Reduced IGF-1 Levels Following Clomiphene Treatment for Male Hypogonadism

Nikita Mogar, M.D.[1] UCLA Medical Center. 757 Westwood Plaza, LA, CA 90095, United States of America. Nmogar@mednet.ucla.edu (914) 960-5658
Dongyun Zhang, PhD.[1] UCLA Medical Center. 757 Westwood Plaza, LA, CA 90095, United States of America. dongyunzhang@mednet.ucla.edu (917) 213-7871
Anthony P. Heaney, M.D, PhD.[1,2] UCLA Medical Center. 757 Westwood Plaza, LA, CA 90095, United States of America. aheaney@mednet.ucla.edu (310) 721-5061

Departments of [1]Medicine, [2]Neurosurgery, David Geffen School of Medicine, University of California, Los Angeles

Corresponding Author: Anthony P. Heaney
Phone: (310) 721-5061
E-mail: aheaney@mednet.ucla.edu
ORCID ID: https://orcid.org/0000-0003-3865-0810

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NM, DZ, APH have nothing to declare.

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Abstract

Context. The selective estrogen receptor modulator clomiphene stimulates pituitary-derived gonadotropins to generate sex steroids including estrogen. Estrogen activates SOCS-3 which can inhibit growth hormone-directed JAK/STAT signaling to reduce serum IGF-1 levels. ***Objective***. We sought to examine the effects of clomiphene therapy on IGF-1 levels in non-acromegalic male patients treated with clomiphene for underlying hypogonadism. ***Design***. We identified 20 male hypogonadal subjects treated with clomiphene citrate for at least three months. ***Setting***. These patients were treated in an ambulatory, academic, tertiary medical center. ***Patients***. The 20 male patients ranged from 27-76 years of age and hypogonadism was due to several etiologies, including prolactinomas, clinically non-functioning pituitary tumors, rathke's cleft cysts, colloid cysts or idiopathic causes. ***Intervention***. Clomiphene citrate 50 mg three days per week was administered for a minimum of three months. ***Main Outcome measure(s).*** IGF-1 measured by LC-MS before and after clomiphene therapy. ***Results***. 15 of 20 (75%) of hypogonadal men treated with clomiphene exhibited a decrease in median (IQR) serum IGF-1 levels of -0.60 (-1.2 - 0.0) ($p<0.01$). Two of the 20 patients (10%) exhibited a decrease in IGF-1 > 2 standard deviations below their age- and sex-matched mean value. ***Conclusions***. Clomiphene therapy can result in a significant reduction in serum IGF-1 levels in some treated hypogonadal men. Given that the decrease in IGF-1 can be >2 SD in some patients and potentially clinically significant, we recommend interval monitoring of serum IGF-1 levels and symptoms of growth hormone deficiency in hypogonadal patients treated with clomiphene citrate.

Introduction

Clomiphene is a selective estrogen receptor modulator (SERM) that stimulates production of the pituitary gonadotropins, follicle stimulating hormone and luteinizing hormone. (1). In light of its action to stimulate estrogen and progesterone, it is approved to induce ovulation in women with polycystic ovarian syndrome where success rates approach 50% (2). It is also used "off-label" to increase testosterone production in hypogonadal male patients and has the advantage that it does not cause testicular atrophy (3).

Prior studies have demonstrated that estrogen negatively regulates growth hormone signaling by activating SOCS-3 to inhibit JAK/STAT signaling and has been shown to reduce IGF-1 levels by 40-80% in healthy adult men with intact pituitary function (4, 5). Further studies have confirmed similar effects in post-menopausal women treated with large doses of oral estrogen resulting in decreased IGF-1 levels (6). Additionally, estrogen stimulates the synthesis of the growth hormone and IGF binding proteins, GHBP & IGFBP, which alters GH action to lower IGF-1 levels (4).

As further evidence of its action to lower IGF-1, clomiphene has been shown to normalize IGF-1 levels in 7/16 (44%) patients with acromegaly and was associated with a concomitant 209% increase in total testosterone levels (7). However, literature on the potential actions of clomiphene to alter IGF-1 levels in normal males treated for hypogonadism is quite sparse.

