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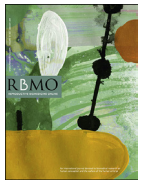

ARTICLE

Do men with normal testosterone–oestradiol ratios benefit from letrozole for the treatment of male infertility?

BIOGRAPHY

Liu Shuling is a Consultant at the Department of Reproductive Medicine, Division of Obstetrics and Gynaecology at KK Women's and Children's Hospital. She obtained her specialist qualification from the National University of Singapore (M.Med O&G) and was conferred as a member of the Royal College of Obstetricians and Gynaecologists, UK, in 2012.

Liu Shuling[1,2,*], Matthew Lau Sie Kuei[1,3], Seyed Ehsan Saffari[4], Zheng Jiayun[2], Tan Tse Yeun[1], Jessie Phoon Wai Leng[1], Veronique Viardot-Foucault[1], Sadhana Nadarajah[1], Jerry Kok Yen Chan[1,5,*], Tan Heng Hao[1]

KEY MESSAGE

Aromatase inhibitors, such as letrozole, have been used to treat subfertile men with reduced testosterone–oestradiol ratios defined as less than 10. This prospective study showed that letrozole can improve sperm concentration in men even if their pre-existing testosterone–oestradiol ratio is normal with no serious adverse effects.

ABSTRACT

Research question: Previous studies of aromatase inhibitors on male infertility have focused on men with low testosterone–oestradiol ratio of less than 10. Can aromatase inhibitors improve spermatogenesis in men with idiopathic male infertility with normal testosterone–oestradiol ratio?

Design: Prospective study of men with idiopathic severe oligozoospermia (sperm concentration <5 million/ml) carried out between February 2015 and March 2017. The objective was to assess if semen-analysis parameters improved after treatment with letrozole. Secondary objectives were to monitor the safety of letrozole in men, and to measure the alterations in serum FSH, LH, oestradiol and testosterone levels.

Results: Fifteen men with normal testosterone–oestradiol ratio (>10) were treated with letrozole 2.5 mg daily for 4 months. This produced a 5.5-fold increase in sperm concentration ($P = 0.0068$). All men had increased total serum testosterone and suppressed oestradiol levels after treatment, thus raising the overall testosterone–oestradiol ratio ($P < 0.0001$). Adverse effects from letrozole were relatively minor and included loss of libido (54%), headaches (25%), fatigue (21%), weakness (13%), loss of hair (8%) and dry mouth (8%).

Conclusions: Letrozole improves sperm concentration and increases testosterone–oestradiol ratio for men with oligozoospermia who have normal testosterone–oestradiol ratio; its role in the treatment of male infertility may be extended to this group of patients. In addition, it is a relatively well-tolerated drug with no serious adverse effects.

[1] Department of Reproductive Medicine, KK Women's and Children's Hospital, 100 Bukit Timah Road, Singapore 229899, Singapore
[2] OBGYN Academic Clinical Program, KK Women's and Children's Hospital, 100 Bukit Timah Road 229899, Singapore
[3] Knox Private Hospital, 262 Mountain Highway, Wantirna Victoria 3152, Australia
[4] Centre for Quantitative Medicine, Office of Clinical Sciences, Duke-NUS Medical School, Academia, 20 College Road, Level 6 169856, Singapore
[5] Program in Cancer and Stem Cell Biology, Duke-NUS Medical School, 8 College Road 169857, Singapore

*Corresponding author. E-mail address: liu.shuling@singhealth.com.sg (L. Shuling), jerry.chan.k.y@singhealth.com.sg (J. K. Y. Chan). https://doi.org/10.1016/j.rbmo.2018.09.016 1472-6483/
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KEYWORDS

Aromatase inhibitor
Letrozole
Male infertility
Oligozoospermia
Sperm concentration
Testosterone–oestradiol ratio

INTRODUCTION

It is well established that high levels of intra-testicular testosterone are necessary for spermatogenesis (*Saylem et al., 2011*). Many treatment options aimed at improving endogenous testosterone production have been described in the treatment of idiopathic male infertility (*Chua et al., 2013; Casamonti et al., 2017*).

