Original Article

Safety and efficacy of enclomiphene and clomiphene for hypogonadal men

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Background: Both clomiphene citrate and its isomer, enclomiphene, have become widespread within urologic practice; thus, understanding these medications' comparative benefits and risks is crucial for optimizing treatment and providing improved therapeutic options. We sought to investigate the longitudinal benefits and risks associated with enclomiphene, compared to clomiphene, and to provide valuable insights for clinicians when making treatment decisions in the management of hypogonadism.

Methods: We retrospectively studied patients at our academic center who had been prescribed clomiphene and, later, enclomiphene for hypogonadism. Baseline laboratory values were documented for each patient before being prescribed clomiphene, followed by subsequent values for each variable in the most recent visit before stopping clomiphene and any noted adverse effects experienced during this time. The same process was repeated for enclomiphene, using the clomiphene levels as an updated baseline. Two-tailed *t*-tests were employed using R to analyze the longitudinal impacts of clomiphene and enclomiphene on serum hormone values as well as a regression analysis to estimate the odds ratio (OR) for adverse events between the two therapies.

Results: Among 66 patients, enclomiphene exhibited a median testosterone increase of 166 (*vs.* 98 ng/dL, P=0.20) with lower estradiol change than clomiphene (–5.92 *vs.* 17.50 pg/mL, P=0.001). Adverse effects were statistically significantly less frequent with enclomiphene, including decreased libido (P=0.001), reduced energy (P=0.044), and mood changes (P=0.03). Regression analysis confirmed lower odds of adverse events with enclomiphene [OR: 0.18; 95% confidence interval (CI): 0.07–0.44, P=0.02].

Conclusions: Our findings demonstrate that enclomiphene provides improvement in testosterone levels with a lower rate of documented adverse events. These findings support enclomiphene as a comparable treatment option for hypogonadal men while minimizing the risk of adverse effects. Further research and more extensive studies are warranted to validate these conclusions and explore the additional long-term effects of enclomiphene to guide future patient counseling regarding these medications.

Keywords: Clomiphene; enclomiphene; hypogonadism; testosterone; safety

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Introduction

Hypogonadism, defined by low testosterone levels with its accompanying signs and symptoms in men, is a prevalent medical condition (1). This condition manifests with a range of symptoms, including decreased libido, sexual dysfunction, reduced energy levels, and depressive mood (2). Hypogonadism can be classified mainly into two types: primary hypogonadism and secondary hypogonadism (2). Both forms can be congenital or acquired; however, primary hypogonadism arises due to testicular disease, while secondary hypogonadism results from disruptions in the hypothalamic-pituitary-gonadal (HPG) axis (3).

The current treatment American Urological Association (AUA) guidelines for hypogonadism typically involve offering testosterone therapy to symptomatic men (4). However, it has the unwanted effect of suppressing follicle stimulating hormone (FSH) and luteinizing hormone (LH), thus decreasing intratesticular testosterone production, consequently affecting spermatogenesis (5). As a result, efforts have been made to develop alternative approaches to treat this condition.

Highlight box

Key findings

- Enclomiphene led to a median testosterone increase of 166 ng/dL, which was not statistically significant compared to clomiphene. Enclomiphene resulted in a statistically significantly lower increase in estradiol levels compared to clomiphene (–5.92 *vs.* 17.50 pg/mL, P=0.001). Adverse effects were statistically significantly less frequent with enclomiphene, including decreased libido, reduced energy, and mood changes. Regression analysis confirmed lower odds of adverse events with enclomiphene (P=0.02).

What is known and what is new?

- Clomiphene citrate, including its isomers enclomiphene (trans) and zuclomiphene (cis), has been used off-label to treat hypogonadism in men. Clomiphene is known to increase testosterone levels but also raises estradiol levels due to its estrogen receptor agonist activity, which can lead to adverse effects.
- This study provides evidence that enclomiphene, can increase testosterone levels without raising estradiol levels.

