Endocrinology, Diabetes & Metabolism CASE REPORTS

S M Twigg and B Lin

ID: 22-0242; February 2023
DOI: 10.1530/EDM-22-0242

Dose-dependent response to long-term clomiphene citrate in male functional hypogonadotropic hypogonadism

Beryl Lin[1] and **Stephen M Twigg**[1,2]

[1]Department of Endocrinology, Royal Prince Alfred Hospital, Sydney, NSW, Australia and [2]Sydney Medical School (Central), University of Sydney, Sydney, NSW, Australia

Correspondence should be addressed to S M Twigg
Email
stephen.twigg@sydney.edu.au

Summary

Functional hypogonadotropic hypogonadism is a relatively common condition in middle-aged to elderly men that can significantly impair quality of life. Besides lifestyle optimisation, androgen replacement remains the mainstay of treatment; however, its adverse effects on spermatogenesis and testicular atrophy are undesirable. Clomiphene citrate is a selective oestrogen receptor modulator that acts centrally to increase endogenous testosterone without affecting fertility. Although it has demonstrated effectiveness in shorter-duration studies, its longer-term outcomes are less well-documented. In this study, we report the case of a 42-year-old male with functional hypogonadotropic hypogonadism who sustained an excellent dose-dependent, titratable clinical and biochemical response to clomiphene citrate with no known adverse effects for 7 years to date. This case highlights that clomiphene citrate has potential as a safe and titratable longer-term treatment option, and the need for further randomised control trials in therapy options to normalise androgen status.

Learning points

- Functional hypogonadotropic hypogonadism is a relatively common, but likely underdiagnosed, condition in middle-aged to older males.
- Testosterone replacement is the current mainstay of endocrine therapy but can cause sub-fertility and testicular atrophy.
- Clomiphene citrate is a serum oestrogen receptor modulator that acts centrally to increase endogenous testosterone production without affecting fertility.
- It has potential as a safe and efficacious longer-term treatment option that can be titrated to increase testosterone and relieve clinical symptoms in a dose-dependent manner.
- Longitudinal prospective studies as randomised control trials evaluating alternatives to exogenous testosterone are required.

Background

Functional hypogonadotropic hypogonadism (FHH) is a frequently underdiagnosed condition in middle-aged to elderly males that can significantly impair quality of life (1, 2, 3). Although its aetiology is not completely understood, the phenotype is characterised by clinical androgen deficiency in the absence of structural hypothalamic–pituitary pathology (3). In addition to lifestyle optimisation, androgen replacement remains the treatment mainstay; however, exogenous testosterone can undesirably impair spermatogenesis and cause testicular atrophy (4).

Clomiphene citrate is a selective oestrogen receptor modulator that acts centrally to increase endogenous testosterone production without causing adverse effects on

ID: 22-0242; February 2023
DOI: 10.1530/EDM-22-0242

fertility (2). It has demonstrated efficacy in short-duration studies; however, there remains a paucity of longer-term data to guide clinical use (2, 5).

In this study, we report the case of an otherwise healthy 42-year-old male with FHH symptoms refractory to lifestyle measures alone. He demonstrated an excellent dose-dependent clinical and hormonal response to clomiphene citrate with no adverse effects over a 7-year period.

Case presentation

A 42-year-old male presented to endocrine clinic with a 6-year history of generalised fatigue, reduced libido, erectile dysfunction, slowed cognition and insomnia. He was otherwise healthy, with a background of mild asthma and well-managed generalised anxiety on escitalopram therapy. As an ambitious finance professional, he acknowledged an intensive work schedule. He reported positive family relationships as a husband and father of three young children with no history of infertility. He was a non-smoker with minimal alcohol intake and had no history of exogenous androgen use.

On examination, he had a BMI of 25 kg/m^2 and normal secondary sex characteristics. His testes were soft with a borderline reduced volume of 12 mL bilaterally. Testicular ultrasound showed a small 2.8 mm left epididymal cyst and a mild varicocele.

