Role of decreased androgens in the ovarian response to stimulation in older women

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Ovarian testosterone increases the response of antral follicles to stimulation, declines with age, and has effects mediated or potentiated by insulin-like growth hormone I (IGF-I). Increased circulating insulin and IGF-I, exogenous testosterone, and increased local ovarian testosterone concentrations due to aromatase inhibition or exogenous luteinizing hormone/human chorionic gonadotropin are all associated with an increased ovarian response to gonadotropins. These factors should be further investigated alone or in combination for enhancing oocyte yield with fertility treatments, particularly in older reproductive-age women. (Fertil Steril® 2012;■:■–■. ©2012 by American Society for Reproductive Medicine.)

Key Words: Age, controlled ovarian hyperstimulation, female, growth hormone, IGF-I, testosterone

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EFFECTS OF TESTOSTERONE ON PREANTRAL AND ANTRAL FOLLICLES

Serum testosterone (T) decreases as age advances in premenopausal women (1–4), paralleling a similar age-related decline of antral follicle count (AFC) and level of antimüllerian hormone (AMH). Because it has been found that the T response to human chorionic gonadotropin (hCG) decreases with age (5), it is assumed that there is an age-related decrease of T secretion from the theca tissue surrounding ovarian follicles. In a study of 425 normally cycling women (1), baseline T remained correlated with the number of retrieved oocytes after adjusting by logistic regression analysis for age, body mass index (BMI), smoking, and timing of the sample during the menstrual cycle. These findings suggest that ovarian T plays a role in the ability of follicles to respond to follicle-stimulating hormone (FSH), and that part of the decreased ovarian response with aging may be due to declining ovarian androgen production.

Dickerson et al. (6) found in normal cycling women that the free androgen index and insulin resistance correlated with the follicle count after stimulation. Nardo et al. (7) similarly found a positive relationship of AMH with T, free androgen index, and insulin resistance in both nonobese polycystic ovary syndrome (PCOS) patients and normally cycling controls. Barbieri et al. (8) first observed that insulin stimulates T secretion from theca tissue cultured from the normal human ovary. These findings suggest that bioavailable T within the ovary may increase follicular response in a continuum from insulin-sensitive low-responding women without PCOS through to obese, insulin-resistant women with severe PCOS, who are at high risk of an excessive response to stimulation.

The effect of T on follicular response appears to be mediated by increasing FSH-receptor activity and by stimulating insulin-like growth factor I (IGF-I). In studies in subhuman primates, androgen receptor gene expression was shown to correlate with follicle growth, and T treatment significantly increased granulosa cell (GC) FSH receptor messenger RNA (mRNA) (9). Growing preantral and small antral follicles were significantly and progressively increased in number and theca layer thickness in T-treated monkeys (10). Testosterone has also been shown to stimulate earlier stages of follicular

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growth. Vendola et al. (11) showed that T increased the number of primordial follicles, increased IGF-I by threefold, and increased IGF-I receptor mRNA by fivefold in primordial follicle oocytes ($P<.0001$). These investigators hypothesized that IGF-I may stimulate primary follicle development, and IGF-I has been shown to enhance oocyte metabolic activity and maturation in vitro. Very strong correlations of follicular fluid T and GC androgen receptor mRNA with FSH receptor expression were also found in 3 to 9 mm antral follicles in adult human ovaries (12).

