Title

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Journal

Translational Andrology and Urology, 13(2)

ISSN

2223-4691

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Publication Date

2024-02-29

DOI

10.21037/tau-23-454

Peer reviewed

Brief Report

Combination clomiphene citrate and anastrozole duotherapy improves semen parameters in a multi-institutional, retrospective cohort of infertile men

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Abstract: In men with impaired semen parameters, empiric medical therapies such as clomiphene citrate, a selective estrogen receptor modulator (SERM), and anastrozole, a selective aromatase inhibitor, are often employed. The effects of jointly administering these agents on semen parameters are not well understood. Here, we describe the findings of our multi-center, retrospective cohort study of men with idiopathic primary or secondary infertility. Twenty-one men were treated with combination therapy (anastrozole and clomiphene) and 69 men were treated with monotherapy (anastrozole). Patients with pre-treatment normozoospermia and recent or current exogenous testosterone therapy were excluded. Baseline and post-treatment semen and sex hormone parameters were compared among groups. The median follow-up duration was 91 days [interquartile range (IQR), 64–117 days]. Following treatment, 43% of men in the combination therapy group demonstrated normozoospermia, compared to 25% in the monotherapy group. Furthermore, men in the combined group demonstrated marked improvements in total motile sperm count (TMSC) [11.3 *vs.* 2.1 million (M), P=0.03]. There were no significant differences in hormone levels among the two groups following treatment. Combination therapy with clomiphene citrate and anastrozole was associated with modest benefits in post-treatment semen parameters, when compared to anastrozole monotherapy. These benefits may contribute to improvements in pregnancy outcomes with less invasive assisted reproductive technologies, such as intrauterine insemination (IUI). Future investigations with larger sample sizes and prospective study designs are necessary.

Keywords: Clomiphene; anastrozole; idiopathic infertility; semen analysis parameters (SA parameters); total motile sperm count (TMSC)

Submitted Sep 01, 2023. Accepted for publication Nov 30, 2023. Published online Feb 22, 2024.
doi: 10.21037/tau-23-454
View this article at: https://dx.doi.org/10.21037/tau-23-454

Introduction

Many couples struggle with infertility worldwide; however, the etiology of abnormal semen analysis (SA) parameters is not identified in up to 45% of men (1,2). These individuals are often initiated on empiric medical therapy consisting of either aromatase inhibitors to block the peripheral conversion of testosterone to estrogen or centrally acting selective estrogen receptor modulators (SERMs) to

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stimulate endogenous secretion of gonadotropin-releasing hormone (3).

The aromatase inhibitor anastrozole is conventionally considered for infertile men with increased peripheral levels of estrogen and an unfavorable testosterone (T) to estradiol (E_2) ratio (typically <10:1), whereas the SERM clomiphene citrate is often employed in the setting of low or inappropriately normal gonadotropin levels with concomitant hypogonadism (3). We recently published a retrospective, multi-institutional cohort study to potentially expand on the ideal patient population that may benefit from anastrozole (4). Our findings revealed that the T to luteinizing hormone (LH) ratio, rather than any measure related to E_2, is critical for predicting improvement in SA parameters. Here, we leverage the same multi-institutional cohort of patients to query whether there is additional benefit in combination therapy with clomiphene and anastrozole, compared to anastrozole alone with respect to semen parameters. We present this article in accordance with the STROBE reporting checklist (available at https://tau.amegroups.com/article/view/10.21037/tau-23-454/rc).

Methods

Study population and biospecimen collection

We performed a multi-center, retrospective cohort study of men with idiopathic infertility who were prescribed anastrozole at two tertiary referral centers: University of California, Los Angeles, and Cleveland Clinic. Semen parameters, in addition to demographic, laboratory and prescription data were captured from the medical record. Exclusion criteria included pretreatment normozoospermia [>15 million (M)/mL], exogenous testosterone use within 6 months of initiating therapy, prior orchiectomy, scrotal surgery during the treatment period, pretreatment SA collected >1 year before anastrozole prescription.

Initiation of clomiphene therapy for off-label, empiric use in the context of hypogonadal symptoms and/or subfertility was determined after careful discussion and shared decision-making between physician and patient. In general, patients with symptomatic hypogonadism (low testosterone or low-normal testosterone) and/or impaired sperm parameters was offered treatment. Testicular volume was assessed by clinical examination and orchidometer if there were difficulties with clinical examination alone.