This retrospective study sought to assess the effect of clomiphene treatment on IGF-1 levels in a consecutive series of male patients treated with clomiphene for central hypogonadism.

Materials and Methods

Study design, setting, and population

Under institutional IRB approval, using encryption password protection software and a secure network server to store data, we interrogated the XDR database, a research tool that contains patient data from all University of California (UC) medical campuses. We identified 99 male UCLA patients aged 18 and older who had been prescribed clomiphene citrate 50 mg by a single investigator (APH) for a minimum of three months between 2012 and 2022.

74 of 99 patients were excluded from the study; 13 because they did not take the clomiphene as prescribed, 51 did not have documented IGF-1 levels prior to and after taking clomiphene, four had IGF-1 measured by a method other than liquid chromatography-mass spectroscopy (LC-MS), six patients who had a diagnosis of acromegaly, and five patients who did not have IGF-1 levels collected within 12 months before and within 24 months after clomiphene treatment (**Figure 1**).

The remaining 20 male subjects included in the study ranged from 27-76 years of age **(Table 1**). They had all taken clomiphene citrate 50 mg three days per week for at least three months and had documented IGF- levels measured by LC-MS on at least one occasion within 12 months before and within 24 months after clomiphene treatment. Fifteen of the 20 study patients (75%) had had space occupying lesions of the pituitary, five had prolactinomas (all of whom had normal serum prolactin levels on cabergoline therapy), six had clinically nonfunctioning pituitary tumors (CNFPTs), five had idiopathic hypogonadism with no imaging abnormalities, two had silent corticotroph tumors, one had a Rathke's Cleft Cyst, and one had a colloid cyst. Four patients (#5, #9, #18, and #19) were on replacement therapy, four were receiving a stable dose of thyroid replacement for at least six months with normal Free T4 levels, and one of these four

patients was also receiving glucocorticoid replacement (#9). Four out of five patients with prolactinomas were being treated with cabergoline and had been on a stable dose for at least six months (Table 2)

Data and Statistical analysis

The diagnosis of hypogonadism was confirmed by measurement of early morning (8-9am) total testosterone (TT) levels by LC-MS for all subjects on at least two occasions <300 ng/dL and/or a free testosterone (FT) <50 pg/mL (8). The normal range for morning total and free testosterone were (250-1100 ng/dL) and (47-244 pg/mL), respectively. All patients reported fatigue and reduced libido. IGF-1 was measured by LC-MS at Quest laboratories in all subjects, and IGF-1 levels are expressed as standard deviation (SD) according to the individuals' age- and sex-matched reference ranges.

Patient demographic, clinical, and biochemical data are depicted in **Table 2**. IGF-1, total, and free testosterone levels before and after clomiphene therapy were compared by non-parametric t-test, and changes in IGF-1 SD were correlated with total and free testosterone levels using GraphPad Prism software.

Results

Fifteen of 20 (75%) patients exhibited a decrease in serum IGF-1 levels, that ranged from –2.1-SD to –0.1-SD with median change and interquartile range (IQR) in IGF-1 SD of -0.60 (-1.2 - 0.0) respectively ($p<0.01$) (**Table 1**, **Figure 2a-b**). Two of these patients (10% of the total cohort, and 13% of the patients with declines in IGF-1) exhibited a decreased IGF-1 greater than or equal to 2 SDs below their age- and sex-matched mean value. Three patients (15%) exhibited an increase in IGF-1 SD of +0.693, 0.4, and 0.4-SD, respectively and in two patients (10%), IGF-1 levels were essentially unchanged.

All twenty (100%) patients exhibited an increase in their serum total testosterone levels ranging from 9 to 829 ng/dL with a median increase in total testosterone of 216 and IQR (100.5 - 363.7) ($p<0.0001$) (**Figure 3a-b**). The observed reduction in IGF-1 SD correlated weakly with the fold-increase in total testosterone with a correlation coefficient 0.36, though this was not statistically significant ($p=0.12$).