Aromatase inhibitors block the enzymatic conversion of testosterone to oestradiol and androstenedione to oestrone. Additionally, they can increase endogenous testosterone production without associated increase in circulating oestrogens as seen with the use of selective oestrogen receptor modulators (*Pavlovich et al., 2001*). Aromatase inhibitors have, therefore, been proposed for the treatment of oligozoospermia since 1981 (*Vigersky and Glass, 1981*); since then, many studies have supported the use of other aromatase inhibitors, such as anastrozole (*Gregoriou et al., 2012; Shoshany et al., 2017*) and letrozole (*Cavallini et al., 2011;2013; Saylem et al., 2011; Gregoriou et al., 2012*).

Letrozole is a member of a novel class of non-steroidal, selective, potent, third-generation aromatase inhibitor, which was first approved for the treatment of breast cancer in 1996 (*Smith, 1998*). It reversibly inhibits the aromatase enzyme and prevents androgen precursors in adipose tissue from being converted into oestradiol (*Ribeiro et al., 2016*). This results in increased gonadotrophin secretion and consequently raised peripheral androgen levels, and thus stimulation of spermatogenesis (*Schulster et al., 2016*).

Following the seminal work of *Pavlovich et al. (2001)*, recent clinical studies on aromatase inhibitors have focused on men with low serum testosterone levels and reduced testosterone–oestradiol ratios (*Saylem et al., 2011; Gregoriou et al., 2012; Cavallini et al., 2013*). In defining the latter, Pavlovich's group determined a normal range for adult men based on 95% confidence intervals obtained from their reference cohort of men with proved fertility and proposed a testosterone (ng/dl)–oestradiol (pg/ml) ratio cut-off point of 10 as the lower limit of normal, as it represented less than the 20th percentile of normal distribution (*Pavlovich et al., 2001*). They proposed that this group of infertile men with low testosterone–oestradiol ratios would benefit from aromatase inhibitor treatment.

In their study, 45 out of 63 men (71%) who were infertile had testosterone–oestradiol ratios less than 10. In our clinical practice, the frequency of testosterone–oestradiol ratio less than 10 is not as prevalent. It is also difficult to ascertain this frequency from existing literature. Because hormonal changes produced by aromatase inhibitor can be observed in all men who take them (*Vigersky and Glass, 1981; Cavallini et al., 2011*), our hypothesis is that spermatogenesis can be improved in men with idiopathic male infertility with normal testosterone–oestradiol ratios.

The primary objective of this study was to assess semen-analysis parameters for men with idiopathic infertility and normal testosterone–oestradiol ratios after treatment with letrozole. The secondary objectives were to monitor the safety of letrozole in men, and to measure the alterations in serum FSH, LH, oestradiol and testosterone produced by letrozole treatment.

MATERIALS AND METHODS

The study was approved by the Institutional Review Board and the Health Science Authority of Singapore on 25 April 2014 (reference 2014/123/D). Written informed consent was obtained from all patients.

This was a prospective study carried out at KK Women's and Children's Hospital between February 2015 and March 2017, which included men with non-obstructive azoospermia and severe oligozoospermia. Non-obstructive azoospermia was defined as the absence of sperm in pellets of two separate centrifuged semen samples collected 30–60 days apart, and obstructive causes of azoospermia were excluded based on history, physical examination and ultrasound of the testis. Severe oligozoospermia was defined as the presence of a sperm concentration of less than 5×10^6/ml in two separate semen samples at least 6 weeks apart. Study participants had to be at least 21 years of age and able to give informed consent. Participants were not admitted into the study if there was any possible identifiable cause of infertility such as infection (defined as the presence of seminal white blood cells concentration greater than 10^6ml; a positive seminal culture analysis or positive urethral swab for chlamydia test); current use of drugs, tobacco or heavy drinking of alcohol (defined as consuming 15 drinks or more per week); ongoing medical treatment (gonadotrophins, anabolic steroids, cancer chemotherapy, previous cancer radiotherapy or chemotherapy); palpable varicocele; X-ray exposure in the previous 8 months; microdeletions in the azoospermia factor region in the Y chromosome; and abnormal karyotypes, e.g. Klinefelter syndrome. In addition, we excluded men on non-steroidal anti-inflammatory drugs in this study as reports in animal studies have demonstrated adverse effects on spermatogenesis (*Biswas et al., 1978; Uzun et al., 2015*).

