12º ENDO SUL

Hot Topics:

Fertilidade

Alexandre Hohl, MD, MSc, PhD

Vice-Presidente da Sociedade Brasileira de Endocrinologia e Metabologia (SBEM)
Professor de Endocrinologia da Universidade Federal de Santa Catarina (UFSC)

Declaração de Conflito de Interesses

Dr. Alexandre Hohl CRM-SC 8773 RQE 5431

De acordo com a Norma do Conselho Federal de Medicina e a Resolução RDC 96/2008 da Agência Nacional de Vigilância Sanitária, declaro que:

- Tenho sido conferencista dos laboratórios: Abbott, AstraZeneca, Besins, Boehringer Ingelheim, Libbs, Lilly, MSD, Novo Nordisk, Sanofi, Takeda
- Tenho sido membro do conselho consultivo dos laboratórios: Astra Zeneca, MSD, Novo Nordisk, Sanofi

Sem Conflito de Interesses

1.0 Diagnosis of Hypogonadism in Men

Hypogonadism is a clinical syndrome that results from failure of the testis to produce physiological concentrations of testosterone (T) (T deficiency) and/or a normal number of spermatozoa due to pathology at one or more concentrations of the hypothalamic–pituitary–testicular axis (5, 6).

Fertility. T therapy suppresses spermatogenesis and is not appropriate in men with hypogonadotropic hypogonadism who desire fertility in the next 6 to 12 months.

Bhasin S, et al. **Testosterone Therapy in Men With Hypogonadism: An Endocrine Society Clinical Practice Guideline**. J Clin Endocrinol Metab. 2018 May 1;103(5):1715-1744.

Spermatogenesis can be stimulated and fertility can be restored with appropriate gonadotropin therapy in patients with secondary hypogonadism but not in patients with primary hypogonadism. Fertility options for men with primary testicular failure are limited to the use of donor sperm, adoption, or (in some patients) assisted reproductive technologies, such as intracytoplasmic sperm injection using sperm in the ejaculate or following testicular sperm extraction.

Bhasin S, et al. **Testosterone Therapy in Men With Hypogonadism: An Endocrine Society Clinical Practice Guideline**. J Clin Endocrinol Metab. 2018 May 1;103(5):1715-1744.

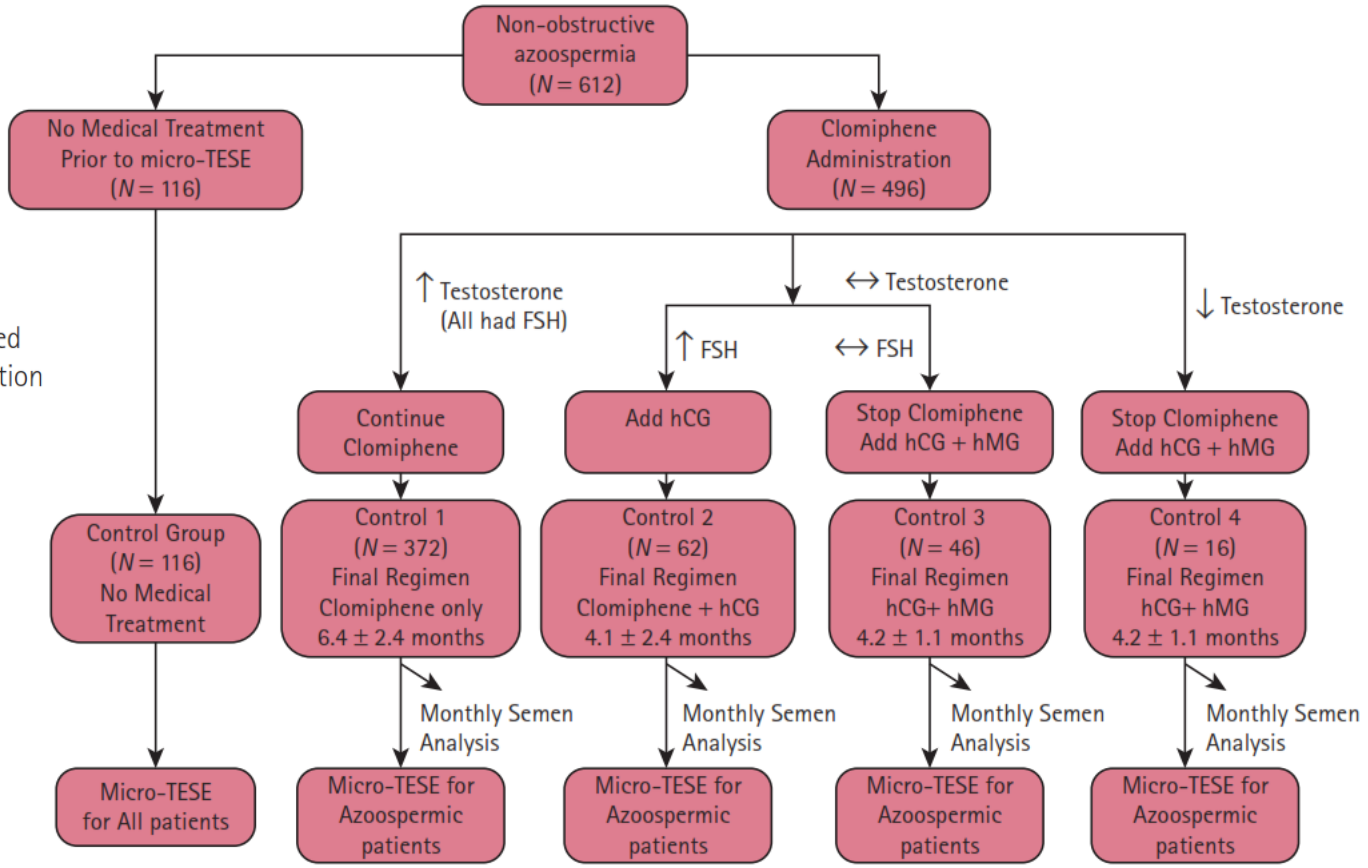
Optimization of spermatogenesis-regulating hormones in patients with non-obstructive azoospermia and its impact on sperm retrieval: a multicentre study

