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Men converting from clomiphene citrate to Natesto with a desire to maintain spermatogenesis should be followed closely.

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Abstract

Objective

To report a case of a testosterone deficient man desiring maintenance of spermatogenesis converting from clomiphene citrate (CC) to Natesto, who had a decrease in gonadotropins and semen parameter values after making this medication

change. The data on men maintaining gonadotropins and semen parameter values after converting from CC to Natesto is also reported.

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

A 32-year-old testosterone deficient man desiring to maintain future fertility potential who had a poor symptomatic response to CC despite an adequate serum testosterone response was converted to Natesto 11 mg twice daily. His gonadotropins diminished as did his semen parameter values but with dose titration of Natesto to 11 mg in the morning and 5.5 mg in the evening he had normalization of gonadotropins and a rise in semen parameter values back towards his values on CC with a continued satisfactory symptomatic response. The remainder of the 49 men to date converting from CC to Natesto revealed stability in gonadotropins and semen parameter values.

Conclusions

Testosterone deficient men interested in maintaining spermatogenesis who convert from CC to Natesto seeking a more robust symptomatic response should be followed closely with repeat serum gonadotropins and semen parameters to confirm that spermatogenesis is not being suppressed. Dose titration of Natesto may be effective at optimizing gonadotropins, semen parameter values, testosterone levels, and symptomatic response to treatment.

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Introduction

The gonadotropins follicle stimulating hormones (FSH) and luteinizing hormone (LH) which are responsible for signaling the testes for spermatogenesis and testosterone production respectively, are suppressed with long-acting traditional modalities of testosterone replacement therapy (TRT) such as transdermal gels and intramuscular injections, and thereby suppress spermatogenesis by decreasing intratesticular testosterone levels.[1-3] Historically, clomiphene citrate (CC) has been prescribed off-label which inhibits estradiol (E2) negative feedback to the hypothalamus increasing LH secretion, stimulating testicular Leydig cells to increase testosterone production in a manner that maintains spermatogenesis.[4] Although the majority of men treated with CC have normalization of their serum testosterone levels, E2 levels tend to rise, and symptomatic response to CC has been reported to be less optimal than on TRT, especially libido.[5,6] The short-acting intranasal TRT, Natesto, allows for maintenance of FSH and LH within normal ranges in most men. Natesto has also been shown to allow for maintenance of spermatogenesis when given to TRT naïve patients or after a washout period from other TRT modalities in most men.[6,7]

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Materials and Methods

Since publishing our initial experience of outcomes in testosterone deficient men converting from CC to Natesto seeking an improved symptomatic response, revealing maintenance of spermatogenesis, one patient was found to fail to maintain adequate levels of spermatogenesis on Natesto 11 mg twice daily dosing. His chart was reviewed

and reported in this study as well as a chart review of the men up to date who had outcomes consistent with the previous published study revealing lower E2 levels and maintenance of gonadotropins and spermatogenesis after converting from CC to Natesto. 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 report this case of variance as well as bringing the data on the other men treated similarly with consistent results as previously reported up to date. The Wilcoxon Signed-Rank test was used for statistical analysis of the cohort of men with results consistent with the previous study showing stability of semen parameter values on both treatments being brought up to date, with a p value of < 0.05 considered statistically significant. Results are expressed as means ± standard deviations.

Results

We published a study in Urology (DOI https://doi.org/10.1016/j.urology.2020.11.047) revealing that 41 men converted from CC to Natesto for testosterone deficiency had improved libido, reduced E2, and maintained semen parameter values.[6] To date, from May of 2018 to March of 2021, this data has been carried out to 50 men and 49 of these men maintained gonadotropins and semen parameter values on Natesto, comparable to when on CC (Table 1). The mean age of these 49 men was 38 ± 8 years. However, one patient, a 32-year-old man with testosterone deficiency who was not trying to conceive at the time but desired to maintain future fertility potential, elected to convert from CC to Natesto after having an adequate biochemical response in serum testosterone levels but a poor symptomatic response on CC. After changing to Natesto

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his gonadotropins decreased to low, although detectable levels. This resulted in a significant decrease in semen parameter values to severe oligoasthenospermic values. It was recommended that he change back to CC, which he declined, due to the significant improvement in symptoms on Natesto over CC. While on CC he complained of no libido and low energy. He agreed to decreasing the Natesto dose from 11 mg twice daily to 11 mg in the morning and 5.5 mg in the evening and maintained eugonadal serum testosterone levels, but also had normalization of gonadotropins as well as a return of semen parameter values back to his baseline and continued to have a positive symptomatic response on Natesto (Table 2).