Before recruitment, study participants underwent a complete evaluation for azoospermia or severe oligozoospermia. This included history-taking, physical examination, laboratory investigations for FSH, LH, testosterone, prolactin, thyroid function, karyotyping and two separate seminal analyses at least 6 weeks apart, or at least 30 days apart, if azoospermia was diagnosed. Y chromosome microdeletion genetic (YCMD) studies in the azoospermia factor regions of the long arm were conducted for all patients with azoospermia. For men with oligozoospermia (n = 15), the attending physicians decided whether YCMD was to be tested. As such, only nine out of 15 men with oligozoospermia had YCMD tested. The investigations were carried out within a 3-month time frame before recruitment. All patients with oligozoospermia were offered sperm cryopreservation before taking letrozole.

All participants were given 2.5 mg letrozole orally per day for 4 months. A follow-up appointment was made for patients 1 month after starting treatment to check on medication compliance and presence of side-effects. Patients were contacted by telephone at 2 months and 3 months to enquire about compliance and side-effects using the same checklist. The post-treatment semen analyses and serum measurements of FSH, LH, testosterone and oestradiol were scheduled together on the day of the last dose of letrozole (day 120). If the participant was unable to turn up on the scheduled day, the semen analysis and blood tests were rescheduled to an earlier date. As such, all men were still

TABLE 1 DISTRIBUTION OF DEMOGRAPHIC VARIABLES OF PATIENTS (*n* = 15)

Characteristic	Unit/level	Mean (SD) Median (IQR)	Frequency (%)
Age	Year	38.7 (5.72) 38 (8)	–
Body mass index	Kg/m^2	27.1 (3.99) 25.7 (7.36)	–
Ethnicity	Chinese	–	13 (86.67)
	Malay	–	1 (6.67)
	Indian	–	1 (6.67)

taking letrozole at the point of repeat semen analysis and blood tests.

In our laboratory, testosterone was reported in nmol/l, and oestradiol was reported in pmol/l. Testosterone–oestradiol ratio was equivalent to Pavlovich's testosterone (ng/dl)–oestradiol (pg/ml) ratio (*Pavlovich et al., 2001*). Serum concentrations of FSH, LH, oestradiol and testosterone were measured using immunoassay and chemiluminescent microparticle immunoassay technology with flexible assay protocols, referred to as Chemiflex (Abbott Laboratories). The resulting chemiluminescent reaction was measured and detected by the ARCHITECT iSystem optics (ARCHITECT FSH, Abbott Ireland; ARCHITECT LH, Abbott Ireland; ARCHITECT Estradiol, Abbott Ireland; ARCHITECT 2nd Generation Testosterone, Abbott GmbH & Co. KG, Germany).

The analytical sensitivity of the ARCHITECT FSH assay was calculated as 0.05 mIU/ml. The intra- and inter-assay coefficients of variation were less than 4% and less than 5%, respectively. The observed limit of quantitation for the ARCHITECT LH assay was 0.09 mIU/ml. The intra-and inter-assay coefficients of variation were less than 4% and less than 9%, respectively. The analytical sensitivity of the ARCHITECT ostradiol assay was 10 pg/ml or less. The intra- and inter-assay variations were less than 7% and less than 8%, respectively. The observed limit of quantitation for ARCHITECT second Generation Testosterone assay was 0.08 nmol/l. The intra- and inter- assay variations were both less than 6%.

