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Editorial Commentary

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CC is not a panacea for male infertility. This selective estrogen receptor modulator has been used off label to treat male infertility for the last 5 decades with mixed success.¹ It was hypothesized that CC stimulates spermatogenesis by inhibiting the negative feedback of estrogen on the hypothalamus and pituitary, resulting in increased gonadotropin production.² Unfortunately there are few controlled trials of CC for male infertility and as such the current meta-analysis of 3 studies does not enable us to reach a definite conclusion on drug efficacy. In the largest study to date performed in 1992 at WHO 190 men were randomized to 25 mg CC daily or to placebo (reference 19 in article). At 6 months there was no change in semen parameters in men treated with CC. More importantly the pregnancy rate in their partners remained similar to that in the partners of men who received placebo. The limitations of the studies of CC and male infertility published to date include small sample sizes, lack of control groups, heterogeneous patient populations and poorly defined outcomes. A Cochrane Review evaluating the role of CC in the treatment of idiopathic male infertility was withdrawn due to numerous flaws in the published literature.³

Despite the lack of strong evidence on the role of CC in male infertility more than 90% of polled AUA members stated that they would use CC to treat idiopathic male infertility (reference 10 in article). CC treatment is not without adverse effects, including fatigue, weight gain, fluid retention, gynecomastia and venous thrombosis. Therefore, it is important to understand which patients would most benefit from CC and how to appropriately select these individuals for CC therapy. Because CC increases gonadotropins (FSH and LH) treatment with CC would be most beneficial in men with gonadotropin levels that are normal or below normal. Theoretically increasing FSH and LH would increase intratesticular testosterone, which in turn would putatively lead to improved spermatogenesis. CC and the newer isomer of CC, enclomiphene citrate, have reliably increased serum testosterone.⁴ Whether improved serum testosterone levels correlate with improved spermatogenesis remains controversial. CC would not be beneficial in men with increased FSH as a result of severe testicular failure. These men typically have azoospermia or severe oligospermia secondary to an inherent germ cell defect and further stimulation of spermatogenesis through increased gonadotropins is unlikely to yield any additional benefit. Until larger, well controlled, randomized studies are performed CC can be used selectively in men with idiopathic infertility and low or normal gonadotropin. However, a positive outcome remains speculative.

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