Nine of these 20 patients (45%) also exhibited an increase in serum free testosterone levels ranging from 10 to 102.8 pg/mL with a median increase of 23.2 and IQR (-4.9 - 91.4) ($p<0.05$) (**Figure 4a-b**). Four patients (20%) exhibited a decrease in free testosterone levels of 14.4, 4.9, 33.6, and 21.7, respectively, one patient had no change in free testosterone, while insufficient samples were available in the remaining six patients. The decrease in IGF-1 levels correlated weakly with the fold-increase in free testosterone with a correlation coefficient of 0.20, but this was not statistically significant ($p=0.45$).

Discussion

Male hypogonadism is a commonly encountered problem, estimated to affect 2-13% of the world's population (9, 10) and causes a wide variety of symptoms including fatigue, poor libido, erectile dysfunction, depressed mood, and decreased muscle mass. Replacement testosterone therapy is an option in symptomatic patients with low testosterone levels, typically defined as an early morning (8-9am) total testosterone (TT) <300 ng/dL and/or free testosterone (FT) <50 pg/mL (8). However, side effects can include erythrocytosis, possible hypercoagulability, and hyperlipidemia. Additionally, parenteral testosterone may be challenging for some patients, and skin reactions and/or androgen transfer to partners can occur with topical testosterone preparations, leading to reduced long-term compliance.

Off-label clomiphene use can be an option for some patients where gonadotroph function is relatively preserved, and it is generally well tolerated. Unlike exogenous testosterone therapy, clomiphene preserves male fertility and does not cause testicular atrophy. As discussed in the introduction, clomiphene acts at the hypothalamic level to prevent estradiol-mediated negative inhibition to increase GnRH pulsatility, thereby increasing FSH and LH production (9). In a study of clomiphene 25 mg used in hypogonadal men for 12 weeks, the testosterone to estradiol (T:E) ratio increased by 61% (11). A further meta-analysis of 19 studies including four randomized clinical trials, found that total and free testosterone, LH, FSH, and estradiol all increased after clomiphene citrate therapy with improvement in hypogonadal symptoms as measured through the Androgen Deficiency in Aging Males questionnaire (12). Clomiphene has also been shown to increase sperm concentration (13) although a multi-center randomized controlled trial of 190 couples did not report increased pregnancy rates with clomiphene therapy versus placebo (14, 15).

Studies evaluating long-term clomiphene use in men are reassuring. In a retrospective study of 400 patients treated with clomiphene citrate for a mean ± SD of 25.5 ± 20.48 months, 88% of patients treated for more than three years achieved normal total testosterone levels (>300 ng/dL), with 77% experiencing improved symptoms, and only 5/400 (8%) reporting side effects such as mood changes, blurred vision, and breast tenderness with no significant adverse events (16).

This is the first retrospective study examining IGF-1 measurements before and after clomiphene treatment in hypogonadal males. We demonstrated a statistically significant decline in IGF-1 SD levels in the majority of patients after treatment with clomiphene citrate for at least three months, and two patients exhibited a decline in IGF-1 levels exceeding –2-SD below their age- and sex-matched mean values (patients 14 and 19). In parallel, all of our clomiphene-treated patients exhibited increased total testosterone levels ($p<0.0001$). It is important to acknowledge that 15/20 (75%) of our patients had been treated for a pituitary space occupying lesion, though no mass was present at the time of clomiphene therapy. Nonetheless, this is clearly a population of patients that are potentially vulnerable to growth hormone deficiency and may therefore be more susceptible to the GH-blocking actions of clomiphene to lower IGF-1 levels.