Investigation

Repeated early morning serum hormonal profile was consistent with secondary hypogonadism: low total testosterone: 8.5 nmol/L (9.5–28), low-normal LH: 1.0 IU/L (0.6–12), low FSH: 0.9 IU/L (1.0–12), high-normal oestradiol: 160 pmol/L (<160), measured in each case by the Abbott ARCHITECT i2000SR platform, and normal SHBG: 23 nmol/L (15–50) plus normal FAI: 37% (15–100). Prolactin, thyroid studies, and β-HCG level were also normal, as was semen analysis. Pituitary MRI did not identify any abnormalities.

These results were consistent with FHH, presumed to be secondary to a stress-related hypothalamic effect.

Treatment

A biopsychosocial approach to management was employed by intensifying lifestyle practices including sleep hygiene, exercise, and stress reduction as first line. Our patient declined androgen replacement due to concerns about testicular atrophy; however, he reported a previous 1-month trial of clomiphene citrate while overseas that yielded good symptom improvement.

Through a shared decision-making process, he was recommenced on clomiphene at 25 mg daily, as off-label therapy, intended initially for the short-term. After 6 weeks, he reported significant improvement in his overall wellbeing and all symptoms including libido, mood and energy, muscular strength, and cognition. His blood total testosterone increased to the upper limit of normal to 20.3 nmol/L with corresponding increases in LH to 1.7 IU/L, FSH to 3.5 IU/L, and oestradiol to 176 pmol/L.

Due to the paucity of long-term safety data, clomiphene was weaned with the intention to cease. However, despite maintenance of intensive lifestyle strategies and adjunctive use of sildenafil citrate, clomiphene dose reductions below 15 mg per day consistently precipitated the recurrence of symptoms including reduced libido and fatigue that significantly impacted on his daily function. Thus, our patient was continued on clomiphene, with dose titrations according to his symptom and hormonal profile, with regular follow-up every 4–6 months.

Outcome and follow-up

To date, our patient has continued on clomiphene citrate for a total duration of 7 years. Over this period, he demonstrated a direct dose-related response to clomiphene therapy in his serum total testosterone, oestradiol, LH, and FSH levels (Fig. 1 and 2). He has maintained a normal prostate-specific antigen, blood haemoglobin, lipid profile, and bone mineral density with no reported adverse effects. His oestradiol has remained

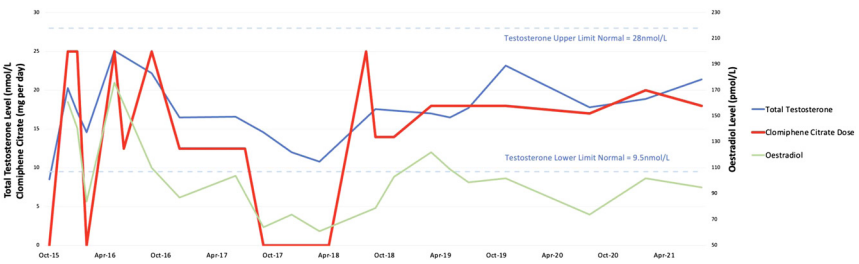

Figure 1
Total testosterone and oestradiol levels on clomiphene citrate over a 7-year period.