BJU INTERNATIONAL © 2012 BJU INTERNATIONAL | 111, E110–E114

Alayman Hussein, Yasar Ozgok*, Lawrence Ross†, Pravin Rao† and Craig Niederberger†

*Minia Infertility Research and Treatment Unit, El-Minia University, El-Minia, Egypt, *Gulhane Military Medical Faculty, Ankara, Turkey, and †University of Illinois at Chicago, Chicago, IL, USA*

- A total of 612 patients with non-obstructive azoospermia were evaluated with routine history, physical examination and hormonal assessment.



Optimization of spermatogenesis-regulating hormones in patients with non-obstructive azoospermia and its impact on sperm retrieval: a multicentre study

BJU INTERNATIONAL © 2012 BJU INTERNATIONAL | 111, E110–E114

Alayman Hussein, Yasar Ozgok*, Lawrence Ross†, Pravin Rao† and Craig Niederberger†

*Minia Infertility Research and Treatment Unit, El-Minia University, El-Minia, Egypt, *Gulhane Military Medical Faculty, Ankara, Turkey, and †University of Illinois at Chicago, Chicago, IL, USA*

TABLE 1 Rate of sperm retrieval in ejaculate, at micro-TESE, and overall for each of the study groups

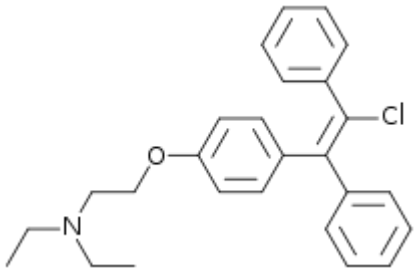
Group	Effect of Clomiphene	*n*	Final regimen**	Sperm in semen, *n* (%)	Sperm at micro-TESE (%)	Overall sperm retrieval rate, (%)	*P* (vs control)
Control	N/A	116	N/A	N/A	33.6	39/11) (33.6)	
1	Increased testosterone(FSH)*	372	Clomiphene	41 (11)	191/331 (57.7)	232/372 (62.4)	<0.001
2	No increase in testosterone Increased FSH	62	Clomiphene + hCG	7 (11.3)	31/55 (56.4)	38/62 (61.3)	<0.001
3	No increase in testosterone No increase FSH				(52.4)	26/46 (56.5)	0.01
4	Decrease in testosterone				(57.1)	(10/16) 62.5	<0.05

CONCLUSION

- For patients with non-obstructive azoospermia, clomiphene citrate, hCG and hMG administration, leading to an increased level of FSH and total testosterone, results in an increased rate of sperm in the ejaculate and increased likelihood of successful micro-TESE.

Clomifeno – Zuclomifeno – Enclomifeno

- **Clomiphene citrate** is a mixture of two diastereoisomers:
  - the cis isomer **zuclomiphene** (38%)
  - the trans isomer **enclomiphene** (62%)



- First used clinically in women in the 1960s as a medication to improve ovulation, **clomiphene citrate has been used off label for decades to treat secondary hypogonadism and to improve male fertility**.

- Clinically, **clomiphene citrate** acts as a selective oestrogen receptor modulator to increase production of luteinizing hormone (LH) and follicle-stimulating hormone (FSH).

Kovac JR. Nat Rev Urol. 2016 Mar;13(3):133-4

Clomifeno – Zuclomifeno – Enclomifeno

- However, it also evokes a paradoxical oestrogenic effect owing to the presence of **zuclomiphene**, an **oestrogen receptor agonist**, which in turn reduces the effectiveness of clomiphene citrate for increasing serum testosterone levels in hypogonadal men.