Interestingly, we did see some variation in the changes in total testosterone (TT) and IGF-1 across the various etiologies of hypogonadism. For example, the greatest increase in TT was seen in the patients with prolactinomas, where 5/5 (100%) exhibited increases in testosterone ranging from 9%-576% (median 421%). Three of these 5 (60%) had reductions in IGF-1-SD (median % change –28.6%, [range –300% - 44.4%], median absolute change [IQR] -0.2 [-0.7 - 0.2]). In contrast the changes seen in 5 patients with idiopathic hypogonadism (IH) and 6 patients with CNFTs were lower but comparable with median increases in testosterone of

(IH: median 56%, [range 31%-181%] and CNFT: median 51%, [range 6%-170%]) respectively. Four of 5 (80%) IH patients had reductions in IGF-1-SD (median % change –323%, [range -1455-133%], median absolute change [IQR] –0.6 [-1.7 - -0.3]) and 6/6 (100%) patients with CNFTs had reductions in IGF-1-SD (median change –333%, [range –750-100%], median absolute change [IQR] –1.35 [-2.4 - -0.3]). Of the remaining 4 patients, 2 with silent corticotroph adenomas had increases in testosterone (median 77%, [range 57%-97%]), and 1/2 (50%) had reductions in IGF-1-SD (median change –21.5%, [range –50 - 93%], median absolute change [IQR] –0.05 [N/A]), one patient with a colloid cyst had an increase in total testosterone by 60% and a reduction in IGF-1-SD by 42% (absolute change -1.2-SD) and the final patient with a rathke's cleft cyst had an increase in total testosterone by 8.4% and a reduction in IGF-1-SD by 39% (absolute change -1.2-SD). Although these findings must be interpreted with caution give the small numbers involved, it is interesting that the greatest increase in TT following clomiphene therapy was seen in the patients with prolactinomas, which perhaps infers a greater response given the underlying mechanism for gonadotrope dysfunction is functional rather than destructive as in a space occupying lesion.

The two patients who exhibited the most significant declines in IGF-1 levels following clomiphene therapy had clinically non-functioning pituitary tumors (CNFTs) which are often large pituitary lesions at presentation. This raises the possibility that these subjects may have had some pre-existing degree of compromised GH action even though they were maintaining normal age- and sex-matched IGF-1 levels prior to clomiphene therapy. Against that however, other than hypogonadism, pituitary function was intact in one of these patients (Patient 14), and the other patient (Patient 19) was only receiving thyroid replacement therapy with normal free thyroid hormone levels (Free T4: 1.0 ng/dL). Furthermore, baseline testosterone levels in patient 14,

where IGF-1 levels decreased from -0.8SD to -2.3SD, were not exceptionally low at 309 ng/dl, as one typically encounters in pituitary-tumor associated hypogonadism. Similarly in patient 19 who exhibited a decrease in IGF-1 from –0.9SD to –2.1SD, total testosterone at baseline was 148ng/dl and increased to 157 ng/dL after five months clomiphene therapy. Interestingly, symptoms of decreased energy and reduced libido did not change in either of these 2 subjects following clomiphene therapy. The dose and duration of clomiphene did not differ in these two patients compared to the rest of the patient population,

Whether the lack of symptomatic improvement in these two patients despite increases in total testosterone while on clomiphene was in part related to their significant reductions in IGF-1 levels is unclear, but our studies would support further investigation of this action of clomiphene. Some studies have shown that testosterone therapy can lead to a dose-dependent increase in serum IGF-1 levels. In one study, male patients aged 18 to 35-years-old given a range of intramuscular testosterone doses (25- 600 mg/week) in combination with GnRH to suppress endogenous testosterone production, exhibited a dose dependent increase in IGF-1 with a 300 and 600 mg testosterone dose (17). Clearly, this mode of androgen replacement using testosterone itself is different to the use of clomiphene, with its SERM action on GnRH.

Our study was retrospective and our patients did not have formal evaluations of their quality of life and symptoms before and after clomiphene initiation. Therefore, although we have observed statistically significant biochemical changes in IGF-1 levels following clomiphene therapy, we cannot tell if any of these changes are clinically important. Furthermore, symptoms due to reductions in IGF-1 levels could be off-set by improvements in androgen levels. Future studies should include a careful assessment of symptoms and quality of life in parallel with serial biochemical measurements of IGF-1 and free and total testosterone measurements before and

after clomiphene therapy to clarify this question. Although our study sample size is small given the rarity of these patients, we believe it adds useful knowledge to this field and may spur additional investigation in this area.