ID: 22-0242; February 2023
DOI: 10.1530/EDM-22-0242

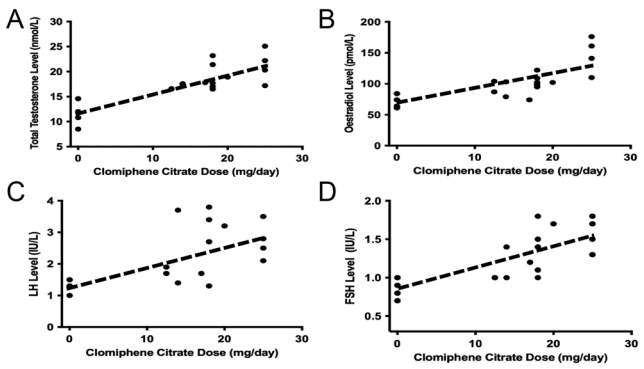

Figure 2
Relationship between hormone levels and clomiphene citrate dose. (A). Statistically significant linear correlation between testosterone levels and clomiphene citrate dose ($r^2 = 0.69$, $P < 0.0001$). (B). Statistically significant linear correlation between oestradiol levels and clomiphene citrate dose ($r^2 = 0.60$, $P < 0.0001$). (C). Statistically significant linear correlation between LH levels and clomiphene citrate dose ($r^2 = 0.41$, $P < 0.01$). (D). Statistically significant linear correlation between FSH levels and clomiphene citrate dose ($r^2 = 0.59$, $P < 0.001$).

in the normal range on middle-range clomiphene doses. His bone densitometry T scores at the lumbar spine and hip were in the normal range and osteopenic range before clomiphene commencement with T scores of +0.1 and −1.1 respectively, and they did not significantly change from their baseline, when measured at 2 and 4 years after treatment onset.

Currently, he continues at his minimum effective dose of clomiphene citrate of 18 mg daily (25 mg 5 days a week) with maintenance of good symptomatic benefit and normal range testosterone levels. He undergoes monitoring with quarterly blood tests and half-yearly clinical reviews.

Discussion

FHH is a common condition in middle-aged and older males that negatively impacts physical and psychological wellbeing (2). Due to variation in its definition and non-specific symptomatology, it is likely often underdiagnosed with an estimated prevalence between 5 and 40% in the adult male population (1, 6). Its pathophysiology remains incompletely understood. While chronic illnesses can precipitate FHH, untreated hypogonadism has also been associated with the development of osteoporosis, cardiovascular disease, and diabetes (3).

Persistently subnormal serum testosterone levels in the presence of symptomatic androgen deficiency despite lifestyle intervention is an indication for endocrine therapy (4). Testosterone replacement remains the mainstay treatment; however, exogenous androgens impair fertility and require monitoring for adverse effects such as polycythemia, prostate cancer, and dyslipidaemia. Furthermore, in Australia for example, androgen replacement is subsidised only for males with a blood total testosterone level <6.0 nmol/L. However, younger men such as our patient can still suffer significant symptoms with testosterone levels above this cut-off while desiring fertility preservation. Longer-term data on alternatives to androgen replacement, such as hCG injections and serum oestrogen receptor modulators, are limited.

This case describes a middle-aged male with minimal comorbidities and symptomatic FHH refractory to lifestyle interventions who responded to clomiphene citrate. Interestingly, he demonstrated a statistically significant linear correlation between clomiphene dose and total testosterone, oestrogen, LH, and FSH levels ($P < 0.01$) (Fig. 2). To our knowledge, this is the first report to suggest that clomiphene citrate effectively induces and sustains a dose-dependent response in pituitary function and subsequent endogenous testosterone production for a period of at least 7 years. Furthermore, our patient reported no adverse effects and maintained normal biochemical and metabolic parameters over this period.

Selective oestrogen receptor modulators (SERMs), such as clomiphene citrate, are thought to primarily function as oestrogen antagonists to the pituitary gland to drive gonadotropin release, which in turn stimulates spermatogenic and steroidogenic testicular function (2). In contrast to exogenous androgen replacement, they do not cause testicular atrophy or infertility and can be a less-expensive oral alternative (2). Two double-blinded, placebo-controlled trials have demonstrated that clomiphene citrate increases testosterone for the duration of up to 3 months (7, 8). Cohort studies, mostly limited to retrospective audits, supported by a recent meta-analysis have also shown that clomiphene citrate increases serum testosterone levels in men with hypogonadism (Table 1) (9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19). However, no randomised controlled trials have compared clomiphene to testosterone replacement (5). One retrospective age-matched study found that patients treated with testosterone injections have higher serum testosterone levels but no difference in hypogonadal symptoms (18). For our patient, personal preference for a fertility-sparing oral agent that did not cause testicular atrophy made clomiphene citrate a more favourable treatment option in the context of regular endocrine follow-up care and monitoring for this current off-label indication.

