

## Letter to the Editor

### Predictors of Inadequate Response to Clomiphene Citrate Therapy 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  $4.5 \pm 2.4$  IU/L versus  $9.2 \pm 6.6$  IU/L in non-responders. Additionally, lower pre-treatment testosterone levels were significantly associated with inadequate response ( $184.1 \pm 80.0$  ng/dL vs.  $217.6 \pm 56.6$  ng/dL;  $p=0.014$ ). Estradiol levels were also lower in non-responders ( $12.8 \pm 13.8$  pg/mL) compared to responders ( $23.3 \pm 12.1$  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  $\leq 6$  IU/mL significantly correlated with treatment success ( $HR=3.5$ ;  $p<0.001$ ). In their study of 76 hypogonadal men, 62% achieved a  $\geq 200$  ng/dL increase in testosterone, with responders showing a mean testosterone rise from  $179 \pm 72$  ng/dL to  $467 \pm 190$  ng/dL. Importantly, testicular volume  $\geq 14$  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].

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**Commented [PP2]:** Kindly remove this in-text citation [5] since you already reference Mazzola et al

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].

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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]

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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. 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. 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.

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**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.

### **Competing Interests**

Author has declared that no competing interests exist.

References :

1 - Huijben M, Lock MTWT, de Kemp VF, de Kort LMO, van Breda HMK. Clomiphene citrate for men with hypogonadism: a systematic review and meta-analysis. *Andrology*. 2022 Mar;10(3):451-469. doi: 10.1111/andr.13146. Epub 2022 Jan 8. PMID: 34933414.

2 - Huijben M, Huijsmans RLN, Lock MTWT, de Kemp VF, de Kort LMO, van Breda JHMK. Clomiphene citrate for male infertility: A systematic review and meta-analysis. *Andrology*. 2023 Sep;11(6):987-996. doi: 10.1111/andr.13388. Epub 2023 Jan 29. PMID: 36680549.

3 - Ko EY, Siddiqi K, Brannigan RE, Sabanegh ES Jr. Empirical medical therapy for idiopathic male infertility: a survey of the American Urological Association. *J Urol*. 2012 Mar;187(3):973-8. doi: 10.1016/j.juro.2011.10.137. Epub 2012 Jan 20. PMID: 22264467.

4 - Nimeh T, Kathrins M, Lujan S, Niederberger. Predictors of inadequate initial response to clomiphene citrate in the treatment of hypogonadism. *Abstract – Volume 104, Issue Supplement, E286-E287, September 2015. DOI: 10.1016/j.fertnstert.2015.07.898*

5 - Mazzola CR, Katz DJ, Loghmanieh N, Nelson CJ, Mulhall JP. Predicting biochemical response to clomiphene citrate in men with hypogonadism. *J Sex Med*. 2014 Sep;11(9):2302-7. doi: 10.1111/jsm.12592. Epub 2014 Jun 5. PMID: 24902614.

6 - Lundy SD, Doolittle J, Farber NJ, Njemanze S, Munoz-Lopez C, Vij SC. Follicle-stimulating hormone modestly predicts improvement in semen parameters in men with infertility treated with clomiphene citrate. *Andrologia*. 2022 Jul;54(6):e14399. doi: 10.1111/and.14399. Epub 2022 Feb 20. PMID: 35187689.

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