- **Enclomiphene**, the shorter-acting isomer, functions primarily as an **oestrogen receptor antagonist** by inhibiting receptors and removing oestrogen's negative feedback loop.

Kovac JR. Nat Rev Urol. 2016 Mar;13(3):133-4

Clomifeno – Zuclomifeno – Enclomifeno

- As such, a medication that only contains the isolate of **enclomiphene** is ideally positioned to act as an **oestrogen blocker** and, as such, a **potent stimulator of LH release**, with resultant benefits on serum total testosterone level.

- **Increases in testosterone levels could thus be achieved without the negative effects on spermatogenesis that are observed with traditional TST.**

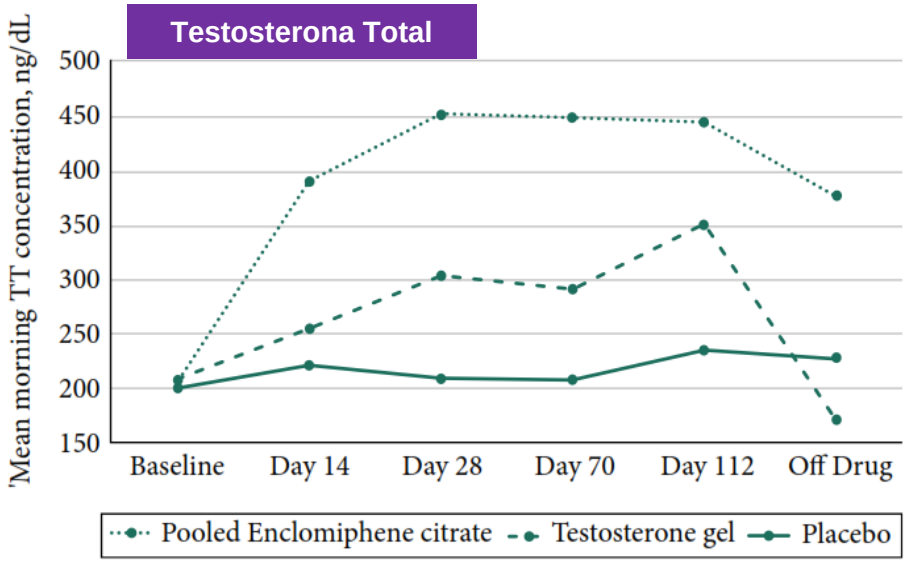
Kovac JR. Nat Rev Urol. 2016 Mar;13(3):133-4

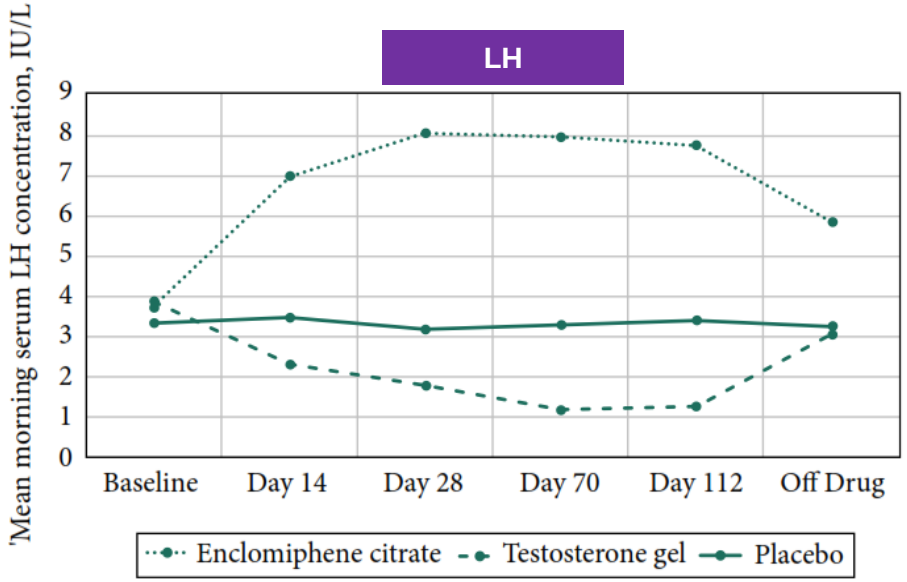
Oral enclomiphene citrate raises testosterone and preserves sperm counts in obese hypogonadal men, unlike topical testosterone: restoration instead of replacement