Quantitative SA was performed according to World Health Organization (WHO) 5th edition criteria using a computer assisted semen analyzer (Medical Electronic Systems, Encino, CA, USA). Samples demonstrating oligozoospermia or azoospermia were independently evaluated using high-powered microscopy. Semen volume, concentration, total motility, strict morphology (Kruger), and pH were obtained. All patients included in the study underwent two semen analyses prior to starting therapy, and the most recent sample was used for pre-intervention data.

Data analysis

Wilcoxon rank-sum tests was used to compare continuous variables; whereas χ^2 and Fisher's exact tests were used for categorical variables. Analyses were performed using JMP 16.0. Given the limited sample size of the combined group, further statistical analysis was not performed. Missing data are noted in the tables where applicable.

Anastrozole dosing was not standardized; for this reason, the median dose and interquartile range (IQR) were reported when baseline patient characteristics were considered. Clomiphene dosage was standardized to 25 mg daily or 50 mg every other day. Total motile sperm counts (TMSCs) were calculated as the product of semen volume, sperm concentration, and motility percentage. We did not record sperm motility percentage for patients with baseline azoospermia or cryptozoospermia.

Both institutions used electrochemiluminescence immunoassays to quantify hormone levels using standard clinical laboratory practices. Estradiol assays used by each institution differed with respect to the lowest level of detectable hormone (Cleveland Clinic Foundation: 25 pg/mL, University of California, Los Angeles: 12 pg/mL). Therefore, baseline E_2 concentration was treated as a binary categorical variable with a cutoff set at ≥25 pg/mL. Although the T:E_2 ratio has traditionally been used in fertility literature, we considered E_2 <25 pg/mL to be equivalent to zero and reported the inverse ratio (E_2:T), so this parameter would remain a rational number for all hormone values.

Ethics

This study was conducted in accordance with the Declaration of Helsinki (as revised in 2013) and approved by the institutional review board of our institutions (Cleveland Clinic Foundation-IRB 19-212, University of California, Los Angeles-IRB 20-000710). Informed consent was waived given the retrospective nature of this study.

Results

Ninety participants were included in this analysis; baseline characteristics of all participants are reported in our recently published study (4). In brief, the median age of participants was 36 (IQR, 32–41) years, body mass index (BMI) 32 (IQR, 27–43) kg/m^2, and anastrozole dose 3 (IQR, 3–7) mg/week. The median follow-up duration was 91 (IQR, 64–117) days. With respect to baseline WHO semen classification categories, 19 participants (21%) demonstrated azoospermia, 11 (12%) cryptozoospermia, 32 (36%) severe oligozoospermia, and 28 (31%) oligozoospermia.

Sixty-nine men were on anastrozole monotherapy and 21 on combination anastrozole and clomiphene. There were largely no differences in baseline features with respect to anastrozole dosing, pre-treatment SA parameters, and pre-treatment WHO 5th edition semen classification. The average number of days between pre- and post-treatment variables was 144 for the anastrozole group compared to 109 for the combination group (P=0.0548). The two groups did differ in pre-treatment hormone levels with men in the combined treatment group demonstrating lower levels of LH (5.0 *vs.* 7.3 IU/L, P=0.03), and higher testosterone to LH ratio (79.3 *vs.* 35.3, P=0.046). There were no major adverse events reported.

Following treatment, 43% of men in the combined group demonstrated normozoospermia, compared to 25% in the anastrozole monotherapy group. Men in the combined group demonstrated marked improvements in TMSC (11.3 *vs.* 2.1 M, P=0.03) and semen concentration, which trended toward significance (6.9 compared to 3.2 M/mL, P=0.06). There were no significant differences in hormone levels among the two groups following treatment. These findings are outlined in greater detail in *Table 1*.

With respect to any improvements in TMSC, the anastrozole monotherapy group, demonstrated the following results stratified by pre-treatment WHO category: azoospermia, 2 participants (13%) with improved TMSC; cryptozoospermia, 4 participants (44%); severe oligozoospermia, 16 (64%); and oligozoospermia, 11 (55%). For the combined group: azoospermia, 0 participant (0%) with improved TMSC; cryptozoospermia, 1 participant (50%); severe oligozoospermia, 7 (100%); and oligozoospermia, 6 (75%). This was not statistically significant.

