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Converting men from Clomiphene Citrate to Natesto for hypogonadism improves libido, maintains semen parameters, and reduces estradiol

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Key Words: Hypogonadism, libido, testosterone, semen analysis, estradiol, sperm

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Abstract:

Objective:

To evaluate outcomes including libido, semen parameters, testosterone, estradiol (E2), follicle stimulating hormone (FSH), and luteinizing hormone (LH) when converting men with low libido on Clomiphene Citrate (CC) to Natesto.

Methods:

A retrospective chart review was performed. Baseline hormones prior to treatment, and again on CC and Natesto, as well as semen parameters on CC and on Natesto were assessed.

Results:

In forty-one men, there was no difference in serum testosterone levels on CC versus Natesto, however; there was a significantly higher E2 on CC than on Natesto. Although FSH levels were significantly lower on Natesto than at baseline, the mean FSH level on Natesto remained in the normal reference range. There was no difference in LH levels at baseline versus on Natesto. There was not a significant difference in semen parameter values when men were on CC versus when they were on Natesto for 3 months. At 3 months after changing to Natesto, 38/41 (92.7%) men reported significantly improved libido on Natesto when compared to CC.

Conclusions:

Men on CC and Natesto reach eugonadal testosterone levels, however; on CC the E2 level nearly doubled from baseline, and converting men from CC to Natesto returned E2

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to nearly baseline levels. There was not a detrimental effect on semen parameters, and there was subjective reporting of improved libido after converting from CC to Natesto in this cohort, but further long-term studies are needed prior to Natesto being established as a definitive treatment for hypogonadism for men desiring to maintain fertility.

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Introduction

There has been a rise in the prevalence of low testosterone in adolescents and young adults, for whom current or future fertility potential may be important.[1,2] Long-acting traditional testosterone replacement therapy (TRT) modalities, such as transdermal gels and intramuscular injections, suppress the gonadotropins follicle stimulating hormone (FSH) and luteinizing hormone (LH), thereby suppressing spermatogenesis downstream by decreasing intratesticular testosterone levels.[3-5] Clomiphene Citrate (CC) is selective estrogen receptor modulator, which is an off-label treatment for men with hypogonadism in a spermatogenic preserving manner. The mechanism of action of CC is inhibition of estradiol negative feedback to the hypothalamus resulting in increased secretion of LH stimulating Leydig cells of the testes to produce testosterone.[6] Most men have normalization of testosterone levels on CC to eugonadal levels, but estradiol (E2) levels commonly rise, and symptomatic response on CC has been reported to be less optimal than on TRT, particularly libido.[7] The 4.5% intranasal TRT, Natesto, is administered at a fairly low dose of 11 mg per dose administration, and is administered at more frequent intervals of twice or three times daily, which allow FSH and LH to remain in normal reference range levels. A clinical trial by Ramasamy et al revealed that men treated with Natesto did not have significant suppression of semen parameter values from baseline.[8] The objective of the current study was to evaluate the impact of converting men who suffered from low libido on CC to Natesto and assessing the effect on serum testosterone levels, FSH, LH, E2, and semen analysis parameter values, as well as libido.

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Materials and Methods

Once the data from the clinical trial regarding the ability of men to maintain spermatogenesis on Natesto was available[8], 60 men who were treated with CC for hypogonadism in a fertility preserving manner at a reproductive urology practice, were offered the option to change treatment from CC to Natesto when they complained of low libido on CC. There were variable CC treatment durations in these men. The mean duration on clomiphene citrate prior to the initial semen analysis prior to converting to Natesto was 31 months ± 26. None of the men were on clomiphene for less than 3 months prior the initial semen analysis. They were initially treated with CC for the original indication of treating hypogonadism in a fertility preserving manner. All men had initial baseline serum testosterone, FSH, LH, and E2 obtained prior to initiating treatment with CC and they had to have 2 total serum testosterone levels of less than 300 ng/dL drawn in the morning, to be considered a candidate for treatment.[9] One month after initiation of CC 25 mg daily; serum testosterone and E2 levels were obtained while on CC, and if the serum testosterone remained less than 300 ng/dl, the dose of CC was increased to 50 mg daily. The results in men while on CC reported were on the dose that achieved eugonadal levels. All men agreed to have a baseline semen analysis obtained while on CC with the plan of obtaining serum testing for testosterone, FSH, LH, E2 1 month after changing to Natesto, and having a repeat semen analysis 3 months after converting to Natesto to confirm stability of spermatogenesis. All semen analyses were performed at a single high complexity andrology laboratory. All men were initiated on Natesto 11 mg twice daily intranasal

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administration, and if they did not achieve eugonadal levels obtained 1 hour after administration of Natesto 1 month after initiation of treatment, the dose was titrated up to 3 times daily. Only 6/41 (14.6%) of the men required up titration to three times daily dosing. The results reported on Natesto were on the treatment regimen that achieved eugonadal levels.