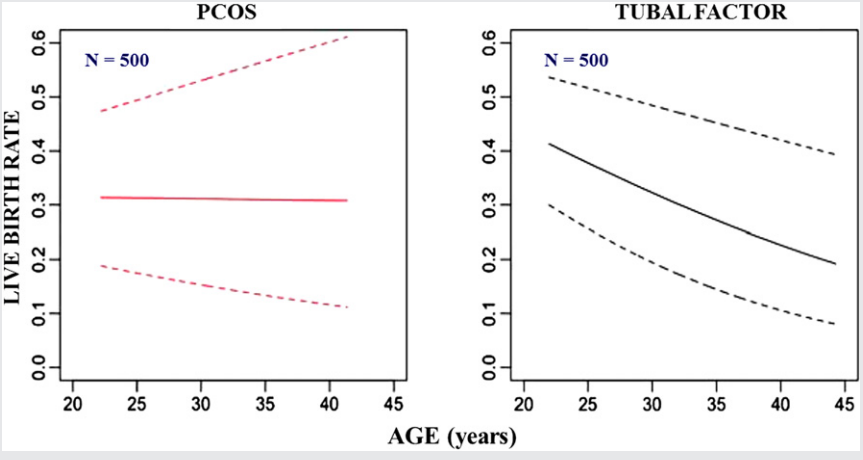
In the human ovary, IGF-II is primarily produced by the granulosa, whereas IGF-I is expressed in the theca (13). Regulation of IGF action in the ovary is complex, with FSH regulating IGF-II in granulosa, growth hormone (GH) regulating IGF-I systemically, and a family of IGF-binding proteins (IGFBPs) and IGFBP proteases within the follicle maximizing IGF action in the dominant follicle and the cohort recruited during ovulation induction with gonadotropins. The adjunctive use of GH as a co-gonadotropin in infertility therapy is believed to be due to its action on the liver, increasing IGF-I systemically and only secondarily within the follicle for oocyte maturation and enhanced follicle growth and steroidogenesis (13). Growth hormone does not have any direct action to increase expression of insulin-like growth factors or their receptor genes in the premenopausal human ovary (14).

In this review, we add to the present evidence supporting a hypothesis that the intraovarian effects of bioavailable T act to cause a continuum of antral follicle number and response from the poor responder—who is often more insulin-sensitive, has lower circulating insulin levels, and has a limited number of FSH-insensitive antral follicles (15)—through to women with severe PCOS, who are generally overweight or obese, insulin-resistant, hyperinsulinemic, and have a profusion of highly FSH-sensitive antral follicles. That concept in turn supports the premise that the decreasing thecal androgen production due to advancing age causes a progressive impairment of the aging ovary's ability to respond to stimulation for fertility treatments.

Women whom we would consider in optimal health paradoxically can be worse candidates for in vitro fertilization (IVF) with advancing age than our PCOS patients, whose success with IVF is relatively maintained (Fig. 1) in part because oocyte yield falls less with age in the women with PCOS compared with controls (not shown) (16). The birth rate with PCOS may also have been maintained with advancing age because of improved oocyte quality. In a large series of IVF patients studied by Holte et al. (17), AFC was found to predict success even after adjusting for oocyte yield and age, suggesting that AFC predicts oocyte quality and not just quantity. As we will outline, T improves GC health and therefore may be the link between a higher AFC and improved oocyte and embryo quality.

From a therapeutic perspective for women who have responded poorly to ovarian stimulation, the dilemma has been how to increase intraovarian androgen exposure to promote FSH receptor expression and an increased number of FSH-sensitive antral follicles. Vendola et al. (10) clearly showed in the subhuman primate model that an amount of systemically applied T (50 μg/kg per day for 5 days), which raised the circulating T concentration into the low male range, was capable of increasing preantral and antral follicles (Table 1); administration of dihydrotestosterone confirmed that the androgen receptor was responsible for the changes observed (10). Granulosa cell proliferation and health (decreased apoptosis) were also increased. Note that increasing the amount and duration (10 days) of T, achieving a circulating T concentration in the high male range, further increased antral follicles. That amount appears to raise the intraovarian concentration of T sufficiently to simulate a state similar to polycystic ovaries (PCO), but it is clearly impractical because of the expected androgenic side effects.

FIGURE 1



Live-birth rate versus age with in vitro fertilization in 500 women with polycystic ovary syndrome (PCOS) compared with 500 women with tubal factor infertility. The delivery rate remained unchanged with PCOS ($P=.96$) compared with a statistically significant decline with age in controls ($P=.03$) (16).

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