undergo safe and effective ovarian biopsy to preserve ovarian tissue is a separate question. Given the intrusiveness of biopsy, the probable lack of insurance coverage for this measure, and the uncertainty of child-rearing plans in young adulthood, the number of younger women who choose this option may be small. However, if ovarian biopsy proves to be a safe and effective method to preserve ovarian function for later reproduction, it will be an important alternative for women who postpone having a family to a later age.

John A. Robertson, J.D.
Law School
University of Texas
Austin, Texas
July 12, 2000

PII S0015-0282(00)01575-2

Insulin-Sensitizing Agents and Their Effect on Adrenal Androgens?

To the Editor:

We read with interest the paper by la Marca et al. (1) about the effects of metformin on adrenal steroidogenesis in women with the polycystic ovary syndrome (PCOS). The study suggested that metformin therapy reduces plasma concentrations of free testosterone and the adrenal steroidogenic response to ACTH and increases the concentration of sex hormone–binding globulin in women with PCOS. It also suggested that the reduced response of 17-hydroxyprogesterone (17-OHP) and androstenedione to ACTH is related to the reduction of insulin levels by metformin therapy.

We studied the effects of metformin on insulin resistance, insulin secretion, and adrenal steroidogenesis in women with PCOS (2). We used a lower dose of metformin than did la Marca and colleagues, but we administered it for a longer time. We found that metformin, 1 g/d for 12 weeks, significantly decreased insulin resistance and insulin levels; however, 17-OHP and androstenedione responses to ACTH did not decrease significantly. We concluded that although the post-treatment levels of insulin were higher than healthy persons, a direct relationship between insulin resistance and adrenal P450c17α enzyme dysregulation seems unlikely. l

la Marca et al. (1) concluded that high insulin levels associated with PCOS may cause an increase in plasma levels of adrenal androgens; however, we believe that their experimental protocol is not comprehensive enough to warrant this suggestion. In our opinion, without evaluating any parameters of insulin resistance, a correlation among insulin resistance, hyperandrogenism, and metformin therapy cannot be made. First, not all studies (3, 4) have showed an effect of metformin therapy on insulin resistance in women with PCOS. In addition, it has been suggested that responses to metformin therapy are not determined solely by the presence of hyperinsulinemia (5).

Finally Figures 1 and 2 and Figure 3 in la Marca et al.'s paper show results that are opposite of the authors' findings. We think that this is merely a technical error.

Kürşad Ünlühizarci, M.D.
Fahrettin Keleştimur, M.D.
Fahri Bayram, M.D.
Department of Endocrinology and Metabolism
Erciyes University School of Medicine
Kayseri, Turkey
May 30, 2000

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PII S0015-0282(00)01576-4

Reply of the Authors:

Although some studies showed no change in insulin plasma levels in women with the polycystic ovary syndrome (PCOS), a recent randomized, double-blind, placebo-controlled trial showed improvement in menstrual abnormality, reduction in plasma insulin levels during fasting and euglycemic clamp study, and increased insulin sensitivity in women with PCOS after metformin treatment (1). That study, conducted in Italy, included women who were only moderately obese (mean body mass index, 30 kg/m^2), and 1,500 mg of metformin was administered daily.

In our opinion, there can be no doubts about the effectiveness of metformin as an insulin-sensitizing agent in patients with PCOS. It is well known that in nonobese women with PCOS, insulin resistance occurs in the presence of normal glucose tolerance. Women with PCOS have a distinct disorder of insulin action that is not secondary to obesity or glucose intolerance per se. Independent of obesity, PCOS was associated with a 35% decrease in insulin action, whereas obesity produces a 50%