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

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Author's contribution

The sole author designed, analyzed, interpreted and prepared the manuscript.

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Letter to the Editor

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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 (Huijben et al., 2022; Huijben et al., 2023) However, clinical responses remain variable, and identifying pre-treatment predictors of therapeutic success or failure is crucial to guide patient selection and optimize outcomes (Ko et al., 2012). This letter highlights relevant findings regarding predictors of CC responsiveness, based on recent clinical studies.

Nimeh et al., (2015) 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

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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 (Nimeh et al., 2015).

Mazzola et al.; (2014) 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 (Mazzola et al., 2014).

Lundy et al., (2022) 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 (Lundy et al., 2022).

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 (Ko et al., 2012; Nimeh et al., 2015; Mazzola et al., 2014; Lundy et al., 2022). 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 (Ko et al., 2012; Nimeh et al., 2015; Mazzola et al., 2014; Lundy et al., 2022).

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 (Joseph et al., 2022; Da Ros et al., 2022). Such evaluations allow for more personalized treatment strategies, identifying patients who may require alternative therapies, such as gonadotropins, for optimal outcomes (Nimeh et al., 2015; Mazzola et al., 2014; Lundy et al., 2022).

Further prospective studies are warranted to validate these predictors and establish more precise practical cutoff values for clinical application (Wu and Sung, 2024; Panner Selvam et al., 2023). 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,
Lucas Caseri Câmara

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.

CONSENT

It’s not applicable.

ETHICAL APPROVAL

It’s not applicable.

COMPETING INTERESTS

Author has declared that no competing interests exist.

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