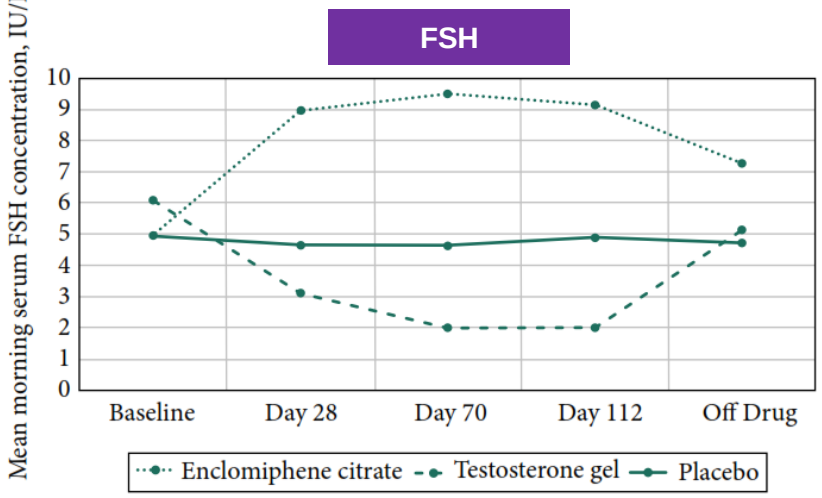
Study	ZA-304 (*P* values testosterone gel vs enclomiphene citrate)			ZA-305 (*P* values testosterone gel vs enclomiphene citrate)		
Treatment	Enclomiphene citrate	Testosterone gel	Placebo	Enclomiphene citrate	Testosterone gel	Placebo
N	41	43	45	44	42	41
Mean (SD)						
Age, years (SD)	49.1 (7.4)	47.4 (7.2)	47.2 (9.0)	47.3 (8.8)	45.0 (8.2)	47.5 (8.9)
BMI, kg/m^2	33.1 (4.4)	34.0 (4.4)	32.6 (4.3)	33.8 (4.6)	33.1 (4.6)	33.5 (4.4)
Baseline TT level, ng/dL	203.3 (52.4)	208.6 (54.0)	200.3 (43.1)	212.9 (48.0)	229.8 (44.0)	206.0 (48.2)
Baseline sperm concentration, million/mL	98.3 (87.2)	78.9 (68.5)	95.3 (90.8)	79.0 (55.2)	75.1 (45.8)	80.5 (62.3)
TT level at 16 weeks, ng/dL	445.8 (186.4)	350.6 (338.1) $P < 0.001$	236.4 (144.7) $P < 0.001$	412.9 (130.3)	387.4 (244.8) $P = 0.037$	214.4 (58.7) $P < 0.001$
% Change in sperm concentration at 16 weeks	11.7 (80.3)	−56.6 (48.2) $P < 0.001$	4.1 (57.2) $P = 0.548$	15.2 (55.8)	−32.8 (63.2) $P < 0.001$	7.6 (89.6) $P = 0.201$
% Sperm concentration <15 10^6/mL	4.9	48.8 $P < 0.001$	4.4 $P = 1.000$	2.3	23.8 $P = 0.003$	2.4 $P = 1.000$

Kim ED, McCullough A, Kaminetsky J. BJU Int. 2016 Apr;117(4):677-85.

Oral enclomiphene citrate raises testosterone and preserves sperm counts in obese hypogonadal men, unlike topical testosterone: restoration instead of replacement







Kim ED, McCullough A, Kaminetsky J. BJU Int. 2016 Apr;117(4):677-85.

Oral enclomiphene citrate raises testosterone and preserves sperm counts in obese hypogonadal men, unlike topical testosterone: restoration instead of replacement

Conclusions

Enclomiphene citrate consistently increased serum TT, LH and FSH, restoring normal levels of serum TT. Enclomiphene citrate treatment maintained sperm concentrations in the normal range. The effects on TT were also seen with testosterone replacement via testosterone gel but sperm counts were not maintained.

Development Status and FDA Approval Process for Androxal

Date	Article
Dec 1, 2015	Repros Therapeutics Receives Complete Response Letter From FDA for Enclomiphene
Oct 29, 2015	Repros Therapeutics Announces Cancellation of FDA Advisory Committee Meeting to Review Enclomiphene for the Treatment of Secondary Hypogonadism
Jun 8, 2015	Repros Announces Date of FDA Advisory Committee Review of NDA
Apr 15, 2015	Repros Announces November 30, 2015 PDUFA Goal Date for Enclomiphene Citrate NDA
Feb 2, 2015	Repros Submits New Drug Application to FDA for Androxal
Mar 27, 2013	Repros Reports Both Primary Endpoints Successfully Met in First Pivotal Study of Androxal
Feb 8, 2010	Repros Submits Response to FDA Regarding Androxal Indication for Treatment of Hypogonadal Men Wishing to Preserve Fertility

Kim ED, McCullough A, Kaminetsky J. BJU Int. 2016 Apr;117(4):677-85.

