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Viewpoints on Polycystic Ovary Syndrome



*The following is a tri-point perspective from a basic scientist, a clinical researcher and a clinical practitioner on the following questions**:*



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- Should all women with PCOS receive metformin?
- Should metformin be continued throughout pregnancy?

*** the perspective written by Walter Miller, M.D., focuses on what PCOS is (and isn't), and what its causes might be.*

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Polycystic ovary syndrome (PCOS)—a group of hyperandrogenic disorders in search of mechanism-based therapies

SUMMARY

The severe, apparently autosomal, dominant form of PCOS characterized by hyperandrogenemia and insulin resistance may be caused by gain-of-function mutations in a signal cascade leading to a serine kinase.

While it is widely agreed that the polycystic ovary syndrome (PCOS) is the most common endocrine disorder, affecting up to 10 percent of reproductive age women, there is little agreement concerning the underlying molecular mechanisms of PCOS, hence precise mechanistically-based therapies are not available. Most investigators, including myself, agree that PCOS encompasses a group of several distinct disorders characterized by oligoanovulation and hyperandrogenism, generally associated with hyperandrogenemia, increased gonadotropins and ovarian cysts. Insulin resistance, metabolic syndrome X and obesity are common¹. The past 20 years of clinical investigation have produced new insights. For many years, investigators debated whether the primary defect was in the hypothalamic-pituitary-gonadal (HPG) axis or in the ovary itself. Most now agree that hyperandrogenemia is primary and, in most patients, is of combined ovarian and adrenal origin.

Three lines of evidence support a primary disorder of androgen biosynthesis in PCOS. First, both ovarian and adrenal 19-carbon

(C19) steroid precursors of androgens are elevated in PCOS². Suppression of either the adrenal with dexamethasone or the HPG axis with gonadotrophin-releasing hormone (GnRH) agonist fails to suppress the hyperandrogenemia, but the combination of both agents does; also, adrenal C19 steroids are increased in the presence of normal ACTH levels, suggesting a primary disorder of adrenal/gonadal steroidogenesis. Second, the hyperandrogenism is genetic. Multiple studies show familial clustering with probable autosomal dominant inheritance, with a male phenotype of elevated dehydroepiandrosterone sulfate (DHEAS) levels³.

Furthermore, studies with cultured theca cells show that the abnormal steroidogenesis persists

Many PCOS women also have a heritable form of insulin resistance and secondary hyperinsulinemia, often associated with the metabolic syndrome, but independent of obesity.

with multiple cell passages, indicating a primary disorder⁴. Third, the prenatal exposure of female fetuses with congenital adrenal hyperplasia to excess androgens or the exposure of fetal rhesus monkeys to exogenous androgens recapitulates many of the features of the disordered HPG axis seen in PCOS⁵.

Many PCOS women also have a heritable form of insulin resistance and secondary hyperinsulinemia, often associated with the metabolic syndrome, but independent of obesity. Insulin binding is normal,

but there is decreased downstream signal transduction⁶. A key breakthrough is the recognition that the hyperandrogenism and insulin resistance are early events, possibly originating in fetal life and manifesting clinically before the onset of puberty⁷. Thus, PCOS is a genetic developmental disorder in both sexes and not an acquired disease confined to adult women. A central challenge for scientists studying PCOS is to identify pathways that can account for both the hyperandrogenism and the insulin resistance through a molecular mechanism that will yield dominant inheritance. As PCOS is probably a group of disorders, no mechanism will explain all forms, however, the “serine phosphorylation hypothesis”⁸, which explains dominant adrenal/ovarian hyper-

androgenemia and insulin resistance, appears to be gaining support.

A single steroidogenic enzyme, P450c17, catalyzes both 17 α -hydroxylation (needed for cortisol synthesis) and 17,20 lyase activity (needed for C19 steroid synthesis) on its single active site, yet these two activities are differentially regulated, with cortisol secretion remaining fairly constant while adrenal C19 steroids rise 100-fold during adrenarche. Serine phosphorylation of P450c17 selectively

increases the 17, 20 lyase activity without affecting the hydrolyase activity⁸. Studies in the 1980's demonstrated that serine phosphorylation of the β -chain of the insulin receptor (IR β) inhibited the receptor's tyrosine phosphorylation and consequent downstream signal transduction. Zhang et al, suggested that a gain-of-function mutation in a single cAMP-in-

lidinedione drugs, only troglitazone, but not rosiglitazone or pioglitazone inhibits P450c17 at clinically-relevant concentrations¹⁰. Thus the mechanism by which metformin lowers circulating androgens is probably by lowering insulin; whether or not this drug is effective in patients with IR β serine hyperphosphorylation remains unknown.