ID: 22-0242; February 2023
DOI: 10.1530/EDM-22-0242

Table 1 Cohort studies of clomiphene citrate for male hypogonadism.

Reference	Country	Type	*n*	Average dose, mg/day	Duration	Population	Outcomes
Keihani *et al.* (19)	USA	RA	322	25–50	2 months	Males (mean 36 years) with hypogonadism, TT< 300 ng/dL and symptoms.	TT mean increases from 249.5 to 329.2 ng/dL. Baseline LH/FSH was not predictors of response. No significant adverse events.
Krzastek *et al.* (11)	USA	RA	400	25–50	12–52 months (median)	Males with hypogonadism TT< 10.4 nmol/L	Eugonadism: 88%. Symptom improvement: 77% on CC >3 years. No difference in results between patients on CC < or >3 years. No significant adverse events.
Tan *et al*. (24)	Taiwan	RA	10	50	1–2 months	Males (mean 50 years) with low TT< 300 ng/dL and symptoms.	TT mean increases from 246 to 548 ng/dL)($P < 0.01$).
Bendre *et al.* (12)	USA	RA	11	12.5	3 months	Young males (18–21 years) with secondary hypogonadism TT< 12.1 nmol/L	TT mean increases from 8 to 18 nmol/L ($P < 0.0001$)
Patel *et al.* (25)	USA	RA	47	25–50	2 weeks–3 months	Males (mean 35 years) with TT < 300 ng/dL.	TT mean improvement of 281 ng/dL ($P < 0.001$). 2 of 11 patients had a decrease in TT after 2 weeks.
Mazzola *et al.* (13)	USA	PCS	76	12.5–50	6–11 months	Males (mean 46 years) with hypogonadism TT< 10.4 nmol/L LH <_6 IU/mL on CC: 12.5–50 mg/day	TT mean increases > 7 nmol/L in 62% patients
Ramasamy *et al.* (18)	USA	RAMC	31	25	NA	Males (median 40 years) with TT< 300 ng/dL and symptoms.$n = 31$ men receiving clomiphene citrate compared to $n = 1150$ on testosterone therapy	TT mean increases from 247 to 504 ng/dL ($P < 0.05$). Median TT lower in patients treated with CC compared to testosterone injections but similar to men using testosterone gels. No difference in symptom scores between CC and testosterone.
Da Ros & Averbeck (14)	Brazil	PCS	125	25	3 months	Males (mean 62 years) with low libido, TT< 13.9 nmol/L on CC 25 mg/day	TT mean increases 310 to 669 ng/dL ($P < 0.001$) No significant adverse events.
Moskovic *et al.* (15)	USA	PCS	46	12.5	1–3 years	Males (mean 44 years) with hypogonadism TT< 10.4 nmol/L, LH<_6 IU/mL	TT mean increases from 7.9 to 20.2 nmol/L at 3 years ($P < 0.001$). ADAM score decreases from 7 to 5 at 3 years. No significant adverse events.
Katz *et al.* (10)	USA	PCS	86	12.5–25	19 months (mean)	Males (mean 29 years) with hypogonadism TT< 10.4 nmol/L LH<_6 IU/mL on CC 25 mg/day	TT mean increases from 192 to 485 ng/dL ($P < 0.01$) Improvement in at least one symptom in 90% patients
Taylor & Levine (9)	USA	RA	65	12.5–25	8–40 months	Males (mean 42 years) with hypogonadism	TT mean increases by 107% from 227 to 573 ng/dL ADAM score decreases from 4.9 to 2.1 at follow-up ($P < 0.05$)
Shabsigh *et al.* (16)	USA	PCS	36	25	4–6 weeks	Males (mean 39 years) with TT < 10.4 nmol/L on CC 25 mg/day.	Mean TT increases by 146% from 248 to 610 ng/dL ($P < 0.001$). No significant adverse events.
Guay *et al.* (17)	USA	RA	173	12.5	4 months	Males (mean 54 years) with hypogonadotropic hypogonadism and erectile dysfunction on CC 21 mg/day.	TT mean increases from 9 to >17pg/mL ($P < 0.001$) Improved sexual function in 75% patients.