Discussion

In this study, although the majority of men (49/50, 98%) who converted from CC to Natesto maintained normal gonadotropin levels and stable semen parameter values, an exception to the rule has been demonstrated. Therefore, it is recommended that men being treated with Natesto for testosterone deficiency with a goal of maintaining spermatogenesis have gonadotropins and semen parameter values followed closely to confirm stability. In some cases, Natesto dose titration may allow for return of gonadotropins and semen parameter values while maintaining a positive symptomatic response. It was noted in this patients case that when his semen parameter values decreased on Natesto 11 mg twice daily, he declined the option of changing back to CC despite the diminishment in semen parameter values. This speaks to the significance of the difference in symptomatic response on TRT versus CC, which is a common clinical finding. Fortunately, in this individual's case, dose titration was adequate to maintain

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his symptomatic response, maintain his gonadotropins, and his semen parameter values.

Our previous study evaluating outcomes in 41 men converting from CC to Natesto only revealed a statistically significant difference in E2 and FSH levels between the 2 treatments. The difference in E2 was quite significant as an advantage of Natesto. Although the difference in FSH levels did reveal a statistically significant difference, on Natesto FSH levels remained in the low normal range by reference range allowing for maintenance of intratesticular testosterone levels by continued LH secretion resulting in maintenance of spermatogenesis.[6] Although the purpose of this current study was to report on the individual patient who demonstrated suppression of gonadotropins and spermatogenesis on Natesto twice daily dosing, the data on a total of 49 men who maintained spermatogenesis with conversion from CC to Natesto was brought up to date, and a statistically significant difference was again noted in E2 levels, confirming the advantage of lower E2 levels on Natesto over CC. A statistically significant difference in semen volume was also demonstrated on CC (2.9 ± 1.3 mL) versus on Natesto (2.6 ± 1.3 mL). However, both means are well within normal ranges for semen volume and it is arguable if this represents a clinically significant difference, and there is no difference in total motile sperm counts on either treatment indicating that this change in semen volume would not be likely to impact fertility treatment options if needed.

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Conclusions

Testosterone deficient men who are interested in maintaining spermatogenesis who convert from CC to Natesto seeking a more robust symptomatic response should be followed closely with repeat FSH and LH levels as well as semen parameter values to confirm that spermatogenesis is not being suppressed. Dose titration of Natesto may be effective at optimizing gonadotropins, semen parameter values, testosterone levels, and symptomatic response to treatment.

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Table 1. Hormonal parameters at baseline, on Clomiphene Citrate, and on Natesto for men with hypogonadism (n = 49) who maintained semen parameter values after changing treatments. Semen parameters compared 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)	215.8 ± 63.4	585.1 ± 19.9	570.2 ± 172.6	0.711
Estradiol (pg/mL)	23.5 ± 9.2	44.9 ± 19.9	26.1 ± 12.3	**0.00001**
Follicle Stimulating Hormone (mIU/mL)	4.5 ± 4.3		3.5 ± 3.7	0.891
Luteinizing Hormone (mIU/mL)	4.5 ± 3.7		3.7 ± 3.0	0.124
Semen Volume (mL)		2.9 ± 1.3	2.6 ± 1.3	**0.042**
Sperm Concentration (mil/mL)		51.1 ± 39.8	48.7 ± 36.1	0.303
Total Motility (%)		54.6 ± 15.0	53.6 ± 16.8	0.465
Forward Progressive Motility (%)		26.7 ± 15.6	28.4 ± 11.3	0.215
Normal Morphology (%)		5.5 ± 3.7	4.7 ± 3.2	0.441
Total Motile Sperm Count (mil)		94.8 ± 121.2	73.8 ± 79.4	0.337

Table 2: The baseline and treatment hormone and semen parameter values in the man who had a diminishment in gonadotropins and semen parameter values with conversion from clomiphene citrate (CC) to Natesto 11 mg twice daily (BID) and titration to Natesto 11 mg in the morning and 5.5 mg in the evening (11mg/5.5mg). Percentage normal morphology is by Strict Kruger morphology criteria.

	Baseline	**CC**	**Natesto 11 mg BID**	**Natesto 11 mg/5.5 mg**
Testosterone (ng/dL)	223	380	812	624
Estradiol (pg/mL)	24.8	45.1	28.2	23.4
FSH (mIU/mL)	3.1	4.6	0.7	2.2
LH (mIU/mL)	5.3	7.2	0.9	2.7
Semen Volume (mL)		1.9	2.1	1.9
Sperm Concentration (mil/mL)		29	4.9	25.5
Motility (%)		40	37	55
Forward Progressive Motility (%)		24	6	18
Normal Morphology (%)		2	5	4
Total Motile Sperm Count (mil)		22	3.8	26.6

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