ÉPOCA

SAÚDE

O que é o SARM, novo e perigoso anabolizante que bomba em sites e academias

Vendido livremente em sites, o medicamento não tem qualquer controle e pesquisas mostram que pode causar problemas cardíacos

RAFAEL CISCATI
03/07/2018 - 11h00 - Atualizado 03/07/2018 12h11

O fisiculturista e youtuber Fernando Maradona, que já usou SARMs. "Bodybuilder é como rato de laboratório", disse (Foto: DIVULGAÇÃO)

Cabral usou o Ligandrol por 49 dias, duas vezes ao dia: de manhã, pouco antes do café, e à noite, antes do treino. Os resultados vieram aos poucos: o volume muscular cresceu, a gordura corporal diminuiu. Mais importante que isso, a estética melhorou. "Deu para notar as pessoas na academia me olhando de um jeito diferente", disse, satisfeito. "Eu não queria usar um anabolizante tradicional. E o Ligandrol me pareceu um bom ponto de partida."

O LGD-4033 é mais uma "bomba", como outras usadas por frequentadores de academias. Desenvolvidas a partir de meados da década de 1990, receberam o complicado título de "moduladores seletivos do receptor de androgênio". Ou, para facilitar, SARMs, da sigla em inglês. O Ligandrol é um entre mais de uma dezena de SARMs, uma resposta da indústria farmacêutica aos dissabores causados pelos esteroides anabolizantes tradicionais. A maioria dos anabolizantes tenta imitar o funcionamento da testosterona, o hormônio sexual masculino. Uma vez injetados nos músculos, conectam-se a estruturas no interior das células e dão a partida numa sequência de reações que culminam na produção de proteína. São usados para tratar pacientes que perdem massa óssea e muscular.

Mas o uso prolongado de anabolizantes — mesmo com acompanhamento médico — pode provocar câncer de próstata ou problemas de fígado. Nas mulheres, provoca o surgimento de características masculinas, como pelos na face ou engrossamento da voz. Um pacote de alterações que a ciência chama de "efeitos androgênicos". Os SARMs têm a vantagem de se conectarem somente aos receptores dos músculos esqueléticos. "Em teoria, isso deveria permitir que eles estimulassem a síntese de proteína sem provocar os mesmos efeitos colaterais", disse o professor Alexandre Hohl, vice-presidente da Sociedade Brasileira de Endocrinologia. O primeiro membro desse novo grupo foi descoberto quase por acidente, por uma equipe de cientistas da Universidade do Tennessee, nos Estados Unidos. Na época, o professor James Dalton estudava uma substância que promovia o aumento dos músculos em ratinhos: "Foi quando percebemos que nosso composto não vinha acompanhado por efeitos androgênicos", disse Dalton a ÉPOCA. "Para nós, foi uma grata surpresa."

Serum levels of enclomiphene and zuclomiphene in men with hypogonadism on long-term clomiphene citrate treatment

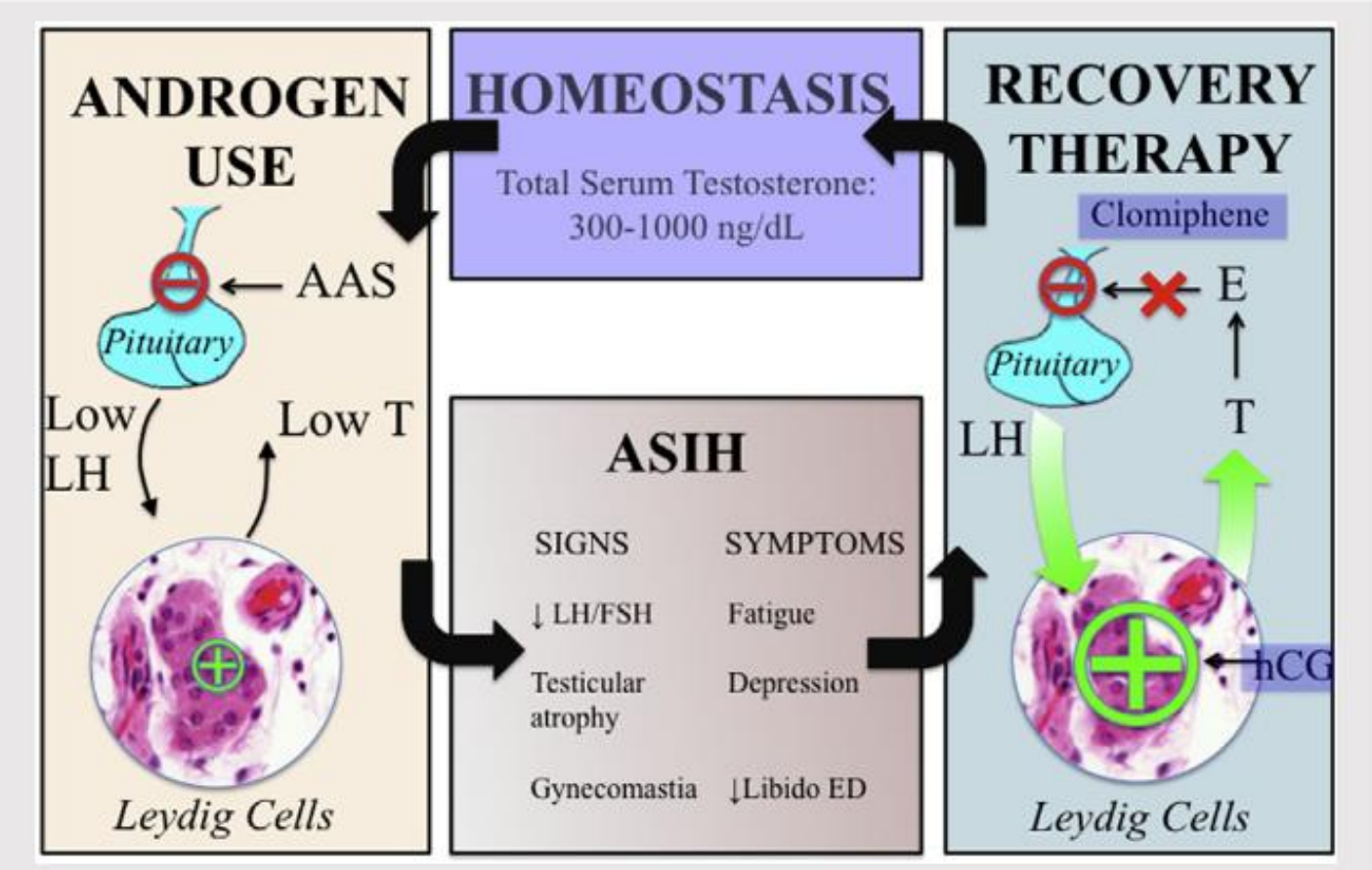
Sevann Helo*, Joseph Mahon*, Joseph Ellen†, Ron Wiehle‡, Gregory Fontenot‡, Kuang Hsu‡, Paul Feustel§, Charles Welliver*¶ and Andrew McCullough*¶