Discussion

Management of idiopathic, male factor infertility with empiric medical therapy remains a challenge as there are limited data to guide clinicians. In this brief report, we explore the effect of clomiphene and anastrozole combination therapy compared to anastrozole monotherapy on semen parameters in a multi-institutional cohort of men with idiopathic infertility. Our results demonstrate that men in the combined therapy group experienced clinically and statistically significant improvements in TMSC, in addition to clinically significant improvements in sperm concentration, which trended toward significance.

Although combination therapy has not previously been studied in this context, the WHO performed a randomized, double-blind, placebo-controlled trial of clomiphene for men with idiopathic infertility in 1992; unfortunately, their results failed to show any difference in pregnancy rates at the end of the study (5). Given our relatively short follow-up time, we did not explore pregnancy rates here; however, given no significant difference in WHO category upstaging, it would be not be surprising if combination therapy would not dramatically improve pregnancy rates. However, combination therapy and the concomitant improvement in TMSC may improve pregnancy rates with assisted reproductive technology. A recently published retrospective analysis by Muthigi *et al.* of over 90,000 intrauterine insemination (IUI) cycles found that pregnancy rates were highest at a TMSC of ≥9 M, with a gradual and continuous decline as TMSC decreased (6). If we interpret our data within the context of this finding, men on combination therapy (median TMSC 11.3 M) would be significantly more likely to succeed during an IUI cycle, compared to those on anastrozole monotherapy (median TMSC 2.1 M).

Although our study did not include a clomiphene monotherapy arm, previous investigations have explored the impact of clomiphene on fertility-related outcomes. In a systematic review and meta-analysis (7) of studies investigating this question, Huijben *et al.* found that clomiphene significantly increases sperm concentration, motility, morphology, total testosterone, estradiol, and gonadotropin levels. There were no major adverse events reported. This meta-analysis should be interpreted within the context of the quality of data reported in the included studies; sample sizes, for example, varied from as low as 11 to as high as 140 participants.

Combination therapy for idiopathic infertility relies on the theoretical synergy of each of the medications' related but distinct mechanisms of action. Clomiphene acts directly on each component of the hypothalamic-pituitary-gonadal axis to stimulate the release of gonadotropins

Table 1 Patient characteristics of men treated with anastrozole alone or in combination with clomiphene citrate

Patient factor*	Anastrozole only (n=69)	Anastrozole and clomiphene (n=21)	P value**
Baseline features			
Age (years)	36 [31–40]	40 [35–41]	0.06
BMI (kg/m^2)	34 [27–44]	31 [27–34]	0.13
Smoking history	22 (32%)	7 (33%)	>0.99
Genitourinary surgery history	13 (19%)	3 (14%)	0.75
Total testicular volume (cc)	30 [24–36]	34 [29–39]	0.04
Missing data (n)	3	0	
Varicocele history	27 (39%)	12 (57%)	0.21
Missing data (n)	2	0	
Medical management of infertility			
Anastrozole dosing (mg/wk)	3 [2–3]	3 [2–7]	0.21
hCG prescription history	6 (9%)	2 (10%)	>0.99
Semen parameters before treatment			
Semen volume (mL)	2.6 [1.6–3.5]	2 [1.3–2.9]	0.33
Missing data (n)	1	0	
Sperm concentration (M/mL)	2.3 [0.0–6.2]	3.6 [0.1–10.8]	0.13
Percent motile (%)***	36 [25–45]	41 [27–64]	0.15
Total motile sperm count (M)	0.6 [0.0–5.0]	4.3 [0.0–6.5]	0.19
Semen parameters after treatment			
Semen volume (mL)	2.8 [1.5–3.7]	2.4 [1.5–3.1]	0.59
Semen concentration (M/mL)	3.2 [0.0–12.4]	6.9 [0.9–39]	0.06
Percent motile (%)***	41 [27–51]	42 [41–49]	0.31
Total motile sperm count (M)	2.1 [0.0–9.9]	11.3 [0.4–43.0]	0.03
WHO semen classification before treatment			0.90
Azoospermia	15 (22%)	4 (19%)	
Cryptozoospermia	9 (13%)	2 (10%)	
Severe oligozoospermia	25 (36%)	7 (33%)	
Oligozoospermia	20 (29%)	8 (38%)	
WHO semen classification after treatment			0.47
Azoospermia	14 (20%)	4 (19%)	
Cryptozoospermia	7 (10%)	1 (5%)	
Severe oligozoospermia	20 (29%)	3 (14%)	
Oligozoospermia	11 (16%)	4 (19%)	
Normozoospermia	17 (25%)	9 (43%)	