Although metformin's actions are mediated by activation of AMP-activated protein kinase11, its precise molecular mechanism of action remains unclear.

ducible serine kinase might hyperphosphorylate both P450c17, causing hyperandrogenism, and IR β , causing insulin resistance, providing a single autosomal dominant mechanism for the two cardinal features of PCOS⁸. Dunaif et al revealed serine phosphorylation of IR β in multiple cell types from PCOS patients⁶ and other studies have implicated a potential cascade of factors leading to the kinase, several of which might also cause a similar autosomal dominant phenotype⁹. Other mechanisms, notably the allosteric action of cytochrome b5, also foster the 17, 20 lyase activity of P450c17, but appear to be unconnected with insulin action. Thus, studies of the biochemistry, cell biology and genetics of androgen-producing tissues have begun to suggest the broad outlines of at least one mechanism likely to account for some, but not all forms of PCOS.

It has been suggested that various insulin-sensitizing drugs specifically inhibit the 17, 20 lyase activity of P450c17. While it is true that such drugs lower circulating concentrations of C19 steroids, metformin has no action on P450c17, and among the thiazo-

Although metformin's actions are mediated by activation of AMP-activated protein kinase¹¹, its precise molecular mechanism of action remains unclear. Therefore, it is premature to suggest that there is a scientific basis for clinical decisions about who should be treated with metformin, or whether it should be used during pregnancy. Metformin is a low-potency compound used in high doses. Data in rats show much higher concentrations in liver than in plasma; concentrations in the human fetus and placenta are not known. Metformin is listed as a Category B drug, meaning safety in pregnancy has not been established, but significant teratogenicity is not apparent, either. As it is clear that infants of hyperglycemic mothers have a higher incidence of congenital malformations, the desirability of glycemic control during pregnancy is clear. Thus conservative physicians generally manage pregnant type 2 diabetic patients with insulin rather than with oral agents; the same logic would seem to apply to pregnant women with PCOS. **EN**

REFERENCES:

- 1 Sam S, Dunaif A. Polycystic ovary syndrome: syndrome XX? *Trends Endocrinol Metab* 2003; 14:365-370.
- 2 Rosenfield RL. Ovarian and adrenal function in polycystic ovary syndrome. *Endocrinol Metab Clin North Am* 1999; 28:265-
- 3 Legro RS, Straus, JF III. Molecular progress in infertility: polycystic ovary syndrome. *Fertil Steril* 2002; 78:569-576.
- 4 Nelson VL, Qin K, Rosenfield RL, et al. The biochemical basis for increased testosterone production in theca cells propagated from patients with polycystic ovary syndrome. *J Clin Endocrinol Metab* 2001; 12:5925-5933.
- 5 Abbott DH, Dumesic DA, Eisner JR, Colman RJ, Kemnitz JW. Insights into the development of polycystic ovary syndrome (PCOS) from studies of prenatally androgenized female rhesus monkeys. *Trends Endocrinol Metab* 1998; 9:62-67.
- 6 Venkatesan AM, Dunaif A, Corbould A. Insulin resistance in polycystic ovary syndrome: Progress and paradoxes. *Rec Prog Horm Res.* 2001; 56:295-308.
- 7 Ibañez L, Valls C, Potau N, Marcos MV, deZegher F. Polycystic ovary syndrome after precocious pubarche: ontogeny of the low-birthweight effect. *Clin Endocrinol* 2001; 55:667-672.
- 8 Zhang L, Rodriguez H, Ohno S, Miller WL. Serine phosphorylation of human P450c17 increases 17,20-lyase activity: Implications for adrenarche and the polycystic ovary syndrome. *Proc Natl Acad Sci USA* 1995; 92 :10619-10623.
- 9 Pandey AV, Mellon SH, Miller WL. Protein phosphatase 2A and phosphoprotein SET regulate androgen production by P450c17. *J Biol Chem* 2003; 278: 2837-2844.
- 10 Arlt W, Auchus RJ, Miller WL. Thiazolidinediones but not metformin directly inhibit the steroidogenic enzymes P450c17 and 3 β -hydroxysteroid dehydrogenase. *J Biol Chem* 2001; 276:16767-16771.
- 11 Zhou G, Myers R, Li Y, et al. Role of AMP-activated protein kinase in mechanism of metformin action. *J Clin Invest* 2001; 108:1167-1174.