What is the implication, and what should change now?

- Clinicians should consider enclomiphene as an alternative to clomiphene for treating hypogonadal men, particularly those concerned about the estrogenic side effects associated with clomiphene. Further research is needed to validate these findings and explore the long-term effects of enclomiphene.

While historically utilized for enhancing fertility in women, AUA guidelines mention clomiphene citrate as an off-label treatment option for hypogonadal men. It is particularly relevant for those aiming to preserve fertility as it has demonstrated efficacy in restoring the HPG axis by promoting the production and secretion of LH and FSH, thus enhancing physiological testosterone levels (6). Clomiphene combines the enclomiphene-(trans) and zuclomiphene-(cis) isomers. Studies have indicated that enclomiphene acts as an estrogen antagonist while zuclomiphene acts as an estrogen agonist (7,8).

Enclomiphene, when appropriately used in specific patient populations, has demonstrated the potential to increase testosterone levels without suppressing LH or FSH (9). Consequently, enclomiphene may lead to normalizing testosterone levels and improving hypogonadal symptoms, all while preserving spermatogenesis. However, recent studies have failed to show its safety profile in a clinical setting (10,11). Thus, this study examines enclomiphene's and clomiphene's safety and efficacy in hypogonadal patients in a real world clinical setting. We present this article in accordance with the STROBE reporting checklist (available at https://tau.amegroups.com/article/view/10.21037/tau-24-238/rc).

Methods

We retrospectively reviewed pharmaceutical data to identify male patients of interest based on their previous prescriptions. Only men aged ≥18 years who had been prescribed enclomiphene and clomiphene and were diagnosed with hypogonadism were included. Men were excluded if they had previously undergone any HPG axis-altering therapy with exogenous testosterone or human chorionic gonadotropin hormone (HCG). Hypogonadism was defined as two serum total testosterone (TT) level <300 ng/dL with clinical symptoms. This investigation was conducted within the purview of our andrology clinic, and the observation period spanned from January 1, 2021, to December 31, 2022. The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). The study was approved by the ethics board of Baylor College of Medicine (No. H-52300), and individual consent for this retrospective analysis was waived.

We narrowed our focus to individuals who underwent an initial course of clomiphene therapy before transitioning to enclomiphene therapy. The study included an assessment of body mass index (BMI) and serum hormone levels,

Table 1 Hormonal and hematocrit levels for each timepoint

Hormonal and hematological parameters	Baseline	After clomiphene therapy	After enclomiphene therapy
Total testosterone, ng/dL	306 [251–490]	436 [320–640]	499 [444–700]
Estradiol, pg/mL	23.4 [17–34]	30 [20–40]	29 [19–47]
Hematocrit, %	45.6 [44.1–47.2]	45.5 [43.7–47.4]	47.0 [44.7–48.6]

Data are presented as median [interquartile range].

including TT and estradiol (E2), in addition to hematocrit measurements. To establish a baseline, we recorded each patient's laboratory values before initiating clomiphene treatment. Furthermore, we documented subsequent laboratory values during the patient's most recent clinic visit before transitioning to enclomiphene while also collecting data on any reported adverse effects experienced during this period in order to provide a baseline assessment prior to initiating enclomiphene, which was done in a standardized manner. The exact process was repeated for the most recent office visit while receiving enclomiphene therapy. Patients with missing data were excluded from the study. There was no washout period between clomiphene and enclomiphene.

We recorded previously defined side effects of clomiphene, which include depressive thoughts, decreased muscle strength, instances of gynecomastia, mood swings, and signs of agitation as evaluated by two healthcare providers (12). These adverse events had to be mentioned in the providers' notes, accompanied by a diagnosis code which allowed us to standardize the way the side effects were collected and to minimize bias. They were further examined to confirm if they were the initial occurrence of the event.