Table 1 (*continued*)

Table 1 (*continued*)

Patient factor*	Anastrozole only (n=69)	Anastrozole and clomiphene (n=21)	P value**
Hormone parameters before treatment			
LH (IU/L)	7.3 [4.0–12.1]	5.0 [3.2–6.8]	0.03
Missing data (n)	1	0	
FSH (IU/mL)	6.1 [3.8–11.1]	5.3 [4.5–7.3]	0.54
Testosterone (ng/dL)	267 [186–430]	337 [217–477]	0.27
Estradiol ≥25 pg/mL****	43 (62%)	18 (86%)	0.16
Missing data (n)	4	0	
E/T ratio	0.09 [0.00–0.18]	0.10 [0.06–0.16]	0.45
Missing data (n)	4	0	
T/LH ratio	35.3 [21.2–66.0]	79.3 [26.5–138.2]	0.046
Missing data	1	0	
Hormone parameters after treatment			
LH (IU/L)	8.9 [6.0–15.1]	6.9 [4.8–11.5]	0.09
Missing data (n)	13	0	
FSH (IU/mL)	8.5 [6.3–15.1]	8.2 [5.7–11.2]	0.38
Missing data (n)	10	0	
Testosterone (ng/dL)	453 [340–579]	529 [428–688]	0.08
Missing data (n)	10	0	
Estradiol ≥25 pg/mL****	9 (16%)	7 (33%)	0.12
Missing data (n)	11	0	
E/T ratio	0.00 [0.00–0.00]	0.00 [0.00–0.05]	0.13
Missing data (n)	11	0	
T/LH ratio	50.9 [27.4–75.2]	87.9 [33.4–121.0]	0.10
Missing data (n)	14	0	

*, categorical variables were described with counts and percentages of the column total (adjusted for missing data). Continuous variables were described with the median value and an interquartile range. **, categorical variables were compared using a chi-squared or Fisher Exact test. Wilcoxon rank-sum tests were used to compare continuous variables across groups. ***, motility percentages were not recorded for men with azoospermia and cryptozoospermia. ****, the estradiol assays utilized by each institution differed with respect to the lowest level of detectable hormone. Therefore, this variable was reported as a categorical variable with the higher of the two detection thresholds used as the cutoff. BMI, body mass index; wk, week; hCG, human chorionic gonadotrophin; M, million; WHO, World Health Organization; LH, luteinizing hormone; FSH, follicle stimulating hormone; E/T, estradiol-to-testosterone ratio; T/LH, testosterone-to-luteinizing.

by disrupting the associated negative feedback arc (8). Anastrozole indirectly disrupts this feedback arc by preventing the aromatization of testosterone to estrogen, thereby stimulating follicle stimulating hormone (FSH) production (8). Despite some degree of overlap between their mechanisms, the side effect profile of combination therapy remains relatively benign. In a report of 51 men on clomiphene and anastrozole for hypogonadism, adverse events were largely mild and self-limiting (decreased libido, irritability, headache) (9).

Our study is not without limitations. In this report, we present real-world, multi-institutional data, which

was retrospectively collected. For this reason, the two comparison groups have innate differences that are not controlled for, limiting the generalizability of our findings. Other factors that may limit generalizability include our participants' demography and baseline characteristics. Of note, the median BMI of both groups is greater than 30, which may impact the efficacy of medications such as anastrozole and results may be different if higher doses were used or if this study were repeated on a patient population with a lower BMI. The medications were well-tolerated and no participants reported stopping the medications; however, treatment adherence was not queried beyond self-report. Most relevant are the pre-treatment levels of LH and the associated T:LH ratio, which differ among the two groups. Furthermore, given the limited sample size of men on combination therapy, we are unable to perform higher level statistical analyses such as multivariate regression with a high degree of fidelity. Given the small sample size, results should be considered preliminary. There are many benefits to a multi-institutional approach, such as the one we employ here; however, with such a collaboration comes potential inter-facility measurement bias for lab testing and SAs. Even with a multi-institutional approach, our sample size remains relatively small—underscoring the innate challenges of studying this patient population. Future investigations with prospective study designs and a more robust number of participants may benefit from higher level statistical methodology that is not possible in this report, including propensity match score analysis.