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The polycystic ovary syndrome (PCOS) affects five to 10 percent of reproductive age women, and is the most common cause of female infertility due to anovulation in the United States. Arguably, the most significant advance in our understanding of the syndrome during the past decade has been the appreciation that women with PCOS suffer from insulin resistance that is independent of obesity. Hence, lean women with PCOS possess a form of insulin resistance that is intrinsic to the syndrome and poorly understood. At the same time obese women with PCOS are markedly insulin resistant because they suffer from the combination of the insulin resistance intrinsic to PCOS and the insulin resistance of excess adiposity.

Treatment of PCOS can be divided into acute therapy to enhance fertility, and chronic therapy to address traditional therapeutic targets such as signs of androgen excess, oligomenorrhea and risk for endometrial hyperplasia/cancer. Because women with PCOS are at markedly increased risk for developing type 2 diabetes and, although more controversial, cardiovascular disease, novel targets for chronic therapy should likely also include prevention of diabetes and cardiovascular disease.

Space limitations and the nature of the two questions posed dictate that this review focus primarily on acute therapy for fertility. However, it should be noted that a cogent argument can be advanced for the use of Metformin as chronic therapy in most women with

PCOS. The basis for such a proposal includes, but is not limited to, the fact that 1) insulin resistance is highly prevalent among women with PCOS, 2) women with PCOS compose one of the groups at highest risk for the development of type 2 diabetes, and 3) the use of insulin sensitizing drugs in non-diabetic women at high risk for diabetes has been shown to decrease conversion to type 2 diabetes^{1,2}. Insulin resistance may also play a role in the putative increased risk for cardiovascular disease in PCOS³⁻⁶, and emerging evidence suggests that insulin-sensitizing drugs may ameliorate this risk⁷⁻⁹. Insulin-sensitizing drug therapy should be coupled with lifestyle modification, a nonpharmacologic intervention for improving insulin sensitivity. The use of insulin-sensi-

effect of insulin resistance on ovulation, improving insulin sensitivity in PCOS, either through diet and exercise or administration of an insulin-sensitizing drug, has been reported to increase the frequency of ovulation, improve menstrual cyclicity, enhance the success rate of induction of ovulation with clomiphene citrate, and decrease ovarian androgen production¹¹. These salutary effects have been observed in both lean and obese women with PCOS, and suggested guidelines for the use of Metformin to enhance pregnancy have been published¹².

The insulin-sensitizing drug studied most widely in PCOS is Metformin. The efficacy of Metformin in enhancing fertility in PCOS was recently confirmed by a meta-analysis published by the

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tizing drugs as chronic therapy for PCOS is a controversial and critical issue, and the reader is referred to an editorial that addresses the issue in greater detail¹⁰.

Insulin resistance and its compensatory hyperinsulinemia may hinder ovulation in PCOS through a variety of mechanisms, including but not limited to increased intraovarian androgens, altered gonadotropin secretory dynamics, or direct actions of insulin on the ovary. Consonant with the adverse

Cochrane Library¹³. This critical analysis of the world literature assessed 13 randomized trials involving 543 women with PCOS, and reported that Metformin significantly increased the frequency of ovulation compared to placebo (odds ratio of 3.9; CI 2.3-6.7). When Metformin was used in conjunction with clomiphene citrate it was superior to clomiphene alone in inducing an ovulation (odds ratio of 4.4; CI 2.4-8.2) and yielding a clinical pregnancy (odds ratio

of 4.4; CI 2.0-9.9). In fact, the number needed to treat (NNT) for Metformin monotherapy was only 4.4, and for Metformin plus clomiphene 3.0. In comparison to drugs administered for the treatment of hypertension, hyperlipi-

demia, or osteoporosis where the NNT is commonly between 15-25, the efficacy of Metformin appears dramatic. Moreover, these studies likely underestimated the true benefit of Metformin, since most were short-term (3-6 months), and Metformin treatment may require several months to achieve a full effect.

Although Metformin is a class B drug that appears to be safe during pregnancy, are there untoward effects of Metformin for ovulation induction that have not been identified?