The laboratory staff carrying out the seminal analysis and hormonal assays were blinded to the study. All semen analyses were carried out in the same andrology laboratory, with laboratory values and cut-offs standardized according to World Health Organization criteria (*Cooper et al., 2010*). All patients were informed of their results.

Data were extracted for statistical analysis using SAS software version 9.4 for Windows (SAS, Inc, Cary, NC). Demographic variables were reported using mean (standard deviation) and median (interquartile range) and frequency (%). The change in sperm analysis parameters and testosterone–oestradiol ratio were calculated based on the pre- and post-treatment results. Because of the small sample size and uncertainty in normality assumption, both mean and median of the differences (post-pre) with 95% confidence intervals were reported for the variables, and both parametric paired T-test and non-parametric Wilcoxon signed rank test were used. Subgroup analysis based on a cut-off point of 10 for testosterone–oestradiol ratio was conducted. Statistical significance was set at $P \leq 0.05$.

RESULTS

A total of 55 men were screened over 2 years. A total of 29 men who fulfilled the inclusion criteria and who agreed to take letrozole as treatment for their male infertility were recruited into the study. One patient dropped out of the study after 3 weeks of medication as his wife achieved a spontaneous pregnancy. All 28 men completed 4 months' of letrozole. Four out of 28 men (14.3%) had pre-treatment testosterone–oestradiol levels less than 10 and were excluded from the final analysis. The numbers were too small to assess statistically significant differences in these four men (Supplementary TABLE 1). Two out of four men with testosterone–oestradiol less than 10 had normal sperm concentration and motility after treatment with letrozole.

Of the remaining 24 men with testosterone–oestradiol greater than 10, nine had non-obstructive azoospermia (FIGURE 1). All men with azoospermia (n = 9) did not have sperm in their ejaculate despite treatment with letrozole and they were excluded from the main analyses. The remaining 15 men with severe oligozoospermia and testosterone–oestradiol ratio over 10 were included in the analysis. Age, body mass index and race of the study participants (n = 15) are presented in TABLE 1. Their mean age was 38.7 years, and mean body mass index was 27.1.

Treatment with letrozole increased total serum testosterone levels by 2.5-fold (n = 15; $P < 0.0001$) and suppressed oestradiol levels by 0.6-fold ($P = 0.0033$), thus raising the overall testosterone–oestradiol ratio ($P < 0.0001$) (TABLE 2). Significant increases were also observed in FSH (2.1-fold; $P = 0.0005$) and LH (2.2-fold; $P < 0.0001$) after treatment (TABLE 2).

Sperm concentration increased 5.5-fold ($P = 0.0068$) and total count increased 4.3-fold ($P = 0.0096$) after treatment with letrozole (TABLE 3). No significant difference was found in motility of sperm and volume of semen after treatment. No statistical analyses could be conducted for morphology, as all except two readings had been less than 1%, which were 1% and 2% normal forms.

Looking at the individual semen analysis, 11 out of 15 patients had improvement in either their sperm concentration or motility. Four had no difference after treatment. None of the included patients achieved a spontaneous pregnancy during the treatment period.