Conclusions

In men with idiopathic infertility, addition of clomiphene to anastrozole provides modest improvement to semen parameters. Although there were no significant differences between WHO semen classification upstaging, men on combination therapy showed a significant improvement in TMSC, which may contribute to improvements in pregnancy outcomes with less invasive assisted reproductive technologies, such as IUI. Future investigations with larger sample sizes and prospective study designs are necessary.

Acknowledgments

We would like to acknowledge the assistance of Neilufar Modiri from Division of Andrology, Department of Urology, David Geffen School of Medicine, University of California, Los Angeles, United States of America in assisting with data collection for this project.
Funding: None.

Footnote

Reporting Checklist: The authors have completed the STROBE reporting checklist. Available at https://tau.amegroups.com/article/view/10.21037/tau-23-454/rc

Peer Review File: Available at https://tau.amegroups.com/article/view/10.21037/tau-23-454/prf

Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at https://tau.amegroups.com/article/view/10.21037/tau-23-454/coif). V.O. received funding from the 2023 Urology Care Foundation Residency Research Award Program and the Russell Scott, Jr., MD, Urology Research. They were in no way involved in any part of the study design, analysis, manuscript writing, etc. J.N.M. is a consultant for Halozyme Pharma, Boston Scientific, and Endo Pharmaceuticals. N.P. is a consultant for Halozyme Pharma. The other authors have no conflicts of interest to declare.

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. This study was conducted in accordance with the Declaration of Helsinki (as revised in 2013) and approved by the institutional review board of our institutions (Cleveland Clinic Foundation-IRB 19-212, University of California, Los Angeles-IRB 20-000710). Informed consent was waived given the retrospective nature of this study.

References

1. Punab M, Poolamets O, Paju P, et al. Causes of male

infertility: a 9-year prospective monocentre study on 1737 patients with reduced total sperm counts. Hum Reprod 2017;32:18-31.
2. Jungwirth A, Giwercman A, Tournaye H, et al. European Association of Urology guidelines on Male Infertility: the 2012 update. Eur Urol 2012;62:324-32.
3. Ring JD, Lwin AA, Köhler TS. Current medical management of endocrine-related male infertility. Asian J Androl 2016;18:357-63.
4. Naelitz BD, Jiang T, Munoz-Lopez C, et al. Testosterone and luteinizing hormone predict semen parameter improvement in infertile men treated with anastrozole. Fertil Steril 2023;120:746-54.
5. A double-blind trial of clomiphene citrate for the treatment of idiopathic male infertility. World Health Organization. Int J Androl 1992;15:299-307.
6. Muthigi A, Jahandideh S, Bishop LA, et al. Clarifying the relationship between total motile sperm counts and intrauterine insemination pregnancy rates. Fertil Steril 2021;115:1454-60.
7. Huijben M, Huijsmans RLN, Lock MTWT, et al. Clomiphene citrate for male infertility: A systematic review and meta-analysis. Andrology 2023;11:987-96.
8. Rambhatla A, Mills JN, Rajfer J. The Role of Estrogen Modulators in Male Hypogonadism and Infertility. Rev Urol 2016;18:66-72.
9. Alder NJ, Keihani S, Stoddard GJ, et al. Combination therapy with clomiphene citrate and anastrozole is a safe and effective alternative for hypoandrogenic subfertile men. BJU Int 2018;122:688-94.

Cite this article as: Osadchiy V, Munoz-Lopez C, Jiang T, Naelitz BD, Parekh N, Vij SC, Mills JN, Lundy SD, Eleswarapu SV. Combination clomiphene citrate and anastrozole duotherapy improves semen parameters in a multi-institutional, retrospective cohort of infertile men. Transl Androl Urol 2024;13(2):245-251. doi: 10.21037/tau-23-454