Men already receiving CC 25 mg daily therapy for secondary hypogonadism for a minimum of 6 weeks were recruited to have their ENC and ZUC levels assessed.

Long-term CC therapy resulted in a significant alteration of ENC and ZUC concentrations, with ZUC as the predominant isomer. Given the vastly different biochemical and toxicological properties of ENC and ZUC, this study supports the need for the development of a pure selective oestrogen receptor antagonist for the treatment of men with hypogonadism.

Helo S, et al. BJU Int. 2017 Jan;119(1):171-176.

Anabolic steroid–induced hypogonadism: diagnosis and treatment



Rahnema CD, Lipshultz LI, Crosnoe LE, Kovac JR, Kim ED. Fertil Steril. 2014 May;101(5):1271-9.

Anabolic steroid–induced hypogonadism: diagnosis and treatment

Commonly reported user-reported side effects and concerns, user strategies for management, and physician recommendations.

Side effect	User strategies for management	What should physicians recommend?
Low endogenous T	SERMs to restart axis	Discontinue AAS Start recovery protocol with TRT, SERMs, or hCG
Gynecomastia	Tamoxifen Aromatase inhibitors Cabergoline and bromocriptine for galactorrhea	Chronic gynecomastia likely unresponsive to medical management Surgical management is best option for chronic gynecomastia Acute gynecomastia may be treated with tamoxifen per SERM recovery protocol Avoid hCG use if possible. Use of aromatase inhibitors is discouraged because of possible sexual side effects
Testicular atrophy	hCG injections	Testicular atrophy will resolve discontinuation of AAS and recovery of HPG axis function hCG should be reserved for cases unresponsive to first line SERM treatment
Sexual dysfunction	PDE5 inhibitors Herbal aphrodisiacs Cabergoline Mesterolone for added androgenic effects Dapoxetine	PDE5 inhibitors should be first-line treatment Herbal aphrodisiacs should be discouraged owing to contamination concerns Dapoxetine not yet approved for sexual dysfunction
Hepatic dysfunction	Users of oral AAS concerned with hepatic function may take herbal supplements such as milk thistle extract for liver protection	Encourage discontinuation of oral AAS and herbal supplementation Perform complete metabolic panel to assess liver function
Alopecia	Users often prophylactically take finasteride to prevent hair loss	Although AAS use may worsen existing alopecia, 5-alpha-reductase inhibitor use should be discouraged because it may worsen symptoms of ASIH

Rahnema CD, Lipshultz LI, Crosnoe LE, Kovac JR, Kim ED. Fertil Steril. 2014 May;101(5):1271-9.

Anabolic steroid–induced hypogonadism: diagnosis and treatment

An example (considerable variations exist) of a bodybuilder's 12-week AAS cycle followed by 4 weeks of post-cycle therapy.