In conclusion, we have observed that clomiphene therapy to treat hypogonadism in men can result in a significant reduction in serum IGF-1 levels in some patients, which could contribute to several clinical consequences including fatigue, increased insulin resistance and adipocyte mass, reduced lean muscle and bone mass as well as reduced quality of life. Given the decrease in IGF-1 can be $\geq$2 SD in some patients and thereby potentially clinically significant, we recommend interval monitoring of serum IGF-1 in patients with hypogonadism treated with clomiphene citrate.

Data Availability

Original data generated and analyzed during this study are included in this published article or in the data repositories listed in References.

Authorship

The work submitted for publication is original and has not been published other than as an abstract or preprint in any language or format and has not been submitted elsewhere for print or electronic publication consideration.

Nikita Mogar, M.D. Writing – original draft, formal analysis, data curation, investigation

Dongyun Zhang, PhD. Software, formal analysis, writing – original draft, visualization

Anthony Heaney, MD, PhD. Conceptualization, methodology, validation, investigation, resources, writing – review & editing, supervision, project administration

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Table 1. Clinical Characteristics of 20 Male Patients Treated With Clomiphene From 2012 to 2022

Median Age—yr (IQR)	47 (38.5 - 55)
Median duration of clomiphene treatment—months (IQR)	14.5 (– 10 - 25)
Patients on pituitary replacement therapy or other pituitary therapy (%)	6 (30%)
Levothyroxine (%)	4 (20%)
Hydrocortisone (%)	1 (5%)
Cabergoline (%)	5 (25%)
Median baseline IGF-1 SD (IQR)	0.10 (-0.5 - 0.85)
Median IGF-1 SD (IQR) after the initiation of clomiphene	-0.55 (-1.2 - 0.2)
Median change in IGF-1 SD (IQR) after the initiation of clomiphene	-0.60 (-1.2 - 0.0)
Median baseline total testosterone (ng/dL) (IQR)	251.2 (193.1 - 375.5)
Median total testosterone (ng/dL) (IQR) after initiation of clomiphene	574.8 (366.5 - 755.5)
Median change in total testosterone (ng/dL) (IQR)	219 (100.5 - 363.7)
Median baseline free testosterone (pg/mL) (IQR)	57.5 (35.6 - 87.3)
Median free testosterone (pg/mL) (IQR) after initiation of clomiphene	98 (64.4 - 136.1)
Median change in free testosterone (pg/mL) (IQR)	23.2 (-4.9 - 91.4)

Legend: Yr: year; IQR: Interquartile range; no.: number.; ID, insufficient data

Table-2. Clinical Characteristics of 20 Patients Treated with Clomiphene Citrate from 2012 to 2022

