Original Article

# The efficacy of anastrozole in subfertile men with and without abnormal testosterone to estradiol ratios

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**Background:** Aromatase inhibitors (AIs), such as anastrozole, have shown effectiveness in treating oligoasthenozoospermia due to abnormal testosterone to estradiol ($T/E_2$) ratio ($T/E_2$ <10). However, its efficacy in subfertile men without abnormal $T/E_2$ ratio ($T/E_2$ >10) remained unevaluated. This retrospective study aimed to investigate whether patients with $T/E_2$ ratio >10 could also benefit from anastrozole treatment.

**Methods:** One hundred and five subfertile patients treated with 1 mg anastrozole daily were included, in which 62 patients had a $T/E_2$ ratio of <10, and 43 patients had this ratio >10. Semen parameters and sex hormone levels (including FSH, LH, PRL, $E_2$ and total T) were measured before and after a three-month treatment. $T/E_2$ ratio and total progressive motility sperm count were calculated from these results.

**Results:** Patients in both groups ($T/E_2$ ratio <10 and >10) showed significant increase in sex hormone levels (FSH, LH and total T), $T/E_2$ ratio and semen parameters (semen volume, sperm concentration, total sperm count, progressive motility and total progressive motility count). The changes of these parameters between two groups were comparable. A subgroup analysis comparing the effect of anastrozole on overweight and normal patients also showed no significant difference. Improvements in semen parameters were seen in some azoospermic and cryptozoospermic patients.

**Conclusions:** The majority of subfertile men with and without abnormal $T/E_2$ ratios responded to anastrozole treatment with significantly improved semen parameters and sex hormone levels. Anastrozole showed potential effectiveness in male subfertile patients with $T/E_2$ >10, to be confirmed by future prospective, randomized, controlled studies.

**Keywords:** Anastrozole; aromatase inhibitors (AIs); male infertility; testosterone to estradiol ratio

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## Introduction

Although not thoroughly understood, the role of estradiol in spermatogenesis has been highlighted in recent years (1). Estradiol negatively feeds back on the hypothalamus and pituitary to reduce secretion of gonadotropins, decrease serum testosterone level and eventually affect spermatogenesis (2). Excessive estradiol and/or low testosterone level have been shown by studies to be associated with oligoasthenozoospermia. This specific type of male infertility has also been described as a treatable

 

endocrinopathy (3), as they show the same manifestation of low testosterone to estradiol ($T/E_2$) ratios.

To correct the high estradiol and/or low testosterone level, endocrinological management has been applied in the treatment of male infertility as an off-label option (4), which could be categorized into two types: selective estrogen receptor modulators (SERMs) and aromatase inhibitors (AIs). SERMs competitively bind estradiol receptors to reduce the negative feedback on hypothalamus and pituitary. On the other hand, aromatase, a cytochrome p450 enzyme, which is expressed in the testes, brain, and adipose tissue in men, is responsible for converting testosterone into estradiol (5). By inhibiting this enzyme, AIs could directly lower serum estradiol level and therefore attenuate the negative feedback (6,7).

Studies have shown that both SERMs and AIs were generally effective in treating oligoasthenozoospermia due to high estradiol and/or low testosterone (8,9). However, both drugs also failed to produce favorable prognosis in some patients (10,11). A drug selection dilemma was therefore raised. To address this issue, based on the cohort study conducted by Pavlovich *et al.* (3), it seems that a consensus has gradually been reached, that patients with $T/E_2$ ratios (T in ng/dL and $E_2$ in pg/mL) less than 10 are advised to be treated with AIs (such as anastrozole and letrozole) (12), as most studies have shown improvement in sperm concentration and sperm motility after AIs treatment.

Still, two studies have showed that semen parameters from patients who failed the SERMs treatment could be restored after switching to AIs administration (13,14). Therefore, it raised the concern that whether AIs could be effective in patients with $T/E_2$ ratios >10. Moreover, there has been another study with much larger sample size to compare $T/E_2$ ratios between idiopathic infertile men and fertile controls, finding the normal $T/E_2$ ratio in fertile men to be more than 10 (15).

Therefore, our study intended to assess the efficacy of anastrozole administration in subfertile men with and without abnormal $T/E_2$ ratios, and to investigate whether patients with $T/E_2$ ratio >10 could also benefit from anastrozole treatment. We present the following article in accordance with the STROBE reporting checklist (available at https://tau.amegroups.com/article/view/10.21037/tau-22-95/rc).