Statistical analysis

Statistical analysis involved a comparison of adverse event rates in patients undergoing both clomiphene and enclomiphene therapies, with each patient serving as their control. This approach allowed us to draw meaningful conclusions about the relative safety profiles of these treatments. We calculated the median change in testosterone, estradiol, and hematocrit levels to enhance our analysis further and compared them between the timepoints. Comparisons using non-parametric tests were made between pre-clomiphene baseline values and the last measurement while on clomiphene, right before they switched to enclomiphene. Lastly, a regression model was utilized to calculate the odds ratio (OR) with a 95% confidence interval (CI), enabling us to quantify the likelihood of experiencing adverse events between patients undergoing both therapies. Statistical significance was set at $P<0.05$. All analyses were conducted using R.

Results

Patient demographics

A total of 66 patients were identified for inclusion, with a mean age of 38.45 [standard deviation (SD) =8.18] years and a mean BMI of 30.19 (SD =5.25) kg/m^2, with 78% of patients having secondary hypogonadism, and the remaining having a primary hypogonadism. The median duration of treatment with clomiphene citrate was 18.7 months [interquartile range (IQR): 6.5–50.2 months], while the median duration of enclomiphene citrate treatment was 8.9 months (IQR: 5.2–13.3 months).

Hormonal changes

Hormonal and hematocrit values for each timepoint are summarized in *Table 1*. Upon comparison between the clomiphene and enclomiphene cohorts, the median change in testosterone levels was 98 ng/dL (IQR –18 to 684.5 ng/dL) in the clomiphene cohort. In contrast, the enclomiphene cohort exhibited a median change of 166 ng/dL (IQR 42.5 to 683 ng/dL), P=0.20, as compared to post-clomiphene levels. Notably, when considering the median change in (E2 levels, the clomiphene cohort manifested a median change of 17.5 pg/mL (IQR 4.1 to 51.8 pg/mL), in stark contrast to the enclomiphene cohort's median change of –5.92 pg/mL (IQR –17.71 to 26.8 pg/mL), P=0.001. Furthermore, the median change in hematocrit levels showed a subtle difference, with the clomiphene cohort demonstrating a median change of 0.4% (IQR –2.1% to 6%) and the enclomiphene cohort exhibiting a median change of 0% (IQR –1.85% to 42.6%), with a non-significant P value of 0.85. *Table 2* summarizes the changes.

Table 2 Median difference between clomiphene and enclomiphene

Parameter change	Clomiphene			Enclomiphene			P
	Median	Percentile 25	Percentile 75	Median	Percentile 25	Percentile 75	
Change in testosterone, ng/dL	98	−18	684.5	166	42.5	683	0.20
Change in estradiol, pg/mL	17.5	4.1	51.8	−5.92	−17.71	26.8	0.001
Change in hematocrit, %	0.4	−2.1	6	0	−1.85	42.6	0.85

Table 3 Rates of side effects for clomiphene and enclomiphene therapy

Side effect	Clomiphene, n (%)	Enclomiphene, n (%)	P
Overall side effects	31 (47%)	8 (13.8%)	0.001
Decreased libido	22 (33.3%)	5 (8.6%)	0.001
Erectile dysfunction	12 (18.2%)	5 (8.6%)	0.12
Fatigue	12 (18.2%)	4 (6.9%)	0.06
Decreased energy	11 (16.7%)	3 (5.2%)	0.044
Depressive thoughts	3 (4.5%)	0 (0%)	0.24
Weakness	4 (6.1%)	1 (1.7%)	0.37
Gynecomastia	2 (3%)	0 (0%)	0.49
Mood changes	6 (9.1%)	0 (0%)	0.03
Agitation	4 (6.1%)	1 (1.7%)	0.37

Table 4 Association of side effects between enclomiphene and clomiphene treatment

Side effect	OR	95% CI	P
Overall adverse events	0.18	0.07–0.44	0.02
Decreased libido	0.18	0.06–0.53	0.002
Erectile dysfunction	0.42	0.14–1.28	0.13
Fatigue	0.33	0.10–1.09	0.07
Decreased energy	0.27	0.07–1.03	0.056
Weakness	0.27	0.03–2.50	0.25
Agitation	0.27	0.03–2.50	0.25

Depressive thoughts, gynecomastia, and mood changes were not included as an odds ratio could not be calculated due to insufficient data. OR, odds ratio; CI, confidence interval.