ADAM, androgen deficiency in ageing men; CC, clomiphene citrate; LH, luteinising hormone; NA, not available; PCs, prospective cohort study; RA, retrospective audit; RAMC, retrospective age-matched comparison; TT, total testosterone.

It is important to note that clinical care guidelines addressing male hypogonadism (20), including in functional hypogonadism (21), are commonly silent about clomiphene citrate therapy, which may well be due to lack of data about long-term safety of this therapy. Recent published expert opinion (22) indicates that SERMs may be an alternative to testosterone replacement therapy but that more research is needed to evaluate their effect on hypogonadal signs and symptoms in males, as well as their long-term safety profile such as effects on bone health. The follow-up period of clomiphene treatment in current literature ranges from 1 to 52 months, and there remains a paucity of prospective longer-term studies (5, 11). The tolerability of clomiphene therapy has been reported in a systematic review that found the self-reported incidence of side effects, most commonly, mood changes, and breast tenderness, is from 4 to 11%, and there has been no evidence of clinically significant changes in lipid profiles, bone density, haemoglobin, or prostate-specific antigen (5). Our patient had been treated for 7 years to date with no known adverse effects and careful surveillance. While prescribed dosages of clomiphene citrate have varied from 12.5 to 50 mg daily across studies, our case suggests an individualised weaning regimen that can identify the minimally acceptable dose-dependent response to manage a patient's symptoms which may also help to optimise the benefit to risk ratio of this therapy.

The effect of clomiphene on the testosterone to oestradiol ratio remains an interesting area for further research. Some studies have reported increased oestradiol levels in a subset of patients, particularly those with a longer duration of clomiphene use, that necessitated co-treatment with anastrozole to address hyper-oestrogenic symptoms (11, 15). However, more recent data suggest that testosterone aromatisation due to increased adiposity over time may confound these results (20). Oestradiol levels related to (Fig. 1) and correlated with (Fig. 2B) clomiphene dose in our patient, who maintained a stable body weight over the duration of his treatment and did not require any additional therapy.

Our case study has some important limitations. While our patient's symptoms were closely monitored, they were not quantified by scales such as the androgen deficiency in ageing men questionnaire. Furthermore, alternative therapies such as β-HCG and androgen replacement have not been trialled in our patient as a comparator. Inherently, larger prospective cohort studies with longer follow-up periods are required to evaluate potential longer-term adverse effects, such as prostate cancer or cardiovascular disease, even though there is no *a priori* reason to expect greater adverse effects than parenteral androgen therapy. Further studies, including randomised controlled trials comparing clomiphene citrate to conventional androgen replacement, are indicated to better inform evidence-based therapy.

Declaration of interest
The authors declare there is no conflict of interest that could be perceived as prejudicing the impartiality of the research reported.

Funding
This work did not receive any specific grant from any funding agency in the public, commercial or not-for-profit sector.

Patient consent
Written informed consent has been obtained from the patient for publication of this case report.

Author contribution statement
Both authors reviewed the case files and wrote the manuscript. S Twigg is the physician responsible for the patient's care.