In the analysis for side-effects, all men with normal testosterone–oestradiol

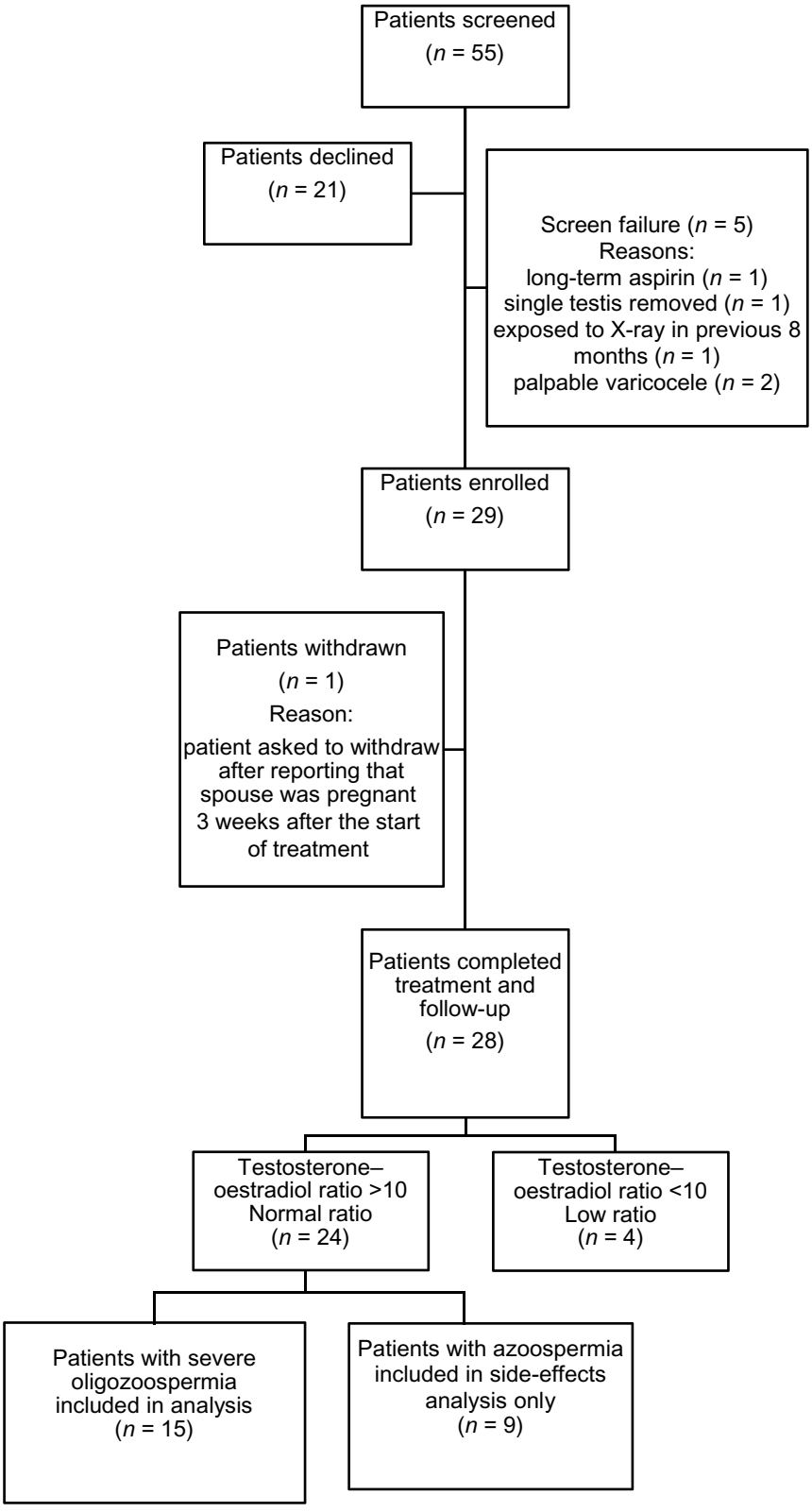

FIGURE 1 Recruitment.

ratio, including men with azoospermia (n = 9) were included in the analysis (n = 24) (TABLE 4). Fifty-four per cent of men (13/24) suffered from a loss of libido, whereas other common side-effects included headaches, fatigue and weakness. Two patients reported loss of hair and two reported dry mouth. None of the patients developed an allergic reaction and nobody dropped out of the study as a result of side-effects from letrozole.