## Methods

Subfertile patients treated with anastrozole (1 mg daily) from our andrology outpatient department were included between February 2018 and August 2021. All patients were treated by the same andrologist (YY). The inclusion criteria were as follows: time since infertility diagnosis more than one year, sperm concentration less than 15 M/mL and/or total sperm count less than 39 M, and progressive motility (PR) less than 32%. Azoospermic and cryptozoospermic patients were also included. Patients were excluded from this study if they had a chromosome disorder, exogenous T use or other hormonal treatment within past 3 months, or other endocrine diseases.

Patients data on basic characteristics, detailed medical and sexual history, physical examination, scrotum ultrasonography, basal semen analysis and hormonal tests (FSH, LH, PRL, $E_2$ and total T) were collected before the onset of anastrozole treatment. Specifically, the diagnosis of azoospermia and cryptozoospermia were made after centrifuged semen sample were analyzed at least twice. After a consecutive three-month treatment, semen parameters and hormonal levels were assessed again and patients' reports on adverse effects were also collected. For azoospermic patients without return of sperm in ejaculates after anastrozole treatment, their micro-TESE results and Johnsen's scores of testicular tissues were also noted.

For semen analysis, every patient was asked to keep abstinence for 3–5 days and to refrain from caffeine, alcohol or nicotine-containing agents 12 h before attendance. Ejaculates were obtained by masturbation into a dry wide-mouth sterile plastic container. Immediately after liquefaction, semen volume, sperm count and concentration, PR and total PR sperm count were assessed following the 2010 WHO recommendations. For sexual hormone tests, blood sample was obtained between 8:00 and 11:00 AM by venipuncture. Concentrations of FSH, LH, PRL, $E_2$ and total T were detected by the clinical laboratory of our hospital using chemiluminescent immunoassay.

The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). The study was approved by institutional review board of Shanghai First Maternity and Infant Hospital (No. KS21181) and individual consent for this retrospective analysis was waived.

### *Statistical analysis*

Patients' characteristics were compared between the $T/E_2>10$ and $T/E_2<10$ groups by $\chi^2$ test for proportions and analysis of variance for means. Paired *t*-tests were used to evaluate the hormone change and semen parameters change

 

**Table 1** Basic characteristics of the study population

| Demographic | Total (n=105) | Group T (n=43) | Group E (n=62) | P value |
|---|---|---|---|---|
| Age (years), mean (SD) | 32.67 (5.03) | 33.28 (5.16) | 32.24 (4.94) | 0.301 |
| BMI (kg/m$^2$), n (%) | | | | |
| <24 | 29 (27.6) | 13 (30.2) | 16 (25.8) | 0.618 |
| ≥24 | 76 (72.4) | 30 (69.8) | 46 (74.2) | |
| Height (cm), mean (SD) | 174.89 (5.70) | 176.44 (5.62) | 175.81 (5.55) | 0.109 |
| Weight (kg), mean (SD) | 79.73 (12.66) | 77.70 (12.40) | 81.15 (12.74) | 0.171 |
| Smoking (number/day), n (%) | | | | |
| 0 | 85 (81.0) | 35 (81.4) | 50 (80.6) | 1 |
| 1–9 | 8 (7.6) | 3 (7.0) | 5 (8.1) | |
| ≥10 | 12 (11.4) | 5 (11.6) | 7 (11.3) | |
| Alcohol consumption (%), n (%) | | | | |
| No | 101 (96.2) | 41 (95.3) | 60 (96.8) | 1 |
| Yes | 4 (3.8) | 2 (4.7) | 2 (3.2) | |
| Left testicle size (mL), mean (SD) | 13.24 (2.22) | 12.95 (2.25) | 13.43 (2.20) | 0.278 |
| Right testicle size (mL), mean (SD) | 13.47 (2.89) | 13.16 (2.35) | 13.68 (3.21) | 0.364 |
| Varicocele, n (%) | | | | |
| No | 99 (94.3) | 41 (95.3) | 58 (93.5) | 1 |
| Yes | 6 (5.7) | 2 (4.7) | 4 (6.5) | |

SD, standard deviation; BMI, body mass index; T/$E_2$, testosterone/estradiol. Group E, patients with T/$E_2$ ratio <10; Group T, patients with T/$E_2$ ratio >10.

(before and after 3-month treatment) in both groups. Standard Student's *t*-tests were used to compare the semen parameters change and hormone change (after 3-month treatment) between the two groups and subgroups stratified by body mass index (BMI). Analyses were conducted using Stata/MP 14.0 (College Station, TX, USA).