	Etiology of Secondary Hypogonadism (Baseline tumor size [cm], TNTS)	PRT, CBG	Clomiphene Dose (mths)	Pre-CC IGF-1 SD (mths)	Post-CC IGF-1 SD (mths)	Pre-CC TT (mths) SHBG (mths)	Post-CC TT (mths)	Pre-CC FT (mths	Post-CC FT (mths)	Baseline FSH, LH	Pre-CC E2 (mths)	Post-CC E2 (mths)	Sxs	Improved?
Patient 1	Colloid Cyst (4.5, N [EVD])	-	50mg TIW (24)	0.8 (11)	-0.4 (3)	535 (7) 37 (7)	855.6 (3) N/A	95 (6)	136.1 (3)	4.6, 5.0	N/A	59 (3)	Low libido	N
Patient 2	CNFT (0.3, N)	-	50mg TIW (21)	0.1 (0.3)	0.2 (6) 0.0 (9)	375 (0.2) N/A	582.5 (6) N/A	N/A	157.5 (6)	5.8, 5.2	16 (0.2)	38 (6)	Fatigue	N
Patient 3	CNFT (1.2, Y)	-	50mg TIW (26)	1.2 (1)	-1.2 (5)	239.2 (0.5) N/A	646 (22) 21 (22)	57.9 (1)	155.5 (10)	NA, 4	N/A	N/A	Fatigue	Y
Patient 4	CNFT (0.5 N)	-	50mg TIW (10)	0.2 (2)	-1.3 (2) -1.4 (5) -1.3 (9)	445 (18) 33 (18)	655 (5) N/A	92 (18)	77.6 (5)	NA, 2.8	35 (18)	19 (2)	Fatigue, low libido	N
Patient 5	Silent corticotroph adenoma (2.5, Y)	T	50mg TIW (13)	-0.74 (1)	-0.047 (10)	267 (1) 27.6 (5)	525 (10) N/A	82.5 (1)	185.3 (11)	NA, NA	N/A	N/A	Fatigue, low libido	N
Patient 6	Idiopathic (0.2, N)	-	50mg TIW (14)	0.3 (1)	0.7 (13)	512 (12) N/A	725 (2) 25 (2)	141 (12)	151 (7)	3.4, 2.3	N/A	N/A	Fatigue	N
Patient 7	CNFT (3.5, Y)	-	50mg TIW (53)	-0.2 (10)	-0.5 (3)	376 (9) N/A	880 (31) N/A	58.6 (9)	108 (31)	3.1, 2.3	N/A	N/A	Fatigue, low libido	Y
Patient 8	Silent corticotroph adenoma (3.5, Y)	-	50mg TIW (17)	1.6 (8)	1.5 (10) 0.8 (20)	253.4 (2) N/A	398.2 (10) N/A	29 (2)	36.3 (17)	2.7, 1.7	N/A	N/A	Fatigue	Y
Patient 9	Idiopathic (N)	T/C	50mg TIW (4)	1.7 (1)	1.1 (4)	178 (0.5) N/A	234 (5) N/A	48.2 (0.5)	43.3 (3)	5.9, 3.2	N/A	N/A	Fatigue, low libido	Y
Patient 10	Idiopathic (N)	-	50mg TIW (12)	0.9 (0.5)	-0.5 (3) -1.2 (9)	228 (0) N/A	641 (9) 22 (12)	43.2 (0)	134.6 (9)	1.7, 1.3	N/A	29 (12)	Low libido	Y
Patient 11	Idiopathic (N)	-	50mg TIW (60)	-0.8 (1)	-1.0 (23)	248 (3) 8.4 (3)	567 (5) 13 (6)	N/A	64.4 (5)	0.6, 1.2	N/A	N/A	Fatigue, hair loss	Y
Patient 12	PRLoma (3, N)	CBG 1.5mg BIW	50mg TIW (10)	0.1 (3)	0.1 (10)	55 (6) 12 (6)	287 (10) N/A	13.2 (6)	N/A	N/A, N/A	N/A	N/A	Fatigue	N/A
Patient 13	RCC (0.7, Y)	-	50mg TIW (84)	1.7 (5)	0.5 (11)	725 (0.5) N/A	786 (66) N/A	99.6 (0.1)	66 (11)	1.8, 2.6	N/A	27 (66)	Fatigue, low libido	Y
Patient 14	CNFT (2.7, Y)	-	50mg TIW (8)	0.3 (12)	-2.3 (9)	309 (8) 20 (8)	344 (9) N/A	42.2 (7)	42.2 (9)	8.7, 3.8	N/A	N/A	Fatigue, low libido	N
Patient 15	Idiopathic (N)	-	50mg TIW (9)	-0.09 (0.5)	-1.4 (0)	249 (0) N/A	389 (9) 23 (9)	N/A	69.6 (9)	5.6, 6	N/A	N/A	Fatigue	Y
Patient 16	PRLoma (0.8, N)	CBG 1mg QW	50mg TIW (13)	0.4 (10)	-0.9 (3) -0.8 (12)	266 (10) 15 (10)	289 (11) N/A	57 (10)	35.3 (11)	N/A, N/A	48 (11)	N/A	Fatigue, low libido	Y
Patient 17	PRLoma (4.5, N)	CBG 2 mg BIW	50mg TIW (28)	0.4 (3)	0.2 (13)	144 (6) N/A	973 (13) N/A	27 (6)	124 (13)	N/A, N/A	N/A	N/A	Fatigue, low libido	Y
Patient 18	PRLoma (2.7, N)	CBG 1mg BIW T	50mg TIW (21)	-0.7 (0.3)	-0.6 (9) -0.9 (20)	178 (0.3) N/A	928 (9) N/A	N/A	88 (20)	N/A, N/A	N/A	N/A	Fatigue	N/A
Patient 19	CNFT (3.2, Y)	T	50mg TIW (6)	-0.9 (7)	-2.1 (5)	148 (2) 29 (2)	157 (6) 24 (6)	27 (2)	N/A	3.6, 2.4	N/A	N/A	Fatigue	N/A