TABLE 2 FSH, LH, TESTOSTERONE, OESTRADIOL LEVELS AND TESTOSTERONE–OESTRADIOL RATIO BEFORE AND AFTER TREATMENT IN PATIENTS WITH TESTOSTERONE–OESTRADIOL RATIO GREATER THAN 10, TREATED WITH LETROZOLE 2.5 MG/DAY FOR 4 MONTHS (*n* = 15)

Variable	Pre-treatment Mean (SD) Median (IQR)	Post-treatment Mean (SD) Median (IQR)	Difference Mean (95% CI) Median (95% CI)	*P*-value[a]
FSH (IU/l)	8.0 (4.8) 7.2 (7.4)	17.1 (9.6) 16.3 (10.7)	9.1 (4.8 to 13.5) 9.8 (3.1 to 12.5)	0.0005 0.0003
LH (IU/l)	5.3 (3.3) 4.4 (2.4)	11.4 (5.6) 10.9 (8.2)	6.2 (4.2 to 8.1) 7.3 (2.4 to 8.1)	<0.0001 <0.0001
Testosterone (nmol/l)	16.1 (9.3) 13.4 (10)	40.9 (20.2) 36.6 (12.4)	24.8 (16.1 to 33.5) 25.8 (17.8 to 34.3)	<0.0001 0.0002
Oestradiol (pmol/l)	75.6 (40.6) 70 (62)	42.5 (10.7) 37 (8)	–33.1 (–53.3 to –13) –18 (–47 to 0)	0.0033 0.0010
Testosterone–oestradiol ratio	24.4 (9.6) 21.7 (21.7)	109.4 (60.6) 90.9 (34.8)	85.0 (53.6 to 116.5) 73.8 (50.9 to 102.6)	<0.0001 0.0001

[a] Comparing means between pre- and post-treatment using paired T-test; comparing medians between pre- and post-treatment using Wilcoxon Signed Rank Test.
CI, confidence interval; IQR, interquartile range; SD, standard deviation.

TABLE 3 DISTRIBUTION OF SPERM ANALYSIS PARAMETERS BEFORE AND AFTER TREATMENT IN PATIENTS WITH TESTOSTERONE–OESTRADIOL RATIO GREATER THAN 10, WITH LETROZOLE 2.5MG PER DAY FOR 4 MONTHS (*n* = 15)

Variable	Pre-treatment Mean (SD) Median (IQR)	Post-treatment Mean (SD) Median (IQR)	Difference Mean (95% CI) Median (95% CI)	*P*-value[a]
Abstinence time (days)	2.9 (0.5) 3 (0)	3.1 (0.5) 3 (0)	0.2 (–0.3 to 0.6) 0 (0 to 1)	NS NS
Sperm concentration (x10^6/ml)	1.9 (1.4) 2.2 (2.2)	10.4 (10.4) 5.2 (18.2)	8.5 (2.7 to 14.2) 3.4 (0 to 18.2)	0.0068 0.0017
Volume (ml)	3.1 (1.8) 3.1 (3.4)	3.2 (1.7) 3.1 (2.6)	0.1 (–0.5 to 0.7) 0.1 (0 to 0.6)	NS NS
Total count (x10^6)	6.6 (6.3) 3.5 (9.6)	28.3 (29.3) 22.9 (49.6)	21.7 (6.2 to 37.2) 12.6 (0.1 to 34.5)	0.0096 0.0034
Motility (%)	20.4 (26.5) 1 (44)	28.7 (22.5) 32 (49)	8.3 (–4.2 to 20.9) 0 (–3 to 20)	NS NS

CI, confidence interval; IQR, interquartile range; NS, not statistically significant; SD, standard deviation.
No statistical analyses could be conducted for morphology as all except two readings had been less than 1%, which were at 1% and 2% normal forms.
[a] Comparing means between before and after treatment using Paired T-test; comparing medians between pre- and post-treatment using Wilcoxon signed rank test.

DISCUSSION

In this small study in men presenting with idiopathic oligozoospermia with normal testosterone–oestradiol ratio, treatment with letrozole over 4 months was associated with a significantly raised sperm concentration after 4 months of treatment, with corresponding increases in testosterone and FSH. The most common side-effect was loss of libido.