References

1 Mulligan T, Frick MF, Zuraw QC, Stemhagen A & McWhirter C. Prevalence of hypogonadism in males aged at least 45 years: the HIM study. *International Journal of Clinical Practice* 2006 **60** 762–769. (https://doi.org/10.1111/j.1742-1241.2006.00992.x)
2 Wheeler KM, Sharma D, Kavoussi PK, Smith RP & Costabile R. Clomiphene citrate for the treatment of hypogonadism. *Sexual Medicine Reviews* 2019 **7** 272–276. (https://doi.org/10.1016/j.sxmr.2018.10.001)
3 Zarotsky V, Huang MY, Carman W, Morgentaler A, Singhal PK, Coffin D & Jones TH. Systematic literature review of the risk factors, comorbidities, and consequences of hypogonadism in men. *Andrology* 2014 **2** 819–834. (https://doi.org/10.1111/andr.274)
4 Bhasin S, Brito JP, Cunningham GR, Hayes FJ, Hodis HN, Matsumoto AM, Snyder PJ, Swerdloff RS, Wu FC & Yialamas MA. Testosterone therapy in men with hypogonadism: an Endocrine Society clinical practice guideline. *Journal of Clinical Endocrinology and Metabolism* 2018 **103** 1715–1744. (https://doi.org/10.1210/jc.2018-00229)
5 Huijben M, Lock MTWT, de Kemp VF, de Kort LMO & van Breda HMK. Clomiphene citrate for men with hypogonadism-A systematic review & meta-analysis. *Andrology* 2022 **10** 451–469. (https://doi.org/10.1111/andr.13146)
6 Araujo AB, Esche GR, Kupelian V, O'Donnell AB, Travison TG, Williams RE, Clark RV & McKinlay JB. Prevalence of symptomatic androgen deficiency in men. *Journal of Clinical Endocrinology and Metabolism* 2007 **92** 4241–4247. (https://doi.org/10.1210/jc.2007-1245)
7 Guay AT, Bansal S & Heatley GJ. Effect of raising endogenous testosterone levels in impotent men with secondary hypogonadism: double blind placebo-controlled trial with clomiphene citrate. *Journal of Clinical Endocrinology and Metabolism* 1995 **80** 3546–3552. (https://doi.org/10.1210/jcem.80.12.8530597)