## Results

A total of 105 oligoasthenozoospermic patients (22 to 48 years old, mean 32.67±5.03) were included, in which 8 patients were cryptozoospermic and 4 patients had non-obstructive azoospermia. In all, 62 patients had a T/$E_2$ ratio of <10, who comprised group E, and 43 patients had this ratio >10, comprising group T. All cryptozoospermic and azoospermic patients had a T/$E_2$ ratio of <10.

Patient's age, height, weight, BMI, smoking and alcohol consumption, testis volume and percentage with clinical varicocele all showed no significant differences between two groups. There were two patients in group T and four patients in group E diagnosed with clinical grade 2 varicocele, respectively. The basic characteristics of the two groups were summarized in *Table 1*.

After a consecutive three-month anastrozole treatment, the levels of FSH, LH, PRL, $E_2$ and TT in group E all showed significant increase (P<0.001 for FSH, LH, $E_2$ and TT, and P=0.002 for PRL, respectively). In group T, the levels of FSH, LH, PRL, $E_2$ and TT were also dramatically increased (P<0.001 for FSH, LH, $E_2$ and TT, and P=0.001 for PRL) (*Table 2*). Both groups had significant increase in T/$E_2$ ratio (P<0.001 for both), and only four patients (3.8%) showed no increase, all from group T.

The changes of FSH, LH, PRL, $E_2$, TT and T/$E_2$ between the two groups were compared. The changes of FSH, LH, $E_2$, TT and T/$E_2$ in Group E were significantly higher than group T (P<0.05 for all), while the changes of PRL were not significant between two groups (P>0.05) (*Table 3*).

 

**Table 2** Hormonal analysis of patients treated with anastrozole in both groups

| Groups | Baseline | Post-treatment | P value |
|---|---|---|---|
| Group T | | | |
| FSH (IU/L) | 4.76 (2.51) | 9.54 (5.11) | <0.001 |
| LH (IU/L) | 3.96 (1.56) | 7.38 (3.61) | <0.001 |
| PRL (ng/mL) | 9.91 (3.53) | 12.90 (4.53) | 0.001 |
| E2 (pg/mL) | 30.26 (8.71) | 21.54 (7.82) | <0.001 |
| TT (ng/dL) | 4.23 (2.00) | 7.14 (2.36) | <0.001 |
| $T/E_2$ | 14.09 (4.25) | 37.57 (18.89) | <0.001 |
| Group E | | | |
| FSH (IU/L) | 4.60 (2.35) | 14.33 (9.66) | <0.001 |
| LH (IU/L) | 3.55 (1.39) | 11.66 (8.59) | <0.001 |
| PRL (ng/mL) | 9.63 (3.61) | 12.17 (5.14) | 0.002 |
| E2 (pg/mL) | 41.16 (25.11) | 24.18 (11.10) | <0.001 |
| TT (ng/dL) | 2.74 (1.12) | 8.26 (2.58) | <0.001 |
| $T/E_2$ | 7.16 (2.12) | 40.05 (19.86) | <0.001 |

Data are expressed as mean (standard deviation). FSH, follicle stimulating hormone; LH, luteinizing hormone; PRL, prolactin; TT, total testosterone; $T/E_2$, testosterone/estradiol; Group E, patients with $T/E_2$ ratio <10; Group T, patients with $T/E_2$ ratio >10.

**Table 3** Hormonal changes between baseline and post-treatment in both groups

| Hormones | Group T | Group E | P value |
|---|---|---|---|
| FSH (IU/L) | 4.78 (4.43) | 9.73 (9.06) | 0.001 |
| LH (IU/L) | 3.42 (3.82) | 8.11 (8.67) | 0.001 |
| PRL (ng/mL) | 2.99 (4.69) | 2.54 (5.45) | 0.664 |
| $E_2$ (pg/mL) | −8.72 (10.48) | −16.97 (20.66) | 0.018 |
| TT (ng/dL) | 2.91 (2.81) | 5.52 (2.52) | <0.001 |
| $T/E_2$ | 23.48 (19.11) | 32.89 (19.49) | 0.016 |

Data are expressed as mean (standard deviation). Group E, patients with $T/E_2$ ratio <10; Group T, patients with $T/E_2$ ratio >10; FSH, follicle stimulating hormone; LH, luteinizing hormone; PRL, prolactin; TT, total testosterone; $T/E_2$, testosterone/estradiol.

