Letter to the Editor

Identifying Factors Predicting Response to Clomiphene Citrate in Male Hypogonadism and Infertility

Dear Editor,

Clomiphene citrate (CC) has emerged as a safe and effective therapy for male hypogonadism and infertility, particularly for men seeking to preserve fertility [1,2]. However, clinical responses remain variable, and identifying pre-treatment predictors of therapeutic success or failure is crucial to guide patient selection and optimize outcomes [3]. This letter highlights relevant findings regarding predictors of CC responsiveness, based on recent clinical studies.

Nimeh et al. (2015) [4] retrospectively evaluated 105 hypogonadal men treated with CC between 2010 and 2014. Of the cohort, 21% exhibited an inadequate response, defined as failure to achieve sufficient testosterone levels post-treatment. Elevated baseline luteinizing hormone (LH) levels emerged as the most significant predictor of treatment failure (p=0.05), with responders showing a mean pre-treatment LH of 4.5 ± 2.4 IU/L versus 9.2 ± 6.6 IU/L in non-responders. Additionally, lower pre-treatment testosterone levels were significantly associated with inadequate response (184.1 ± 80.0 ng/dL vs. 217.6 ± 56.6 ng/dL; p=0.014). Estradiol levels were also lower in non-responders (12.8 ± 13.8 pg/mL) compared to responders (23.3 ± 12.1 pg/mL; p=0.004), suggesting an interdependent hormonal profile that warrants closer evaluation [4].

Mazzola et al. (2014) [5] further reinforced the relevance of baseline LH as a predictor, observing that LH levels ≤6 IU/mL significantly correlated with treatment success (HR=3.5; p<0.001). In their study of 76 hypogonadal men, 62% achieved a ≥200 ng/dL increase in testosterone, with responders showing a mean testosterone rise from 179 ± 72 ng/dL to 467 ± 190 ng/dL. Importantly, testicular volume ≥14 mL was also identified as a significant predictor (HR=2.2; p<0.01), emphasizing the importance of assessing gonadal reserve when initiating CC therapy [5].

Lundy et al. (2022) [6] evaluated CC effects on semen parameters in 140 infertile men and demonstrated a strong inverse correlation between baseline follicle-stimulating hormone (FSH) and response. Men with lower pre-treatment FSH showed significant improvements in sperm concentration and total motile sperm count (TMSC) post-treatment, with 56% improving sperm concentration and 23% achieving eligibility for intrauterine insemination. These findings align with the hypothesis that elevated gonadotropins, reflective of impaired gonadal function, predict poorer CC outcomes [6].

Collectively, the data suggest that higher baseline gonadotropin levels (LH and FSH), reduced testicular volume, and lower pre-treatment testosterone levels are associated with suboptimal responses to CC [3-6]. These parameters likely reflect underlying testicular dysfunction, limiting the efficacy of CC in stimulating endogenous testosterone production and improving fertility parameters. Conversely, patients with moderate hypogonadism (lower LH/FSH) and preserved gonadal reserve are more likely to achieve favorable outcomes. [3-6]

For this reason, in clinical practice, a careful pre-treatment assessment—including hormonal profiles, testicular volume, and semen analysis—can aid in predicting CC responsiveness [7,8]. Such evaluations allow for more personalized treatment strategies, identifying patients who may require alternative therapies, such as gonadotropins, for optimal outcomes [4-6].

Further prospective studies are warranted to validate these predictors and establish more precise practical cutoff values for clinical application [9,10]. Nonetheless, current evidence underscores the importance of baseline hormonal and testicular parameters as key determinants of CC therapy success in men with hypogonadism and infertility.

Sincerely,

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Disclaimer (Artificial intelligence)

The authors declare that generative AI was used only at the final stage of manuscript preparation (after writing) and exclusively for linguistic refinement in English Language (Name: ChatGPT; Version: GPT-4; Model: OpenAI's Large Language Model; Source: OpenAI - https://openai.com). No original text was generated or substantively edited by the AI.

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