Adverse events

Statistically significant differences in the adverse effects were observed between the clomiphene and enclomiphene groups. *Table 3* summarizes these findings. Overall, adverse effects were reported in 47% and 13.8% of patients in the clomiphene and enclomiphene groups, respectively (P=0.001). Decreased libido was noted in 33.3% of clomiphene recipients and 8.6% of enclomiphene recipients (P=0.001). Notably, reduced energy was reported by 16.7% of clomiphene users compared to 5.2% of those receiving enclomiphene, with a statistically significant P value of 0.044. Mood changes were documented in 9.1% of the patients in the clomiphene group, whereas they were absent in the enclomiphene group (P=0.03).

Regression analysis revealed statistically significant associations between certain adverse events and the treatment groups, as summarized in *Table 4*. Adverse events were less likely to occur with enclomiphene (OR: 0.18; 95% CI: 0.07–0.44, P=0.02). Similarly, decreased libido was less likely to occur with enclomiphene than with clomiphene (OR: 0.18; 95% CI: 0.06–0.53, P=0.002). No statistically significant associations were found for erectile dysfunction (OR: 0.42; 95% CI: 0.14–1.28, P=0.13), fatigue (OR: 0.33; 95% CI: 0.10–1.09, P=0.07), or weakness (OR: 0.27; 95% CI: 0.03–2.50, P=0.25). Additionally, ORs could not be calculated for depressive thoughts, gynecomastia, mood changes, and agitation due to insufficient data.

Discussion

The off-label use of clomiphene and enclomiphene has opened new possibilities for the treatment of hypogonadism in men who wish to avoid fertility concerns related to testosterone therapy. We aimed to study the differences between these new options to address their efficacy and adverse effects. The results of this study suggest that the difference in the mechanism of action of these two medications affects estradiol levels and estrogenic side effects. When comparing estradiol levels, clomiphene showed an increase compared with enclomiphene. Accordingly, with lower estradiol levels, enclomiphene

appears to have an advantage in terms of side effects. The incidence of adverse events such as decreased libido, decreased energy, and mood changes was lower in the enclomiphene group. We also found statistically significantly lower odds of experiencing any adverse events in the enclomiphene group than in the clomiphene group.

Numerous studies have shown the efficacy of clomiphene in ameliorating the symptoms associated with hypogonadism (13,14). A relevant contribution to this body of evidence was made by Katz *et al.*, who extensively investigated the effect of clomiphene on hypogonadal symptoms. Katz *et al.* observed remarkable improvements in the spectrum of hypogonadal symptoms in study participants. Moreover, almost all the enrolled patients experienced positive outcomes in relation to at least one hypogonadal symptom. This finding underlines the broad-reaching effects of clomiphene in addressing the multifaceted nature of hypogonadism. Moreover, the study revealed that more than half of the participants exhibited enhancement of three distinct hypogonadal symptoms, further emphasizing its therapeutic potential (15).

The variations in adverse effects observed between enclomiphene and clomiphene might be due to the distinct ways these two compounds interact with the estrogen receptor located within the pituitary gland. Several studies have collectively underscored the significance of estrogen in male physiology, particularly in relation to overall libido and sexual function (16,17). Notably, Finkelstein *et al.* reported a pivotal connection between changes in fat measurements and fluctuations in estradiol levels. This dynamic interplay between androgens and estrogens has emerged as a key determinant for sustaining normal libido and erectile function in men. They reported that when men exhibited serum testosterone levels ranging from 200 to 400 ng/mL, sexual desire scores declined by 13% when estradiol levels were 10 pg/mL or above and declined by 31% when estradiol levels fell below 10 pg/mL (18). Another study by Ramasamy *et al.* showed that men on testosterone therapy demonstrated elevated serum levels of estradiol and were associated with increased libido in men (19).