Semen volume, sperm concentration, total sperm count, PR% and total PR count (TPMC) in both groups all significantly increased (P<0.01 for all) (*Table 4*), and the changes of these parameters between two groups were comparable (P>0.05 for all) (*Table 5*).

A subgroup analysis was further performed on overweight patients in both groups. The changes of semen parameters pre- and post-treatment were compared between patients with BMI <24 and ≥24 [as 24 is the dividing value for normal and overweight for Chinese people (16)]. No significant change was observed (*Table 6*).

Of the 4 non-obstructive azoospermic patients in group E, 2 showed a return of sperm in their ejaculates. For the rest two patients, subsequent micro-TESE managed to retrieve sperm in one patient but failed the other. Their Johnsen's score were 8 and 5, respectively. Five of the eight patients with cryptozoospermia managed to increase their sperm concentration to more than 2 M/mL and the other three, though with numeric increase, remained cryptozoospermic.

Of all the 6 patients with clinical grade 2 varicocele in both groups, one from group E failed to show improvement

 

**Table 4** Semen parameters analysis of patients treated with anastrozole in both groups

| Groups | Baseline | Post-treatment | P value |
|---|---|---|---|
| Group T | | | |
| Semen volume (mL) | 3.37 (1.56) | 3.96 (1.77) | 0.002 |
| Sperm concentration (M/mL) | 6.96 (5.07) | 14.75 (13.38) | 0.001 |
| Total sperm count (M) | 23.18 (17.72) | 50.99 (43.92) | <0.001 |
| PR (%) | 10.65 (8.45) | 18.40 (12.30) | 0.001 |
| TPMC (M) | 2.44 (2.77) | 9.42 (9.02) | <0.001 |
| Group E | | | |
| Semen volume (mL) | 3.50 (1.56) | 3.95 (1.75) | 0.003 |
| Sperm concentration (M/mL) | 4.59 (3.11) | 12.66 (10.77) | <0.001 |
| Total sperm count (M) | 15.75 (13.19) | 47.72 (46.38) | <0.001 |
| PR (%) | 10.36 (9.27) | 18.08 (13.15) | <0.001 |
| TPMC (M) | 1.97 (2.20) | 10.88 (16.21) | <0.001 |

Data are expressed as mean (standard deviation). Group E, patients with $T/E_2$ ratio <10; Group T, patients with $T/E_2$ ratio >10; PR, progressive motility; TPMC, total progressive motility count.

**Table 5** Semen parameters changes between baseline and post-treatment in both groups

| Semen parameters | Group T | Group E | P value |
|---|---|---|---|
| Semen volume (mL) | 0.39 (1.00) | 0.44 (1.25) | 0.81 |
| Sperm concentration (M/mL) | 7.78 (12.05) | 8.07 (9.71) | 0.894 |
| Total sperm count (M) | 27.81 (45.79) | 31.96 (43.73) | 0.64 |
| PR (%) | 7.75 (9.97) | 7.89 (9.31) | 0.941 |
| TPMC (M) | 6.98 (8.44) | 8.94 (15.76) | 0.458 |

Data are expressed as mean (standard deviation). Group E, patients with $T/E_2$ ratio <10; Group T, patients with $T/E_2$ ratio >10; PR, progressive motility; TPMC, total progressive motility count.

**Table 6** Semen parameters changes between baseline and post-treatment in both groups, stratified by BMI

| Semen parameters | BMI (<24) | | | BMI (≥24) | | |
|---|---|---|---|---|---|---|
| | Group T (n=13) | Group E (n=16) | P value | Group T (n=30) | Group E (n=46) | P value |
| Semen volume (mL) | 0.63 (1.14) | 0.4 (1.23) | 0.597 | 0.46 (1.27) | 0.2 (0.85) | 0.376 |
| Sperm concentration (M/mL) | 7.63 (14.77) | 7.01 (5.64) | 0.888 | 8.35 (10.56) | 7.91 (9.71) | 0.864 |
| Total sperm count (M) | 29.34 (52.98) | 28.18 (27.15) | 0.943 | 32.97 (47.34) | 26.61(40.35) | 0.574 |
| PR (%) | 11.83 (11.1) | 9.71 (10.16) | 0.580 | 6.85 (8.6) | 6.2 (9.75) | 0.775 |
| TPMC (M) | 10.07 (10.43) | 8.05 (8.44) | 0.551 | 8.64 (16.97) | 6.13 (8.52) | 0.497 |

Data are expressed as mean (standard deviation). Group E, patients with $T/E_2$ ratio <10; Group T, patients with $T/E_2$ ratio >10; PR, progressive motility; TPMC, total progressive motility count.