Week	Testosterone cypionate, mg/wk	Nandrolone (Deca-Durabolin), mg/wk	Metadienone (Dianabol), mg/d	hCG (IU/2–3 d)	Anastrazole (Arimidex), mg/d	Clomiphene citrate (Clomid)	Tamoxifen (Nolvadex), mg/d
1	500	500	25				
2	750	500	25				
3	750	500	25				
4	750	500	25				
5	1000	500	50				
6	1000	500	50				
7	1000	500	50				
8	1000	500	50				
9	1000	500	0	500	0.25		
10	1000	500	0	500	0.25		
11	750	500	0	500	0.25		
12	500	500	0	500	0.25		
13						200	40
14						100	40
15						50	20
16						50	20

Note: AAS = anabolic-androgenic steroid.

Rahnema. Anabolic steroid–induced hypogonadism. Fertil Steril 2014.

Rahnema CD, Lipshultz LI, Crosnoe LE, Kovac JR, Kim ED. Fertil Steril. 2014 May;101(5):1271-9.

The Use of HCG-Based Combination Therapy for Recovery of Spermatogenesis after Testosterone Use

We **retrospectively** reviewed charts from **two tertiary care infertility clinics** to identify men presenting with **azoospermia** or **severe oligospermia** (<1 million sperm/mL) while taking exogenous testosterone.

All were noted to have been placed on combination therapy, which included **3,000 units hCG subcutaneously** every other day supplemented with:

- clomiphene citrate
- tamoxifen
- anastrozole, or
- recombinant FSH (or combination) according to physician preference.

The supplemental therapies were added to raise native FSH levels, as hCG does not raise FSH levels and has no activity on FSH receptors.

Semen and hormone analyses were performed after 4 weeks of hCG therapy and monthly thereafter until semen parameters became stable or a pregnancy was achieved.

Wenker EP, Dupree JM, Langille GM, Kovac J, Ramasamy R, Lamb D, Mills JN, and Lipshultz LI. J Sex Med 2015;12:1334–1337.

The Use of HCG-Based Combination Therapy for Recovery of Spermatogenesis after Testosterone Use

Table 1 Testosterone (T) levels and time to sperm recovery for infertile men (n = 49) presenting on various types of testosterone therapy

		n	Age* (SD)	Mean testosterone† prior to HCG therapy (SD)	Mean testosterone† while on HCG therapy (SD)	Mean time (months) to first sperm recovery‡ or improvement§
Testosterone therapy	Injection	16	41.3 (9.0)	610 (398)	542 (244)	4.4 (4.2)
	Transdermal	16	39.0 (6.5)	645 (288)	447 (137)	4.4 (5.0)
	Pellet	7	43.9 (9.5)	498 (324)	465 (215)	3.4 (1.3)
	Combination	6	42.8 (3.3)	503 (442)	399 (127)	6.2 (3.4)
	Unknown	4	33.5 (4.7)	378 (177)	475 (213)	5.7 (3.1)
ANOVA *P* value			0.25	0.66	0.63	0.78

*In years
†In ng/dL
‡For men initially azoospermic
§For men initially severely oligospermic
ANOVA, analysis of variance; HCG, human chorionic gonadotropin; SD, standard deviation

Wenker EP, Dupree JM, Langille GM, Kovac J, Ramasamy R, Lamb D, Mills JN, and Lipshultz LI. J Sex Med 2015;12:1334–1337.

The Use of HCG-Based Combination Therapy for Recovery of Spermatogenesis after Testosterone Use

This HCG-based combination regimen has a number of advantages, including its use of established (albeit off-label), well-tolerated medications. Additionally, this regimen accomplishes the goal of inducing a speedy recovery of spermatogenesis. However, this study's single-arm, observational, and retrospective nature makes definitive proof of this HCG-based combination therapy's efficacy impossible to prove. Future studies should focus on comparing this combination regimen with HCG monotherapy, oral monotherapy, and unaided testosterone cessation, as well as the ability of HCG to mitigate hypogonadal symptoms associated with abrupt discontinuation of TST.

Wenker EP, Dupree JM, Langille GM, Kovac J, Ramasamy R, Lamb D, Mills JN, and Lipshultz LI. J Sex Med 2015;12:1334–1337.

Combination therapy with clomiphene citrate and anastrozole is a safe and effective alternative for hypoandrogenic subfertile men

Table 1 Patient characteristics and laboratory values at baseline ($n = 51$).

Variable	Value
Age, years	35.4 (7.4)
BMI, kg/m^2	35.0 (8.0)
SHIM score	20.8 (5.6)
ADAM score	3.6 (2.9)
Total testosterone, ng/dL	257.6 (127.3)
Bioavailable testosterone, ng/dL	147.3 (98.0)
Oestradiol, pg/mL	21.0 (8.0)
LH, mIU/L	4.7 (2.7)
FSH, mIU/L	5.1 (4.9)
SHBG, nmol/L	25.6 (9.2)
Albumin, g/dL	4.4 (0.4)
Baseline semen analysis ($n = 38$)	
Azoospermia, n (%)	9 (23.7)
Oligozoospermia, n (%)	20 (52.6)
Normozoospermia, n (%)	9 (23.7)

- **CC** dose varied from **25 to 100 mg** daily to every other day and was titrated based on patients' response to treatment.
- **AZ** was added to CC if **oestradiol levels were >50 pg/mL** or **testosterone:oestradiol ratio were <10** usually in presence of symptoms.
- AZ was usually started at **1 mg twice to thrice weekly** and was titrated based on response to treatment.

