyperinsulinemia in the pathogenesis of the polycystic ovary syndrome, and its clinical implications. Semin Reprod Endocrinol 1997;15:111-22.
28. Ciotta L, De Leo V, Galvani F, La Marca A, Cianci A. Endocrine and metabolic effects of octreotide, a somatostatin analogue, in lean PCOS patients with either hyperinsulinaemia or lean normoinsulinaemia. Hum Reprod 1999;14:2951-8.
29. Norman RJ, Homan G, Moran L, Noakes M. Lifestyle choices, diet, and insulin sensitizers in polycystic ovary syndrome. Endocrine 2006;30:35-43.
30. Lord JM, Flight IH, Norman RJ. Metformin in polycystic ovary syndrome: systematic review and meta-analysis. BMJ 2003;327:951-3.
31. Cheang KI, Sharma ST, Nestler JE. Is metformin a primary ovulatory agent in patients with polycystic ovary syndrome? Gynecol Endocrinol 2006;22:595-604.
32. Azziz R, Ehrmann D, Legro RS, et al. Troglitazone improves ovulation and hirsutism in the polycystic ovary syndrome: a multicenter, double blind, placebo-controlled trial. J Clin Endocrinol Metab 2001;86:1626-32.
33. Rautio K, Tapanainen JS, Ruokonen A, Morin-Papunen LC. Endocrine and metabolic effects of rosiglitazone in overweight women with PCOS: a randomized placebo-controlled study. Hum Reprod 2006;21:1400-7.
34. Brettenthaler N, De Geyter C, Huber PR, Keller U. Effect of the insulin sensitizer pioglitazone on insulin resistance, hyperandrogenism, and ovulatory dysfunction in women with polycystic ovary syndrome. J Clin Endocrinol Metab 2004; 89:3835-40.
35. Penna IA, Canella PR, Reis RM, Silva de Sá MF, Ferriani RA. Acarbose in obese patients with polycystic ovarian syndrome: a double-blind, randomized, placebo-controlled study. Hum Reprod 2005; 20:2396-401.
36. Bailey CJ, Turner RC. Metformin. N Engl J Med 1996;334:574-9.
37. Diamanti-Kandarakis E, Kouli C, Tsianateli T, Bergiele A. Therapeutic effects of metformin on insulin resistance and hyperandrogenism in polycystic ovary syndrome. Eur J Endocrinol 1998;138:269-74.
38. Harborne L, Fleming R, Lyall H, Sattar N, Norman J. Metformin or antiandrogen in the treatment of hirsutism in polycystic ovary syndrome. J Clin Endocrinol Metab 2003;88:4116-23.
39. Sharma ST, Wickham EP III, Nestler JE. Changes in glucose tolerance with metformin treatment in polycystic ovary syndrome: a retrospective analysis. Endocr Pract 2007;13:373-9.
40. Nestler JE, Jakubowicz DJ. Decreases in ovarian cytochrome P450c17α activity and serum free testosterone after reduction in insulin secretion in polycystic ovary syndrome. N Engl J Med 1996;335: 617-23.
41. Nestler JE, Jakubowicz DJ, Evans WS, Pasquali R. Effects of metformin on spontaneous and clomiphene-induced ovulation in the polycystic ovary syndrome. N Engl J Med 1998;338:1876-80.
42. Legro RS, Barnhart HX, Schlaff WD, et al. Clomiphene, metformin, or both for infertility in the polycystic ovary syndrome. N Engl J Med 2007;356:551-66.
43. Moll E, Bossuyt PM, Korevaar JC, Lambalk CB, van der Veen F. Effect of clomifene citrate plus metformin and clomifene citrate plus placebo on induction of ovulation in women with newly diagnosed polycystic ovary syndrome: randomised double blind clinical trial. BMJ 2006;332:1485-90.

44. Palomba S, Orio F Jr, Falbo A, et al. Prospective parallel randomized, double-blind, double-dummy controlled clinical trial comparing clomiphene citrate and metformin as the first-line treatment for ovulation induction in nonobese anovulatory women with polycystic ovary syndrome. J Clin Endocrinol Metab 2005;90:4068-74.
45. Ramachandran A, Snehalatha C, Mary S, Mukesh B, Bhaskar AD, Vijay V. The Indian Diabetes Prevention Programme shows that lifestyle modification and metformin prevent type 2 diabetes in Asian Indian subjects with impaired glucose tolerance (IDPP-1). Diabetologia 2006;49:289-97.
46. Diabetes Prevention Program Research Group. Reduction in the incidence of type 2 diabetes with lifestyle intervention or metformin. N Engl J Med 2002;346:393-403.
47. *Idem.* Effects of withdrawal from metformin on the development of diabetes in the Diabetes Prevention Program. Diabetes Care 2003;26:977-80.
48. Diamanti-Kandarakis E, Baillargeon JP, Iuorno MJ, Jakubowicz DJ, Nestler JE. A modern medical quandary: polycystic ovary syndrome, insulin resistance, and oral contraceptive pills. J Clin Endocrinol Metab 2003;88:1927-32.
49. Baillargeon JP, McClish DK, Essah PA, Nestler JE. Association between the current use of low-dose oral contraceptives and cardiovascular arterial disease: a meta-analysis. J Clin Endocrinol Metab 2005;90:3863-70.
50. Garber AJ, Duncan TG, Goodman AM, Mills DJ, Rohlf JL. Efficacy of metformin in type II diabetes: results of a double-blind, placebo-controlled, dose-response trial. Am J Med 1997;103:491-7.
51. Norman RJ, Davies MJ, Lord J, Moran LJ. The role of lifestyle modification in polycystic ovary syndrome. Trends Endocrinol Metab 2002;13:251-7.
52. Ting RZ, Szeto CC, Chan MH, Chow KM. Risk factors of vitamin B12 deficiency in patients receiving metformin. Arch Intern Med 2006;166:1975-9.
53. Salley KES, Wickham EP, Cheang KI, Essah PA, Karjane NW, Nestler JE. Glucose intolerance in polycystic ovary syndrome: a position statement of the Androgen Excess Society. J Clin Endocrinol Metab 2007;92:4546-56.
54. Polycystic Ovary Syndrome Writing Committee. American Association of Clinical Endocrinologists position statement on metabolic and cardiovascular consequences of polycystic ovary syndrome. Endocr Pract 2005;11:126-34.
55. Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults. Executive summary of the third report of the National Cholesterol Education Program (NCEP) Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults (Adult Treatment Panel III). JAMA 2001;285:2486-97.
56. Grundy SM, Cleeman JI, Daniels SR, et al. Diagnosis and management of the metabolic syndrome: an American Heart Association/National Heart, Lung, and Blood Institute scientific statement. Circulation 2005;112:2735-52. [Erratum, Circulation 2005;112(17):e297-e298.]