 

in TPMC, and together with another patient from the same group, they both showed no increase in PR%. The other four patients all showed improvement in sperm concentration, total sperm count, PR% and TPMC.

Fifty-five (88.7%) patients in group E and 37 (86%) patients in group T showed increase in TPMC, making the overall response rate of anastrozole in this study to be 87.6%.

One patient, whose wife achieved spontaneous pregnancy after his taking anastrozole for two months, continued to accomplish all treatment.

Overall, anastrozole was well tolerated in all patients included, with only one patient in group T reporting loss of libido and mild erectile dysfunction during treatment. After ceasing anastrozole for one month, the patient's sexual function and desire returned to normal.

## Discussion

The administration of AIs for treating male infertility could be traced back to 1981, when Vigersky and Glass (17) reported to give ten consecutive patients with idiopathic oligospermia delta 1-testolactone, a steroidal AI, 1 g daily for 6 to 12 months. They managed to observe significant lowered serum $E_2$ (–34%) level, elevated T (+47%) level and $T/E_2$ ratio (+126%), and eight of in those patients had a significant increase in sperm concentration and total sperm count. Since then, a number of studies have evaluated the effect of both steroidal and non-steroidal AIs on oligospermic and oligoasthenozoospermic patients.

However, the cut-off value of a $T/E_2$ ratio for AIs treatment was not established until the study conducted by Pavlovich *et al.* (3) was published in 2001. Men with severe male infertility in their study were characterized as having a $T/E_2$ ratio of 6.9, while fertile controls were with a mean $T/E_2$ ratio of 14.5. Therefore, a cut-off value of 10 as the lower limit of normal $T/E_2$ ratio (T in ng/dL and $E_2$ in pg/mL) was proposed according to the lower 20th percentile of the fertile controls.

Based on this proposal, nearly all the subsequent studies were conducted using $T/E_2$ ratio <10 as the indication of AIs treatment for male subfertile patients, which generally showed effectiveness both in normalization of $T/E_2$ ratios and semen parameters (18-20). Nevertheless, no study has evaluated the effect of AIs, especially the more selective and more widely-used, non-steroidal AIs, in patients with $T/E_2$ ratio >10. Whether these patients could also benefit from AIs treatment remained unknown.

Still, three studies provided hints on this issue. In a prospective cohort study comparing serum T, LH, $E_2$ levels and $E_2$/T ratio between 357 idiopathic infertile men and 318 proven fertile men, Andersson *et al.* (15) observed significant differences between these two groups. More importantly, for the vast majority of their fertile controls, the $T/E_2$ ratios lay between 14 to 71, although the exact figures were not presented. Under such circumstances, the true cut-off value of "normal" $T/E_2$ ratio for fertile male should be at least >10, not to mention that the sample size of the fertile controls in Andersson's study was much larger than that of Pavlovich *et al.* (318 *vs.* 40). Therefore, the rationality of 10 as the defining value for normal $T/E_2$ ratio was questioned.

The other two studies provided indirect evidence. Çakan *et al.* (13) evaluated the effect of tamoxifen citrate (TAM) on 127 normogonadotropic patients with idiopathic oligoasthenoteratozoospermia and found a significant decrease in the $T/E_2$ ratio in the majority of the patients during treatment. Normalization of this ratio by using anastrozole to replace TAM for another three months could effectively improve sperm concentration and motility. More recently, Shoshany *et al.* (14) performed a retrospective study to evaluate the effect of anastrozole in oligozoospermic hypoandrogenic subfertile men, in which a small number of patients (n=8) had previous adverse reaction to clomiphene citrate (CC). All these eight patients showed significant increases in sperm concentration, motility and $T/E_2$ ratios. These findings indicated that the non-responders of CC and TAM could still benefit from anastrozole treatment, thus the use of anastrozole on patients with $T/E_2$ >10 might be promising.