After institutional review board exemption was obtained due to the de-identified nature of the data collected, a retrospective chart review was performed of the electronic health record to assess the hormonal and semen parameter value responses from changing from CC to Natesto in the 41 out of the 60 men who had reached the 3 month time period after changing treatments and had a second semen analysis obtained. At 3 months after changing from CC to Natesto, all men were asked by the prescribing physician if there was any change in libido on Natesto versus while they were on CC. Three men out of the 60 elected to change back to CC because of discontent with the intranasal route of administration of Natesto which they did not tolerate well. The Wilcoxon Signed-Rank test and the student's t-test were used where appropriate with a p value of < 0.05 considered statistically significant. Results are expressed as means ± standard deviations.

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Results

The mean age of the 41 men who were converted from CC to Natesto due to complaints of low libido on CC and who had their semen reassessed 3 months after changing treatments, was 38 ± 7.1 years of age. Baseline demographics of these men are described in Table 1. There was no statistically significant difference in serum testosterone levels on CC versus Natesto (p 0.842), however; there was a significantly higher E2 level on CC than on Natesto (p 0.0001). Although FSH levels were significantly lower in the men on Natesto than at baseline (p 0.016), the mean FSH level of the men on Natesto remained in the normal reference range. There was no difference in LH levels at baseline versus on Natesto (p 0.178). There was not a significant difference in semen parameter values when men were on CC versus when they were on Natesto for 3 months, when assessing for semen volume (p 0.085), sperm concentration (p 0.322), percent sperm total motility (p 0.646), percent forward progressive motility (p 0.226), percent of sperm with normal morphology by strict Kruger morphology criteria (p 0.873), and total motile sperm counts (p 0.289) (Table 2). At 3 months after changing to Natesto, all men were queried clinically about their libido response to the change in treatment and 38/41 (92.7%) reported significantly improved libido on Natesto when compared to CC. There were no identifiable commonalities amongst the 3 men who did not have an improvement in libido after converting to Natesto.

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Discussion

Hypogonadism is a common diagnosis in men presenting with a constellation of symptoms prompting an evaluation to initiate treatment. Testosterone levels may start to decline in men at 30 years of age. Once this decline in testosterone levels begins, there may be a decrease by 1-2% per year.[10] However, the prevalence of low testosterone in younger men is increasing, which complicates the treatment options.[1,2] Classically, TRT has been the treatment of choice for hypogonadism, however; other long-acting TRT modalities suppress the hypothalamic-pituitary-gonadal (HPG) axis and thereby, downstream spermatogenesis, and result in testicular atrophy due to the diminishment of spermatogenesis.[11] This makes TRT a poor choice for hypogonadal men trying to achieve a pregnancy or for those wanting to maintain fertility potential.[3,4] To avoid suppression of the HPG axis and spermatogenesis, CC is commonly prescribed off-label to increase serum testosterone levels in a manner that does not suppress spermatogenesis, and long-term studies on safety and efficacy on CC have been published.[6] However, men on CC have demonstrated high rates of hyperestrogenemia necessitating co-administration of aromatase inhibitors. This is seen commonly in clinical practice and has been published in multiple studies.[6,12-14] CC can have other undesirable side effects such as gynecomastia, weight gain, and fatigue.[12]

The cohort in this current study showed similar improvements in serum testosterone levels to eugonadal levels as previously published studies on CC.[12,13,15-18] However, the concerns with the use of CC in this population of men include the common complaint of low libido on CC as well as the frequently reported rise in E2 levels. Dadhich et al

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published a study revealing that men on CC have a less robust symptomatic response, especially with libido, in comparison to men on direct TRT.[7] This is a common clinical complaint in practice when treating men with CC. The long-standing challenge has been a treatment for hypogonadal men desiring to maintain fertility potential which could increase serum testosterone levels to eugonadal levels, not increase estradiol significantly, and offer the symptomatic response, particularly with libido, that TRT offers.