It is noteworthy that the majority of studies of Metformin in PCOS did not screen women for the presence of insulin resistance or use insulin resistance as an inclusion criterion. Moreover, studies involving lean women with PCOS have reported equally positive findings. No clear predictors of a positive response to Metformin have been identified, and even lean women with seemingly normal indices of insulin action respond to treatment with Metformin.

Given the demonstrated efficacy of Metformin in PCOS, the lack of confirmed predictors of positive response, and the limited risk of toxicity, a strong case can be made for an empiric trial of Metformin in all women with PCOS pursuing pregnancy.

Nonetheless, several questions remain. Is Metformin monotherapy superior to clomiphene citrate in the induction of ovulation? Should Metformin be added to clomiphene immediately, or only after demonstrated failure of

clomiphene alone? Although Metformin is a class B drug that appears to be safe during pregnancy, are there untoward effects of Metformin for ovulation induction that have not been identified?

An National Institutes of Health (NIH) trial, currently being conducted by the Reproductive Medicine Network (RMN) will soon answer many of these queries. The goal of the trial is to determine the optimal pharmacologic therapy for initial induction of ovulation in women with PCOS who are seeking pregnancy. Eligible women are randomized to one of three treatment arms (Metformin alone, clomiphene alone, or Metformin plus clomiphene), and the primary outcome measure is a live birth. Approximately 450 women have entered the trial thus far, and a total of 678 women will be studied. More information on the trial and participating sites can be found at <http://rmn.dcri.duke.edu>

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Whether women with PCOS should remain on Metformin during pregnancy is a more difficult and controversial question. PCOS is associated with a 30 to 40 percent rate of early pregnancy loss (EPL), defined as miscarriage of a clinically recognized pregnancy during the first trimester. In most

cases no apparent cause can be identified but, in addition to defects in the developing embryo, adverse alterations in endometrial function may play a role.

In this regard, hyperinsulinemia has been identified as an independent risk factor for EPL. Studies in PCOS suggest that hyperinsulinemia suppresses endometrial expression of glycodeilin¹⁴, a protein whose circulating concentration may reflect endometrial function. Conversely, administration of Metformin to women with PCOS has been shown to increase circulating glycodeilin¹⁵. Glycodeilin is secreted by the endometrium, may inhibit the endometrial immune response to the embryo, and likely plays a critical role during implantation and in the maintenance of pregnancy. Moreover, both EPL and retarded endometrial development are associated with decreased secretion of glycodeilin from secretory endometrium.

Two retrospective studies have reported that continued administration of Metformin during pregnancy markedly decreased EPL in PCOS^{16,17}. However, neither study identified the requisite duration of administration of Metformin, nor did they exclude the possibility that simply conceiving on Metformin might have conferred full benefit.

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With these caveats in mind, it may be reasonable to maintain a pregnant woman with PCOS on Metformin through the first



trimester if there is a history of prior miscarriage, and then discontinuing the Metformin since the period of greatest risk will have passed. What should we do with a woman with PCOS who is pregnant for the first time? My personal approach is to discuss with the woman our understanding of the literature to date, and to let her wishes help guide the decision process.

In summary, Metformin is an important and effective treatment of infertility in PCOS. Since predictors of response have not been identified, the response rate is high (as reflected by a low NNT), and risks are low, an empiric trial of Metformin in all women with PCOS seeking pregnancy seems reasonable. Guidelines for the use of Metformin for this purpose have been suggested. However, many questions regarding the treatment of infertility with Metformin remain outstanding, and we all await the findings of large-scale trials such as the RMN trial currently underway. **EN**

REFERENCES

¹ Buchanan TA, Xiang AH, Peters

RK, Kjos SL, Marroquin A, Goico J, Ochoa C, Tan S, Berkowitz K, Hodis HN, Azen SP. Preservation of pancreatic beta-cell function and prevention of type 2 diabetes by pharmacological treatment of insulin resistance in high-risk hispanic women. *Diabetes* 2002; 51(9):2796-2803.

² Knowler WC, Barrett-Connor E, Fowler SE, Hamman RF, Lachin JM, Walker EA, Nathan DM. Reduction in the incidence of type 2 diabetes with lifestyle intervention or Metformin. *N Engl J Med* 2002; 346:393-403.