Consensus on treatment of men with idiopathic oligozoospermia is currently lacking. Empirical treatment to raise the serum FSH and LH levels with selective oestrogen receptor modulators, such as like clomifene citrate and tamoxifen, have been given with some success (*Chua et al., 2013*). They work by antagonizing oestrogen at the level of the pituitary gland, which in turn increases FSH and LH release, thereby improving spermatogenesis. They also have oestrogenic effects on other tissues, which can lead to undesirable effects in men (*Wibowo et al., 2016*). In men, FSH injections have also been used for treating idiopathic infertility, but these are expensive and require regular injections, which are less acceptable to some patients (*Casamonti et al., 2017*).

Other early studies with aromatase inhibitors using high-dose oral testolactone suggested a beneficial effect on semen parameters and hormonal profiles in men with normal gonadotrophins and idiopathic oligozoospermia (*Vigersky and Glass, 1981*).

Pavlovich et al. (2001) identified that men with normal spermatogenesis had a mean testosterone–oestradiol ratio of 14.5 and men with severe male infertility had a testosterone–oestradiol ratio of 6.9. On the basis of these observations, they proposed a cut-off point of 10 as the lower limit of normal for testosterone–oestradiol ratios in men, which represented the 20th percentile of normal distribution (*Pavlovich et al., 2001*). They treated 45 infertile men with testosterone–oestradiol ratio less than 10, with 50–100 mg oral testoslactone twice daily for 5 months, and found a significant increase in sperm concentration and motility in 12 men. They included men with non-obstructive azoospermia and sperm concentration of less than 10 million sperm per cubic centimeters of semen. The cause of infertility among these 45 men were heterogeneous, including Klinefelter's syndrome, other chromosomal abnormalities, cryptorchidism, post-chemotherapy infertility, and varicocele and idiopathic causes; mean FSH was 20.5 IU/l. Since then, clinical studies of aromatase inhibitors in male infertility have focused on men with low testosterone–oestradiol ratios, with three other studies using letrozole for treatment of oligozoospermia

TABLE 4 SIDE-EFFECTS OF LETROZOLE IN MEN WITH SEVERE OLIGOZOOSPERMIA (*n* = 15) AND AZOOSPERMIA (*n* = 9) WITH NORMAL TESTOSTERONE–OESTRADIOL RATIO

Side-effect	*n*	%
Loss of libido[a]	13	54.2
Headache	6	25.0
Fatigue	5	20.8
Weakness[a]	3	12.5
Loss of hair[a]	2	8.3
Dry mouth	2	8.3
Nausea[a]	1	4.2
Nervousness[a]	1	4.2
Stomach discomfort	1	4.2
Weight gain	1	4.2
Nose bleed	1	4.2
Increased urination frequency	1	4.2
Bad sleep	1	4.2
Rash[a]	0	0

[a] Side effects that were asked specifically as part of the checklist at clinic and phone consults.

in men with testosterone–oestradiol ratios less than 10 showing apparent benefit.

In the first study, *Saylem et al. (2011)* reported 27 infertile men with a mean sperm count of 3.04 million with testosterone–oestradiol ratios less than, or equal to, 10 who were treated with letrozole for more than 6 months (*Saylem et al., 2011*). They excluded men who had, or had a history of, varicocele or ejaculatory duct obstruction. They found that testosterone–oestradiol ratio, ejaculate volume, sperm count, motility and total motile sperm count significantly increased after treatment. Four of 17 patients with azoospermia (23.5%) had spermatozoa in the ejaculate after treatment. Two of 10 oligospermic men achieved spontaneous pregnancy after treatment.

In the second study, *Cavallini et al. (2011)* reported four patients with non-obstructive azoospermia and FSH levels less than 10 IU/l who were given letrozole 2.5 mg per day for 3 months. All four patients who previously diagnosed with azoospermia achieve improved sperm concentration after treatment, ranging from 40,000 to 90,000/ml. Three of these patients had testosterone–oestradiol ratio less than 10.