Alder NJ, Keihani S, Stoddard GJ, Myers JB, Hotaling JM.BJU Int. 2018 Jun 6.

Combination therapy with clomiphene citrate and anastrozole is a safe and effective alternative for hypoandrogenic subfertile men

Variable	Baseline	Follow-up	P*
Volume, mL	2.6 (1.8–3.9)	2.7 (1.8–4.2)	0.87
Concentration, million/mL	8.6 (0.0–15.8)	12.9 (1.0–65.7)	0.03
Motility, %	29 (0–48)	24 (3–44)	0.45
Total motile count, million	5.9 (0–18.5)	5.8 (0.0–93)	0.39

*All values presented as median (25th–75th interquartile range). *Using Wilcoxon's signed rank test for paired samples.*

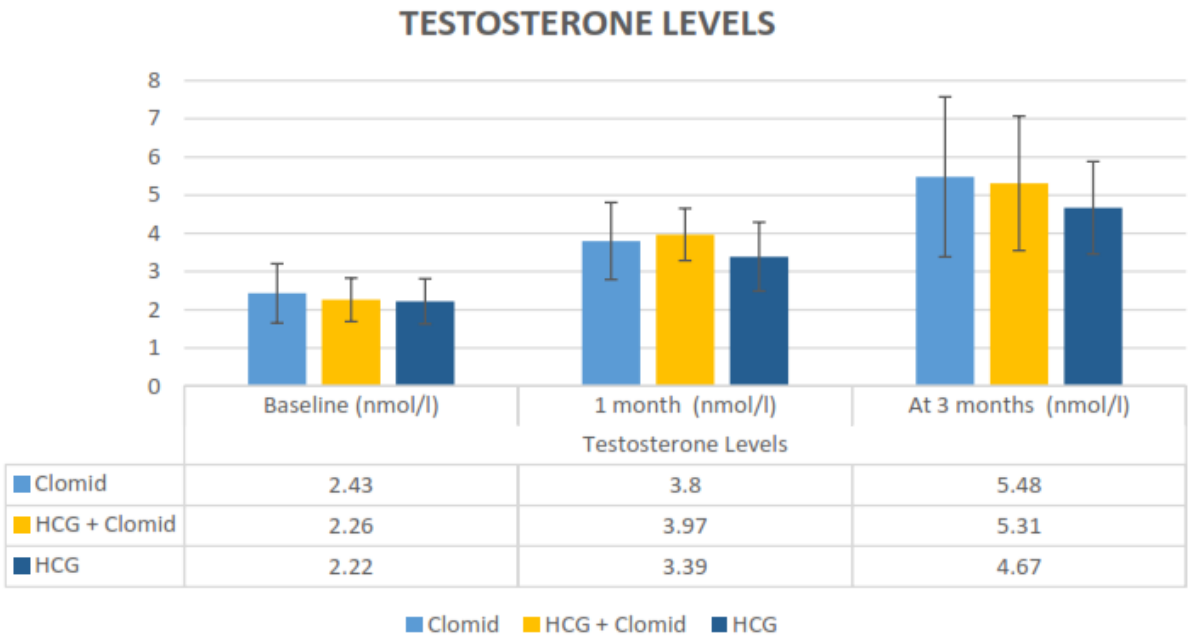
In conclusion, we found that AZ provided an effective means of lowering oestradiol levels and increasing the testosterone: oestradiol ratio after the initiation of CC therapy. Our results show that combination therapy is a safe approach with no effect on PSA levels. We recommend monitoring haematocrit levels both before and during treatment.

Alder NJ, Keihani S, Stoddard GJ, Myers JB, Hotaling JM.BJU Int. 2018 Jun 6.

Clomiphene Citrate And Human Chorionic Gonadotropin Are Both Effective In Restoring Testosterone In Hypogonadism – A Short Course Randomised Study

<u>282 hypogonadal adult</u>, willing to preserve their fertility, were randomised in three arms treated respectively with:

- **50 mg of (CC)** (n=95),
- **5000IU of hCG injections** twice a week(n=94) or
- **combination** of both therapy(n=94).



Habous M, et al. BJU Int. 2018 May 17. doi: 10.1111/bju.14401. [Epub ahead of print]

UNIVERSIDADE FEDERAL
DE SANTA CATARINA

Endocrinologia e Metabologia
HU - UFSC

SBEM
Sociedade Brasileira de
Endocrinologia e Metabologia