³ Christian RC, Dumesic DA, Behrenbeck T, Oberg AL, Sheedy PF, Fitzpatrick LA. Prevalence and predictors of coronary artery calcification in women with polycystic ovary syndrome. *J Clin Endocrinol Metab* 2003; 88(6):2562-2568.

⁴ Paradisi G, Steinberg HO, Hempling A, Cronin J, Hook G, Shepard MK, Baron AD. Polycystic ovary syndrome is associated with endothelial dysfunction. *Circulation* 2001; 103(10):1410-1415.

⁵ Talbot EO, Guzik DS, Sutton-Tyrell K, McHugh-Pemu KP, Zborowski JV, Remsberg KE, Kuller LH. Evidence for association between polycystic ovary syndrome and premature carotid atherosclerosis in middle-aged women. *Arterioscler Thromb Vasc Biol* 2000; 20(11):2414-2421.

⁶ Dereli D, Ozgen G, Buyukkececi F, Guney E, Yilmaz C. Platelet dysfunction in lean women with polycystic ovary syndrome and association with insulin sensitivity. *J Clin Endocrinol Metab* 2003; 88(5):2263-2268.

⁷ Morin-Papunen L, Rautio K, Ruokonen A, Hedberg P, Puukka M, Tapanainen JS. Metformin reduces serum C-reactive protein levels in women with polycystic ovary syndrome. *J Clin Endocrinol Metab* 2003; 88(10):4649-4654.

⁸ Paradisi G, Steinberg HO, Shepard MK, Hook G, Baron AD. Troglitazone therapy improves endothelial function to near normal levels in women with polycystic ovary syndrome. *J Clin Endocrinol Metab* 2003; 88(2):576-580.

⁹ Diamanti-Kandarakis E, Spina G, Kouli C, Migdalis I. Increased endothelin-1 levels in women with polycystic ovary syndrome and the ben-

eficial effect of Metformin therapy. *J Clin Endocrinol Metab* 2001; 86(10):4666-4673.

¹⁰ 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(5):1927-1932.

¹¹ Baillargeon JP, Iuorno MJ, Nestler JE. Insulin sensitizers for polycystic ovary syndrome. *Clin Obstet Gynecol* 2003; 46(2):325-340.

¹² Nestler JE, Stovall DW, Akhter N, Iuorno MJ, Jakubowicz DJ. Strategies for the use of insulin-sensitizing drugs to treat infertility in women with polycystic ovary syndrome. *Fertil Steril* 2002; 77:209-215.

¹³ Lord JM, Flight IH, Norman RJ. Metformin in polycystic ovary syndrome: systematic review and meta-analysis. *BMJ* 2003; 327(7421):951-953.

¹⁴ Jakubowicz DJ, Essah PA, Seppala M, Jakubowicz S, Baillargeon JP, Koistinen R, Nestler JE. Reduced Serum Glycodelin and Insulin-Like Growth Factor-Binding Protein-1 in Women with Polycystic Ovary Syndrome during First Trimester of Pregnancy. *J Clin Endocrinol Metab* 2004; 89(2):833-839.

¹⁵ Jakubowicz DJ, Seppala M, Jakubowicz S, Rodriguez-Armas O, Rivas-Santiago A, Koistinen H, Koistinen R, Nestler JE. Insulin reduction with Metformin increases luteal phase serum glycodelin and insulin-like growth factorbinding protein 1 concentrations and enhances uterine vascularity and blood flow in the polycystic ovary syndrome. *J Clin Endocrinol Metab* 2001; 86:1126-1133.

¹⁶ Glueck CJ, Phillips H, Cameron D, Sieve-Smith L, Wang P. Continuing Metformin throughout pregnancy in women with polycystic ovary syndrome appears to safely reduce first-trimester spontaneous abortion: a pilot study. *Fertil Steril* 2001; 75:46-52.

¹⁷ Jakubowicz DJ, Iuorno MJ, Jakubowicz S, Roberts KA, Nestler JE. Effects of Metformin on early pregnancy loss in the polycystic ovary syndrome. *J Clin Endocrinol Metab* 2002; 87:524-529.