Patient 20	PRLoma (1.7, N)	CBG 0.5mg BIW	50mg TIW (15)	0.9 (4)	1.3 (16)	208.2 (1) N/A	490.1 (3) N/A	71.8 (1)	108.2 (3)	N/A, N/A	N/A	N/A	Low libido	N/A

Legend: PRT: pituitary replacement therapy; CBG: cabergoline; T: thyroid hormone replacement; C: glucocorticoid replacement; CC: clomiphene citrate; mths: months; FT: free testosterone; TT: total testosterone; SHBG: sex hormone binding globulin; Sxs: symptoms; TIW: three times weekly; OW: once weekly; BIW: two times weekly; Y: Yes; N: No; CNFT: Clinically nonfunctional tumor; PRLoma; prolactinoma; N/A: Not applicable; RCC: Rathke cleft cyst; EVD; external ventricular drain; **Reference Ranges:** Sex hormone binding globulin [ref. 13-90 nmol/L]; Total Testosterone [ref. 300-1080 ng/dL]; Free Testosterone [ref. 47-244 pg/mL]; Estradiol [ref. <39 pg/mL]; FSH [ref. 1.6-9.0 mIU/mL]; LH [ref. 2.0-12.0 mIU/mL]

Figure Legend

Figure 1. Key inclusion and exclusion criteria.

Figure 2. a. Box plot depiction of trend in IGF-1-SD after clomiphene citrate initiation. ** $p<0.01$. **b.** Estimation plot depiction of trend in IGF-1-SD before and after clomiphene citrate initiation.

Figure 3. a. Box plot depiction of trend in total testosterone (TT) after initiation of clomiphene citrate. Pre-TT: Total testosterone before clomiphene initiation; Post-TT: total testosterone after clomiphene initiation. **b.** Estimation plot depiction of trend in total testosterone (TT) after initiation of clomiphene citrate. Pre-TT: Total testosterone before clomiphene initiation; Post-TT: total testosterone after clomiphene initiation. **** $p<0.001$.

Figure 4. a. Box plot depiction of trend in free testosterone (FT) after initiation of clomiphene citrate. Pre-FT: Free testosterone before clomiphene initiation; Post-FT: free testosterone after clomiphene initiation. **b.** Estimation plot depiction of trend in free testosterone (FT) after initiation of clomiphene citrate. Pre-FT: free testosterone before clomiphene initiation; Post-FT: free testosterone after clomiphene initiation. *$p<0.05$.

