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# Commentary: Polycystic Ovary Syndrome—Increased or Preserved Ovarian Sensitivity to Insulin?

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IT HAS BEEN proposed recently that polycystic ovary syndrome (PCOS) develops as a result of increased ovarian sensitivity to insulin (1). Although there is evidence to support the notion of preserved ovarian sensitivity to insulin in the ovaries of patients with PCOS, in my view the evidence for increased ovarian sensitivity in such ovaries is lacking.

The three main pieces of evidence advanced in favor of the hypothesis proposing increased ovarian sensitivity to insulin in PCOS patients are as follows: first, ovarian cells from patients with PCOS produce higher amounts of androgens in response to stimulation by insulin than ovarian cells from patients without PCOS; second, not all patients with PCOS are insulin resistant or hyperinsulinemic; and third, treatment with insulin-sensitizing agents reduces ovarian androgen synthesis, even in those patients whose circulating insulin levels change only modestly with administration of these medications (1).

In regard to the first observation, it is important to remember that ovarian cells from patients with PCOS produce larger-than-normal amounts of androgens not only in response to insulin but also regardless of the stimulus used (2). Therefore, the larger-than-normal production of androgens in response to insulin in cultured ovarian cells from patients with PCOS is likely to be a consequence of the presence of PCOS, rather than a primary defect that precedes the development of PCOS. Further arguing against the presence of increased sensitivity to insulin in the ovaries of PCOS patients are the studies in obese children (3) and PCOS patients (4 and reviewed in Ref. 5), which demonstrated that serum androgen levels normalize after weight loss. Additionally, studies of granulosa cells from PCOS patients revealed no difference in their steroidogenic response to insulin, compared with the granulosa cells from the normal ovaries, and abnormalities of glucose uptake in the granulosa cells from PCOS patients were demonstrated only in the presence of supraphysiological concentrations of insulin (100 or 1000 ng/ml) (6). Insulin, particularly if present in high concentrations, stimulates not only ovarian androgen production but also synthesis of estrogens and progesterone, affects a variety of steroidogenic enzymes, inhibits production of IGF binding protein (IGFBP)-1, up-regulates ovarian IGF-I binding, promotes ovarian growth and cyst formation, stimulates theca cell proliferation, and enhances ovulation (reviewed in Ref. 7). It seems unlikely that increased sensitivity to insulin in the ovary would affect only one of its multiple effects, namely androgen synthesis. Besides, to describe a state of increased ovarian sensitivity to insulin, one would need to define normal ovarian sensitivity to insulin for each of its effects in the ovary, a task that has not yet been accomplished.

In regard to the second point, the lack of insulin resistance in many nonobese PCOS patients (8), who comprise up to 50% of PCOS population (reviewed in Ref. 5), does not necessarily imply increased ovarian sensitivity to insulin in these patients but may be interpreted rather as evidence against significant involvement of insulin in the pathogenesis of PCOS in individuals who are not insulin resistant. Furthermore, insulin hypersecretion may be present even in those PCOS patients who are not insulin resistant (8), once again arguing against increased ovarian sensitivity to insulin.

Finally, in regard to the third point, it is important to remember that the insulin-sensitizing agents used for the treatment of PCOS exhibit a variety of direct ovarian effects, both insulin independent and insulin sensitizing (9). Thiazolidinediones, for example, directly inhibit ovarian androgen production in human ovarian cells in the absence of insulin (9). In addition, insulin-sensitizing agents elicit a variety of nonovarian effects. For instance, because SHBG production in the liver is under inhibitory control by insulin (reviewed in Ref. 7), serum SHBG levels rise with thiazolidinedione administration and a fall in circulating free androgen levels follows (10). But as mentioned above, ovarian androgen production is inhibited by thiazolidinediones directly as well (9). Therefore, when one tries to analyze the causes of a reduction in free testosterone levels observed *in vivo* with thiazolidinedione administration, it is necessary to take into account contributions of both direct (ovarian) and indirect (SHBG-related action in the liver) effects of thiazolidinediones on serum testosterone. Thus, serum androgen responses to insulin-sensitizing agents do not necessarily reflect the state of ovarian insulin sensitivity.

For these reasons it may be premature to postulate either global or effect-specific increased sensitivity to insulin in the ovaries of patients with PCOS. On the other hand, there is significant evidence for the hypothesis proposing preserved ovarian insulin sensitivity in patients with PCOS who exhibit systemic insulin resistance (reviewed in Ref. 11). This hy-

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Abbreviations: IGFBP, IGF binding protein; PCOS, polycystic ovary syndrome.

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pothesis was originally developed because of observations of hyperthecosis, polycystic ovaries, and severe ovarian hyperandrogenism in patients with syndromes of extreme insulin resistance due to mutations of the insulin receptor gene or to the presence of circulating antiinsulin receptor autoantibodies (12). Such insulin resistance can be referred to as systemic insulin resistance because it leads to the development of defects in glucose transport in multiple classical target organs (*e.g.* liver, muscle, and adipose tissue). The preserved ovarian insulin sensitivity in these patients, as well as in patients with PCOS, appears to be due to the fact that the signaling pathways for the ovarian effects of insulin other than glucose transport are distinct from classical insulin signaling pathways. For example, the phosphatidylinositol-3 kinase or MAPK signaling pathways, both of which are activated by insulin in classical target organs, need not be activated to elicit stimulation of ovarian steroidogenesis or inhibition of ovarian IGFBP-1 production by insulin (13, 14). However, there is no evidence that these alternate insulin signaling pathways are hypersensitive to insulin.

Unlike the effects of insulin, the stimulatory effects of IGF-I in the ovary are MAPK dependent (14). The IGF system is probably involved in the mediation of insulin signaling in the ovary in hyperinsulinemic insulin-resistant states because insulin can both up-regulate and activate ovarian type I IGF receptors and, by inhibiting IGFBP-1 production, increases bioavailable amount of IGFs (reviewed in Ref. 7). However, hyperinsulinemia is required to produce such activation of the IGF system in the ovary (7).

In summary, with the currently available data, it appears to be more accurate to refer to the PCOS as a syndrome of preserved, rather than increased, ovarian sensitivity to insulin in patients with systemic resistance of glucose transport to insulin action. Whether increased sensitivity to physiological concentrations of insulin does indeed exist in the ovaries of PCOS patients, whether such increased ovarian sensitivity relates to one (*e.g.* androgen synthesis) or multiple ovarian effects of insulin, and whether increased ovarian sensitivity to insulin (if it exists) contributes to the pathogenesis of PCOS are all excellent topics for further investigation.

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