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The effectiveness of the biguanide metformin in the treatment of the polycystic ovary syndrome (PCOS) has been amply confirmed. It is generally preferred to insulin-sensitizing agents such as the available thiozolidinediones pioglitazone and rosiglitazone which may induce further weight gain, edema and rare hepatic laboratory abnormalities. Improved insulin resistance in PCOS is frequently associated with improved menstrual cyclicity and some anti-androgenic effect such as the reduction of hirsutism, acne and reduction of acanthosis nigricans secondary to the hyperinsulinism. In association with a modified carbohydrate diet, caloric restriction and exercise, a number of patients demonstrate weight reduction, which is associated with improved parameters of hyperinsulinism, increased sex-hormone binding globulin (SHBG), reduction of steroidogenic dysregulation and possible coincident decrease in luteinizing hormone (LH) secretion reducing ovarian androgen production.¹ The latter findings are more evident in women with higher insulin levels, lower androgen levels, and less severe menstrual abnormalities.²

The question of whom to treat with metformin is an important consideration in women with PCOS. Should all women with PCOS be treated with metformin? The fact that at least one in three show evidence of ovulatory cycles with the drug makes it, in my view and those of some other clinical researchers, the initial drug of choice in any woman with PCOS, particularly those desiring fertility.

In my experience with 600 PCOS patients treated with metformin, as the insulin level declines with or without significant weight loss, approximately 50 percent have improved menstrual cyclicity, often occurring as early as two months after initiation of therapy, and of these desiring fertility, nearly 30 to 40 percent become pregnant. The response rate is often better in nonobese patients with PCOS who are treated with metformin.³ Parenthetically, the use of metformin in those with evidence of insulin resistance (IR) and/or

with PCOS. Although, a recent landmark study by Diamanti-Kandarakis et al of 59 women with PCOS of varying body weights, demonstrated a lack of correlation of the HOMA and QUICKI methodologies and insulin sensitivity as determined by the euglycemic-hyperinsulinemic clamp.⁶ This study underscores a probable underestimation of published studies of IR in women with PCOS, who have a unique form of IR, and where mild IR may be present with borderline normal fasting glucose and insulin levels..

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impaired glucose tolerance (IGT) is clear, but what about those with normal glucose and insulin levels? In view of demonstrable changes in IR in lean and obese adolescents with PCOS aged 12 to 18 years⁴ as well as older subjects⁵ it is reasonable to start metformin in conjunction with caloric restriction and exercise in obese and nonobese patients at the time of diagnosis of PCOS.

Recently, data has shown the failure of the usual means of assessing IR with methodologies that only measure fasting glucose and insulin levels including homeostasis model assessment (HOMA) and the quantitative insulin sensitivity check index (QUICKI) in assessing insulin sensitivity.⁶ These had not been specifically assessed in women

Perhaps other hormonal factors, as well as ethnicity, may influence the degree of IR, and yield conflicting reports of the incidence of IR in women with PCOS. Thus the use of metformin in most women with PCOS appears to be a desirable treatment option.

Contraindications to the use of metformin include women with impairment of renal function, namely a serum creatinine level of 1.4 mg percent or greater, significant hepatic dysfunction, alcohol binge drinkers, and inability to tolerate some of the side effects of the drug. Initial side effects are common including, nausea, bloating, flatulence, occasional vomiting and frequent bowel movements. Most are significantly reduced after the first four to eight weeks, but bowel

frequency often remains an intermittently annoying symptom. The patient is advised to take the drugs with food, and to plan a snack between breakfast and lunch, in the afternoon and before bedtime, to avoid symptoms of postprandial hypoglycemia (tiredness, lack of concentration, possible tremulousness, sleepiness, hunger and irritability). The latter is unlikely to be related to metformin and usually due to reactive hyperinsulinism particularly after a carbohydrate-rich meal. It is standard practice to stop the drug at the time of an iodine-contrast study, intercurrent infection, and prior to major surgery. Most patients are able to tolerate the drug when given in slow increments (500 mg with a meal per 10 to 14 day intervals) to a desired level of at least 1500 mg/day in divided doses, with a view to increasing this to 2000-2500 mg daily as necessary. The use of supplementing these patients with folic acid and vitamin B12 is also recommended due to a reduction in their intestinal absorption with metformin.

Improvement of mental status and energy is noted in most patients treated with the drug. The frequent sense of well-being and a reduction of depression encourage many to improve their lifestyle and thus reduce potential cardiovascular risks inherent in PCOS. Parenthetically, combined systematic weight loss and exercise may be more effective than metformin alone in women with PCOS and IR. The addition of nonandrogenic oral contraceptive formulations in association with antiandrogens are used in conjunction with metformin in those seeking relief from common symptoms of persistent acne, hirsutism and alopecia noted in this syndrome.⁷ These drugs are effective in buffering the effects of some of the factors involved in the pathophysiology of PCOS.