Mogar et al. Fig. 1

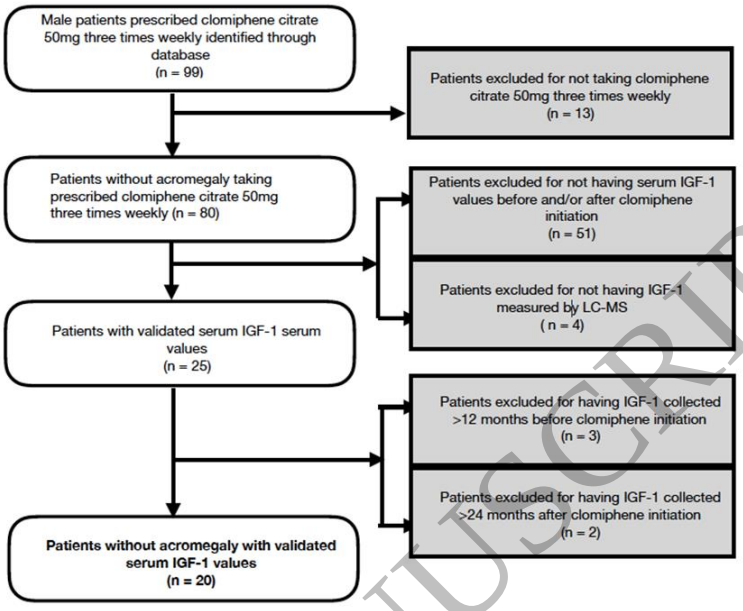

Figure 1
23x15 mm (x DPI)

Mogar et al. Fig. 2

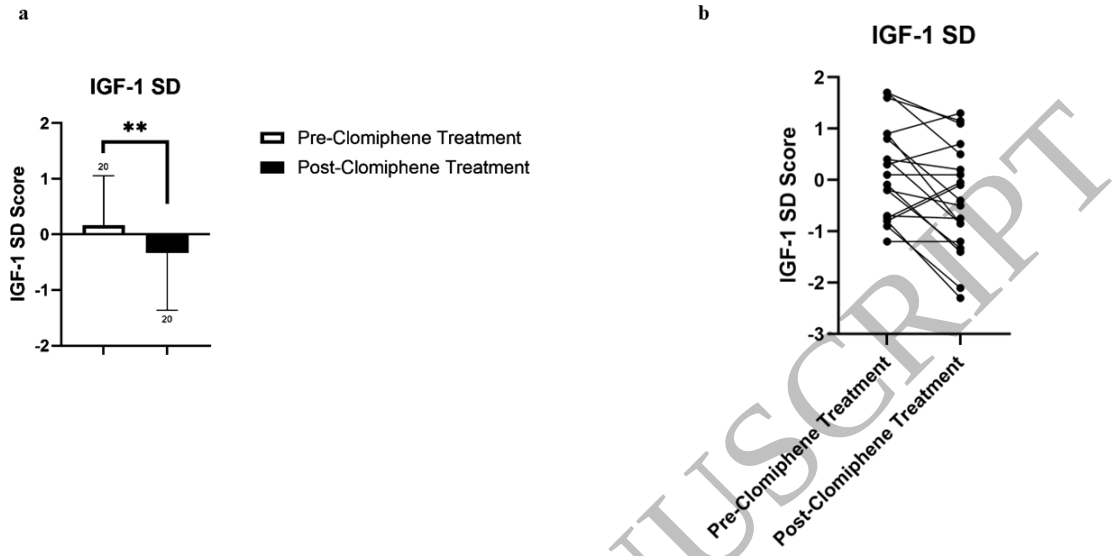

Figure 2
25x15 mm (x DPI)

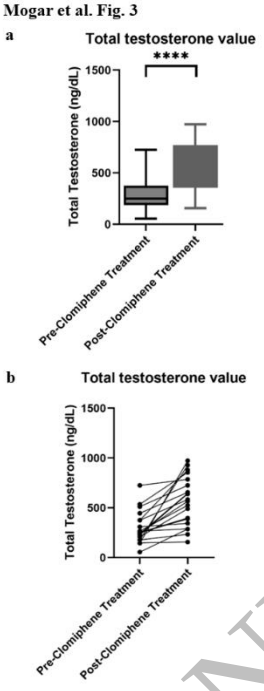

Figure 3
8x20 mm (x DPI)

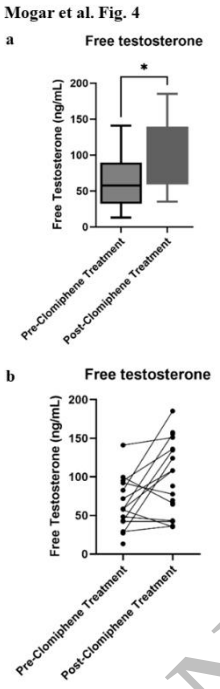

Figure 4
7x20 mm (x DPI)