The current study suggests that Natesto is an alternative treatment for hypogonadal men desiring to maintain fertility potential in a manner that optimizes libido response and minimizes aromatization of testosterone to E2. In comparison to other forms of TRT the more frequent and short-acting formulation of Natesto mimics the physiologic testosterone release which is the hypothesis for the potential to maintain gonadotropins and spermatogenesis.[8,19,20] It has been described that diurnal variation of serum testosterone levels and modalities of TRT with a short half-life, such as Natesto, more closely duplicate physiology.[21,22] In the current study, the lower levels of normal for FSH and LH in the reference laboratory were 1.5 IU/L and 1.2 IU/L respectively. While on Natesto, seven men (17%) had a FSH level of below 1.5 IU/L, only one of which suppressed below 1.0 IU/L, none of which became undetectably low. Only one of the men had LH suppress below 1.2 IU/L (2%). In that man the LH was 1.0 IU/L. Although some men did suppress gonadotropins below the laboratory reference range cutoff for low, the majority did not, and of those who did, the gonadotropins remained detectable. Having less profound LH suppression likely accounts for the maintenance of spermatogenesis even in these men, by allowing for intratesticular testosterone

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production to continue. The study by Ramasamy et al revealed one man who became azoospermic and three men who became severely oligospermic when treated with Natesto.[8] There were not similar findings in men in the current study, but that may be a limitation of sample size. Therefore, it is recommended that clinicians offering Natesto as a treatment for hypogonadal men desiring to maintain fertility potential closely monitor gonadotropins and semen analysis parameter values on Natesto to confirm that they are being maintained, until further long-term studies have definitively confirmed the use of Natesto as a treatment for hypogonadal men interested in maintaining fertility potential.

Limitations of this current study include sample size, however; the results within this cohort are extremely consistent and appropriate statistical models were applied. An additional limitation is that assessment of patient libido was by subjective reporting of improvement in the electronic health record. As a retrospective study based on clinical data from the electronic health records, symptom inventories were not utilized in accordance with the American Urological Association evaluation and management of testosterone deficiency clinical guideline number 5, published in 2018. This guideline states “The use of validated questionnaires is not currently recommended to either define which patients are candidates for testosterone therapy or to monitor symptoms response in patients on testosterone therapy”.[9] Therefore, libido was assessed as subjectively reported by patients and documented in the electronic health record. Libido is a purely subjective measurement by report; therefore, this is a fair assessment in change in libido from one treatment option to the other. Libido was the primary hypogonadal symptoms clinical queried in these men on the 2 treatments as it was the

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symptom previously reported to be most significantly improved in men on TRT over CC and clinically is a very commonly reported persistent symptom on CC despite eugonadal testosterone levels.[7] Other limitations include a lack of a control group for comparison, lack of blinding to intervention (particularly when a subjective determined and psychologically influenced outcome such as libido is measured), and the high variability inherent in semen parameters that confound our ability to draw statistically significant conclusions compared to other less variable parameters.

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Conclusions

Although men reached eugonadal testosterone levels on both CC and Natesto, men on CC nearly doubled their E2 levels from baseline, and converting men from CC to Natesto returned E2 to nearly baseline levels. In this patient cohort, there was not a detrimental effect on semen parameters, and there was subjective reporting of improved libido after converting from CC to Natesto, however; there is a need for longer term studies beyond six months of treatment prior to concluding that Natesto is an appropriate treatment for hypogonadal men desiring to maintain fertility.

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Table 1. Baseline Demographics. Age and BMI expressed in means ± stand deviation.

Age	38 ± 7.1 (years)
White	36/41 (88%)
Latino	2/41 (5%)
African American	3/41 (7%)
Asian	0
BMI	31.2 ± 4.7 (kg/m^2)

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Table 2. Hormonal parameters at baseline, on Clomiphene Citrate, and on Natesto for men with hypogonadism (n = 41). Semen parameters on Clomiphene Citrate and on Natesto. Results are expressed as means ± standard deviations. P values for testosterone and estradiol levels are comparing men on Clomiphene Citrate vs Natesto. P values for follicle stimulating hormone and luteinizing hormone levels are comparing baseline levels to men treated with Natesto.

	Baseline	**Clomiphene Citrate**	**Natesto**	**P value**
Testosterone (ng/dL)	210.5 ± 64.5	573.0 ± 190.0	565.5 ± 145.7	0.842
Estradiol (pg/mL)	23.3 ± 9.7	44.2 ± 20.8	26.0 ± 12.4	**0.0001**
Follicle Stimulating Hormone (mIU/mL)	4.1 ± 2.2		2.9 ± 2.2	**0.016**
Luteinizing Hormone (mIU/mL)	4.1 ± 2.0		3.5 ± 2.0	0.178
Semen Volume (mL)		3.0 ± 1.3	2.7 ± 1.3	0.085
Sperm Concentration (mil/mL)		49.8 ± 37.2	48.5 ± 31.8	0.322
Total Motility (%)		54.9 ± 14.6	54.6 ± 16.2	0.646
Forward Progressive Motility (%)		26.1 ± 13.4	29.2 ± 10.	0.226
Normal Morphology (%)		5.2 ± 3.2	5.2 ± 3.3	0.873
Total Motile Sperm Count (mil)		100.1 ± 127.8	74.2 ± 69.2	0.289

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