Recent data confirm earlier studies suggesting the use of metformin

in PCOS women with recurrent miscarriages.⁸ Jakubowicz et al conducted a retrospective study of 36 pregnancies in women with PCOS with a prior history of miscarriage and compared the results obtained with the use of metformin to those in a control group of 12 pregnant women.⁹ Four of the 36 PCOS treated women miscarried (11.1 percent) as compared with seven of 12 pregnancies in the control group (58.3 percent). The hypothesis that hyperinsulinemic IR contributes to the high frequency of first-trimester pregnancy loss appears tenable, and administration of metformin during the first trimester of pregnancy to these women may be a reasonable option. The experience in my practice supports this conclusion in six women with PCOS and a history of one or two early miscarriages, with four achieving full-term pregnancies with no maternal complications or birth defects following use of metformin during the entire course of the pregnancy. In PCOS patients with no prior history of early pregnancy loss, I routinely discontinue metformin once pregnancy is established.

In conclusion, my view as a clinical practitioner, is that most women with PCOS should be on metformin as initial monotherapy for infertility and if unsuccessful have concomitant treatment with clomiphene citrate. Women with symptoms related to the pilosebaceous unit should be treated conjointly with antiandrogens (usually spironolactone, and sometimes flutamide) and oral contraceptives. What I call, "triple therapy," in association with lifestyle modifications, is the preferred treatment for PCOS patients with skin manifestations and/or menstrual dysfunction. Long-term use for PCOS patients, awaits longitudinal or cross-sectional studies demonstrating a reduced incidence of cardiovascular disease and diabetes mellitus in this heterogeneous entity. **EN**

REFERENCES:

- ¹ Nestler JE, Jakubowicz DJ. Lean women with polycystic ovary syndrome respond to insulin reduction with decreases in ovarian P450c17 alpha activity and serum androgens. *J Clin Endocrinol Metab* 1997;82:524-30.
- ² Fleming R, Hopkinson ZE, Wallace AM, Greer IA, Sattar N. Ovarian function and metabolic factors in women with oligomenorrhea treated with metformin in a randomized, double-blind, placebo-controlled trial. *J Clin Endocrinol Metab* 2002;87:569-74.
- ³ Maciel GA, Soares Junior JM, Alves da Motta EL, Abi Haidar M, deLima GR, Baracat ECD, Mouslech T, Rousso D. Nonobese women with polycystic ovary syndrome respond better than obese women to treatment with metformin. *Fertil Steril* 2004;81:355-60.
- ⁴ Silfen ME, Denburg MR, Manibo AM, Lobo RA, Jaffe R, Ferin M, Levine LS, Oberfield SE. Early endocrine, metabolic and sonographic characteristics of polycystic ovary syndrome (PCOS): comparison between nonobese and obese adolescents. *J Clin Endocrinol Metab* 2003;88:4682-8.
- ⁵ Dunaif A, Segal KR, Futterweit W, Dubrjansky A. Profound peripheral insulin resistance, independent of obesity, in polycystic ovary syndrome. *Diabetes* 1989;38:1165-74.
- ⁶ Diamanti-Kandarakis E, Houli C, Alexandraki K, Spina G. Failure of mathematical indices to accurately assess insulin resistance in lean, overweight, or obese women with polycystic ovary syndrome. *J Clin Endocrinol Metab* 2004;89:1273-6.
- ⁷ Futterweit W. Polycystic ovary syndrome: clinical perspectives and management. *Obstet Gynecol Survey* 1999;40:3-13.
- ⁸ Glueck CJ, Phillips H, Cameron D, Sieve-Smith L, Wang P. Continuing metformin throughout pregnancy in women with polycystic ovary syndrome appears to safely reduce first-trimester spontaneous abortion: a pilot study. *Fertil Steril* 2001;75:46-52.
- ⁹ Jakubowicz DJ, Iuorno MJ, Jakubowicz S, Roberts KA, Nestler JE. Effects of metformin on early pregnancy loss in the polycystic ovary syndrome. *J Clin Endocrinol Metab* 2002;87:524-9.