In a follow-up study, a group of 22 men with non-obstructive azoospermia or cryptozoospermis, with testosterone–oestradiol ratio less than 10, received letrozole 2.5 mg per day for 6 months and compared with 24 patients receiving placebo (*Cavallini et al., 2013*). Sperm concentration, motility, FSH, testosterone and LH improved in the letrozole group, but not in the placebo group. All patients with non-obstructive azoospermia treated with letrozole had sperm in the post-treatment ejaculate, whereas those treated with placebo remained azoospermic.

In the last study, *Gregoriou et al. (2012)* treated 29 men with testosterone–oestradiol ratios less than 10 with either anastrazole or letrozole, and found an increase in sperm concentration, motility and morphologically normal sperm and ejaculate after treatment. Seminal parameters in four out of the 15 patients in the letrozole group did not improve (*Gregoriou et al., 2012*).

Since 2001, no studies using letrozole for the treatment of male infertility have included men with normal testosterone–oestradiol ratios, which was the motivation for our study. Our study included only men with normal testosterone–oestradiol ratios and showed that sperm concentration and testosterone–oestradiol ratio also improved in this group of men who would otherwise not be given aromatase inhibitor treatment.

None of the patients in our study with non-obstructive azoospermia (*n* = 9) had spermatozoa in their ejaculate after treatment. All our patients with non-obstructive azoospermia had normal testosterone–oestradiol ratios compared with the study by *Cavallini (2013)*, in which sperm was only seen in men with non-obstructive azoospermia with testosterone–oestradiol less than 10 who were treated with letrozole. In these severe cases of male infertility, the role of testosterone–oestradiol might play a bigger role.

It is difficult to determine the incidence of low testosterone–oestradiol from published data. The incidence of low testosterone–oestradiol ratio is only 14% (4/28) in our study, which means that most men with idiopathic oligozoospermia would not normally be considered as candidates for treatment with letrozole.

The complaint of loss of libido is the most common reported side-effect in our study. This is a well-documented side-effect in other studies that used aromatase inhibitors for the treatment of male infertility. In the present study, other side-effects were mild and none of our study patients dropped out because of drug side-effects.

In the initial study by *Cavallini (2011)*, all four patients experienced loss of libido. Two experienced a cutaneous rash and one complained of nervousness. In their follow-up study, side-effects were higher in the group treated with letrozole (*Cavallini et al., 2013*). Five out of 26 patients complained of loss of libido and hair, two experienced a cutaneous rash and one patient reported only loss of libido. Four out of 26 patients

(15.4%) assigned to the letrozole group dropped out because of side-effects (loss of libido [n = 2]; loss of hair [n = 1]; cutaneous rash [n = 1]). *Saylem et al. (2011)* reported two patients with mild headaches, whereas no severe side-effects were observed. *Gregoriou et al. (2012)* reported only mild side-effects in their study.

The strength of our study was our deliberate inclusion of men with normal testosterone–oestradiol ratio who had severe oligozoospermia. In our prospective cohort, letrozole treatment led to a five-fold improvement in sperm concentration. The limitation of our study is the non-randomized nature of the intervention and the absence of a control group, which would be difficult to pursue in our setting.

In conclusion, the role of aromatase inhibitors such as letrozole in the management of male infertility has been limited to men with testosterone–oestradiol ratio of less than 10 since the publication of the study by *Pavlovich et al. (2001)*. Our data suggest that treatment with letrozole improves testosterone–oestradiol ratio even in men with normal testosterone–oestradiol ratio, and its role can potentially be extended to all men with severe idiopathic oligospermia regardless of their initial testosterone–oestradiol ratio, as it is a relatively well-tolerated drug with no serious adverse effects. Considering the relatively small sample size of this study, additional studies are still needed to validate these findings and show that improved sperm parameters and testosterone–oestradiol ratios achieved with letrozole can translate into improved pregnancy outcomes.

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SUPPLEMENTARY MATERIALS

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.rbmo.2018.09.016.

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