8 Soares AH, Horie NC, Chiang LAP, Caramelli B, Matheus MG, Campos AH, Marti LC, Rocha FA, Mancini MC, Costa EMF, *et al*. Effects of clomiphene citrate on male obesity-associated hypogonadism: a randomized, double-blind, placebo-controlled study. *International Journal of Obesity* 2018 **42** 953–963. (https://doi.org/10.1038/s41366-018-0105-2)
9 Taylor F & Levine L. Clomiphene citrate and testosterone gel replacement therapy for male hypogonadism: efficacy and treatment cost. *Journal of Sexual Medicine* 2010 **7** 269–276. (https://doi.org/10.1111/j.1743-6109.2009.01454.x)
10 Katz DJ, Nabulsi O, Tal R & Mulhall JP. Outcomes of clomiphene citrate treatment in young hypogonadal men. *BJU International* 2012 **110** 573–578. (https://doi.org/10.1111/j.1464-410X.2011.10702.x)
11 Krzastek SC, Sharma D, Abdullah N, Sultan M, Machen GL, Wenzel JL, Ells A, Chen X, Kavoussi M, Costabile RA, *et al*. Long-term safety and efficacy of clomiphene citrate for the treatment of hypogonadism. *Journal of Urology* 2019 **202** 1029–1035. (https://doi.org/10.1097/JU.0000000000000396)
12 Bendre SV, Murray PJ & Basaria S. Clomiphene citrate effectively increases testosterone in obese, young, hypogonadal men. *Reproductive System and Sexual Disorders: Current Research* 2015 **4**. (https://doi.org/10.4172/2161-038X.1000155)
13 Mazzola CR, Katz DJ, Loghmanieh N, Nelson CJ & Mulhall JP. Predicting biochemical response to clomiphene citrate in men with hypogonadism. *Journal of Sexual Medicine* 2014 **11** 2302–2307. (https://doi.org/10.1111/jsm.12592)
14 Da Ros CT & Averbeck MA. Twenty-five milligrams of clomiphene citrate presents positive effect on treatment of male testosterone deficiency-a prospective study. *International Braz j Urol* 2012 **38** 512–518. (https://doi.org/10.1590/s1677-55382012000400011)
15 Moskovic DJ, Katz DJ, Akhavan A, Park K & Mulhall JP. Clomiphene citrate is safe and effective for long-term management of hypogonadism. *BJU International* 2012 **110** 1524–1528. (https://doi.org/10.1111/j.1464-410X.2012.10968.x)
16 Shabsigh A, Kang Y, Shabsign R, Gonzalez M, Liberson G, Fisch H & Goluboff E. Clomiphene citrate effects on testosterone/estrogen ratio in male hypogonadism. *Journal of Sexual Medicine* 2005 **2** 716–721. (https://doi.org/10.1111/j.1743-6109.2005.00075.x)
17 Guay AT, Jacobson J, Perez JB, Hodge MB & Velasquez E. Clomiphene increases free testosterone levels in men with both secondary hypogonadism and erectile dysfunction: who does and does not benefit? *International Journal of Impotence Research* 2003 **15** 156–165. (https://doi.org/10.1038/sj.ijir.3900981)
18 Ramasamy R, Scovell JM, Kovac JR & Lipshultz LI. Testosterone supplementation versus clomiphene citrate for hypogonadism: an age matched comparison of satisfaction and efficacy. *Journal of Urology* 2014 **192** 875–879. (https://doi.org/10.1016/j.juro.2014.03.089)
19 Keihani S, Wright LN, Alder NJ, Jiang J, Cheng PJ, Stoddard GJ, Pastuszak AW, Deibert CM & Hotaling JM. Baseline gonadotropin levels and testosterone response in hypogonadal men treated with clomiphene citrate. *Urology* 2020 **142** 119–124. (https://doi.org/10.1016/j.urology.2020.04.074)
20 Isodori AM, Aversa A, Calogero A, Ferlin A, Francavilla S, Lanfranco F, Pivonello R, Rochira V, Corona G & Maggi M. Adult- and late-onset male hypogonadism: the clinical practice guidelines of the Italian Society of Andrology and Sexual Medicine (SIAMS) and the Italian Society of Endocrinology (SIE). *Journal of Endocrinological Investigation* 2022 **45** 2385–2403. (https://doi.org/10.1007/s40618-022-01859-7)
21 Corona G, Goulis DG, Huhtaniemi I, Zitzmann M, Toppari J, Forti G,Vanderschueren D & Wu FC. European Academy of Andrology (EAA) guidelines on investigation, treatment and monitoring of functional hypogonadism in males: endorsing organization: European Society of Endocrinology. *Andrology* 2020 **8** 970–987. (https://doi.org/10.1111/andr.12770)
22 Awouters M, Vanderschueren D & Antonio L. Aromatase inhibitors and selective estrogen receptor modulators: unconventional therapies for functional hypogonadism?*Andrology* 2020 **8** 1590–1597. (https://doi.org/10.1111/andr.12725)
23 Keihani S, Alder NJ, Cheng PJ, Stoddard GJ, Pastuszak AW & Hotaling JM. Obesity and baseline estradiol levels are independent predictors for initiation of anastrozole in hypogonadal men on clomiphene citrate. *World Journal of Men's Health* 2020 **38** 582–590. (https://doi.org/10.5534/wjmh.190160)
24 Tan JS, Chang HC, Chung SD, Chen PH & Wu WC. Clomiphene citrate treatment outcomes in Taiwanese hypogonadal men: A single-center preliminary report. *Urological Science* 2017 **28** 50–52. (https://doi.org/10.1016/j.urols.2016.03.001)
25 Patel D, Brant W, Myers J, Presson A, Johnstone E, Dorais JA, Aston KI, Carrell DT & Hotaling JM. The safety and efficacy of clomiphene citrate in hypoandrogenic and subfertile men. *International Journal of Impotence Research* 2015 **27** 221–224. (https://doi.org/10.1038/ijir.2015.21)

Received 4 March 2022
Received in final form 9 January 2023
Accepted 11 January 2023