Our study provided certain validation for this hypothesis. In group T, patients showed dramatic increase in semen volume, sperm concentration, total sperm count, PR%, TPMC, serum T and $T/E_2$ ratio, and the response rate reached 86%. The changes of these parameters were also comparable to patients with $T/E_2$ ratio <10, suggesting the increase of T, decrease of $E_2$ and elevated $T/E_2$ ratio due to aromatase inhibition could stimulate spermatogenesis, even in oligoasthenoteratozoospermic patients with normal serum T level and $T/E_2$ ratio. The effectiveness of AIs on this type of patients might be explained by the role of intratesticular T and intratesticular $T/E_2$ ratio, which could be different from serum T level and $T/E_2$ ratio. This was supported by Lardone *et al.* (21), who have identified a significantly decreased intratesticular $T/E_2$ ratio in complete Sertoli cell-only syndrome patients compared with

 

controls, while their serum T, $E_2$ and $T/E_2$ ratio remained within normal range. Also, the activity of intratesticular aromatase might be overwhelming in comparison with that of peripheral adipose tissue, as was shown by the subgroup analysis for overweight patients in our study, that there were no significant benefits seen on semen parameters compared with normal patients with BMI <24. Nevertheless, more direct evidence is warranted to prove this idea.

The results from group E coincided with most previous studies about AIs treating patients with $T/E_2$ ratio <10. Saylam *et al.* (22) also reported a significant rise of $T/E_2$ ratio, semen volume, sperm motility, and total motile sperm count after letrozole treatment. However, the improvement of AIs on several semen parameters remained controversial. Results from Shoshany *et al.* (14) showed increase in sperm concentration and total motile sperm count, but no significant improvement in ejaculate volume and sperm motility. Specifically in group E, 2 of the 4 patients with non-obstructive azoospermia showed a return of sperm to the ejaculate, and 5 of the 8 cryptozoospermic patients also had a rise of sperm concentration to >2 M/mL, adding evidence to the standpoint that AIs treatment could benefit $T/E_2$ ratio <10 patients with severely impaired spermatogenesis.

Our results also contributed to solve the drug selection dilemma between AIs and SERMs, especially when patients were with $T/E_2$ ratio >10. Helo *et al.* (23) have compared the efficacy between anastrozole and CC in hypogonadal infertile men. However, the mean $T/E_2$ ratio of all 26 patients enrolled in their study were <10. Although SERMs have long been advocated as an empiric treatment in idiopathic oligospermia, a latest meta-analysis including 16 studies has failed to show significant effect of SERMs treatment on sperm concentration, progressive and total motility in idiopathic infertile patients (9). Moreover, adverse effects and decreased semen parameters of CC and TAM have been reported by several comparative studies (24). In a case report, Pasqualotto *et al.* (11) even found three azoospermia occurred after CC treatment in patients with severe oligozoospermia. Therefore, our study favored AIs over SERMs, regardless of the $T/E_2$ ratio.

Inevitably, with its retrospective design, our study bore several limitations, such as the selection bias. We've tried to include all the patients treated with anastrozole to minimize the bias. The sample size of group T was also relatively small, which might diminish the evidence. Moreover, with one patient's wife achieved spontaneous pregnancy during treatment, the pregnancy outcomes of other patients were not followed, thus the clinical significance of the improvement seen in semen parameters might be underestimated.

Despite these limitations, our study supported the effectiveness of anastrozole in oligoasthenozoospermic men in a more generalized clinical scenario. Patients with $T/E_2$ ratio <10 and >10 could equally benefit from anastrozole administration. Thus, the $T/E_2$ ratio should not be regarded as a dividing value for AIs treatment, and a true normal $T/E_2$ ratio is warranted to be determined by future studies with larger sample size of fertile controls. Our results also suggested that AIs could take precedence over SERMs in treating oligoasthenozoospermic patients, with its efficacy and well tolerance. Furthermore, the role of intratesticular $T/E_2$ ratio and aromatase activity could be investigated, and prospective, randomized, blinded, placebo-controlled studies are also needed to verify our results.

## Conclusions

The majority of subfertile men with and without abnormal $T/E_2$ ratio responded to anastrozole treatment with significantly improved semen parameters and sex hormone levels. Anastrozole showed potential effectiveness in male subfertile patients with $T/E_2$ more than 10, to be confirmed by future prospective, randomized, controlled studies.

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## Footnote

*Reporting Checklist:* The authors have completed the STROBE reporting checklist. Available at https://tau.amegroups.com/article/view/10.21037/tau-22-95/rc

*Data Sharing Statement:* Available at https://tau.amegroups.com/article/view/10.21037/tau-22-95/dss

*Conflicts of Interest:* All authors have completed the ICMJE uniform disclosure form (available at https://tau.amegroups.com/article/view/10.21037/tau-22-95/coif). The 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. The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). The study was approved by institutional review board of Shanghai First Maternity and Infant Hospital (No. KS21181) and individual consent for this retrospective analysis was waived.



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