Our findings suggest that enclomiphene might have fewer troublesome side effects than clomiphene while maintaining the same degree of therapeutic effect on TT levels. This may make it an even safer option for men trying to avoid testosterone replacement therapy. However, it is vital to keep in mind that this study focused specifically on how clomiphene and enclomiphene affect hormone levels and the hormonal side effects of these therapies. The scope of this study does not provide a complete picture of other significant side effects, such as long-term effects on bone health, sexual function, and body composition. Additionally, due to the nature of this study being executed at a single institution, there are inherent limitations, restricting the potential sample size. Further studies exploring other side effects are warranted to understand both medications' profiles better. This will become important when providers are counseling patients regarding these medications, especially when patients may become uncompliant owing to unwanted side effects.

The observed differences in estradiol levels and associated side effects between clomiphene and enclomiphene suggest that enclomiphene may be a more favorable option for some patients. Clinicians should consider these differences when selecting treatment options, particularly for men who are sensitive to estrogenic side effects. The lower incidence of adverse events such as decreased libido, energy, and mood changes in the enclomiphene group may lead to improved patient compliance and quality of life during treatment. However, it is crucial for healthcare providers to weigh these potential benefits against the limitations of the study, including its single-institution design and relatively small sample size. Furthermore, the long-term effects of both medications on bone health, sexual function, and body composition require further investigation. As personalized medicine continues to evolve, these findings may help guide clinicians in tailoring treatment plans to individual patient needs and preferences, potentially improving overall outcomes in the management of male hypogonadism.

It is worth noting that while the study indicated fewer side effects in the enclomiphene group, we should be mindful of the study's limitations. For instance, the study did not exclude patients with a history of mental health conditions that could confound their response to mood changes, agitation, or fatigue. The number of participants in this study was relatively small, so caution should be exercised when interpreting the results. One important limitation was the absence of a washout period between clomiphene and enclomiphene treatments. Clomiphene has a relatively long half-life due to the presence of the zuclomiphene (cis) isomer (20). Transitioning directly from clomiphene to enclomiphene without an adequate washout period raises the possibility of carry-over effects, where residual clomiphene or its metabolites could have influenced the observed outcomes with enclomiphene treatment. Moreover, each patient might have switched to enclomiphene for different reasons, introducing bias.

Additionally, the baseline hormonal status of patients differed between the two treatment groups. Clomiphene was initially prescribed to patients in a hypogonadal state, while enclomiphene was administered after clomiphene had exerted its effects, potentially restoring patients to a eugonadal state. These differences in baseline hormonal values could have impacted the observed treatment responses and should be considered when interpreting the comparative effects of clomiphene and enclomiphene. However, our study aimed to reflect real-world clinical practice, where patients often transition from one treatment to another without a washout period. Further studies that explore the differences between enclomiphene and clomiphene in larger population samples with patients from different institutions are needed to help provide more generalizable results to the overall population. Future studies should also explore the impact of potentially confounding variables, such as mental health conditions, to explore the accuracy of the difference in adverse events between these two medications. With further and more generalizable studies, providers can better understand the benefits and drawbacks of these two medications for patients. Lastly, we recommend studies to assess clomiphene and enclomiphene in a blinded randomized controlled trial methodology to verify these initial findings.

Conclusions

Our findings demonstrate that enclomiphene provides the same magnitude of improvement in testosterone levels with a lower rate of documented adverse events. These findings support enclomiphene as a comparable treatment option for hypogonadal men while minimizing the risk of adverse effects. Further research and more extensive studies are warranted to validate these conclusions.

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Footnote

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Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). The study was approved by the ethics board of Baylor College of Medicine (No. H-52300), and individual consent for this retrospective analysis was waived.

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