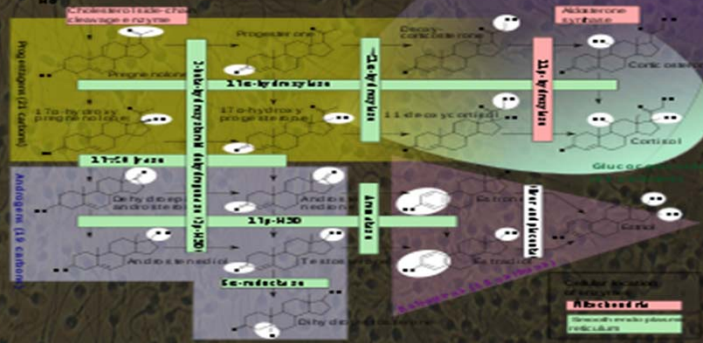


Treatment of the Young Hypogonadal Male

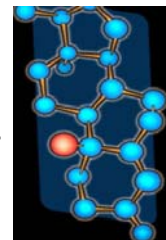


Paul J. Turek MD, FACS, FRSM
 Director, The Turek Clinic
 Beverly Hills and San Francisco, CA

Learning Objectives

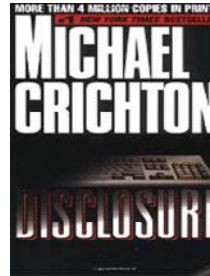
At the conclusion of this presentation, participants should be able to:

- Describe the “saturation point” concept of T effects on the body.
- Delineate two ways of providing T replacement that also maintain fertility.
- Provide a differential diagnosis of at least 5 conditions besides hypogonadism that result in low libido or erectile dysfunction.



Disclosures

Doximity.com
Fertility Planit.com
Healthloop.com
BioQuiddity, Inc
MandalMed, Inc
Essential Beginnings, Inc



Case #1

30 yo engaged man with azoospermia. Arrives in office alone. Admits to recent history of anabolic steroids (4 cycles/year for past 3 years) but stopped 6 mos ago.

Labs:	Testosterone	1050 ng/mL
	LH	0.7 IU/mL
	FSH	0.9 mIU/mL
	Prolactin	9 ng/mL

Case #1 cont

Asked what he is taking now.

Admits to taking 6 pumps of testosterone gel daily.

“I’m scared to stop the juice....really need your help.”

Anabolic Steroids: Abuse

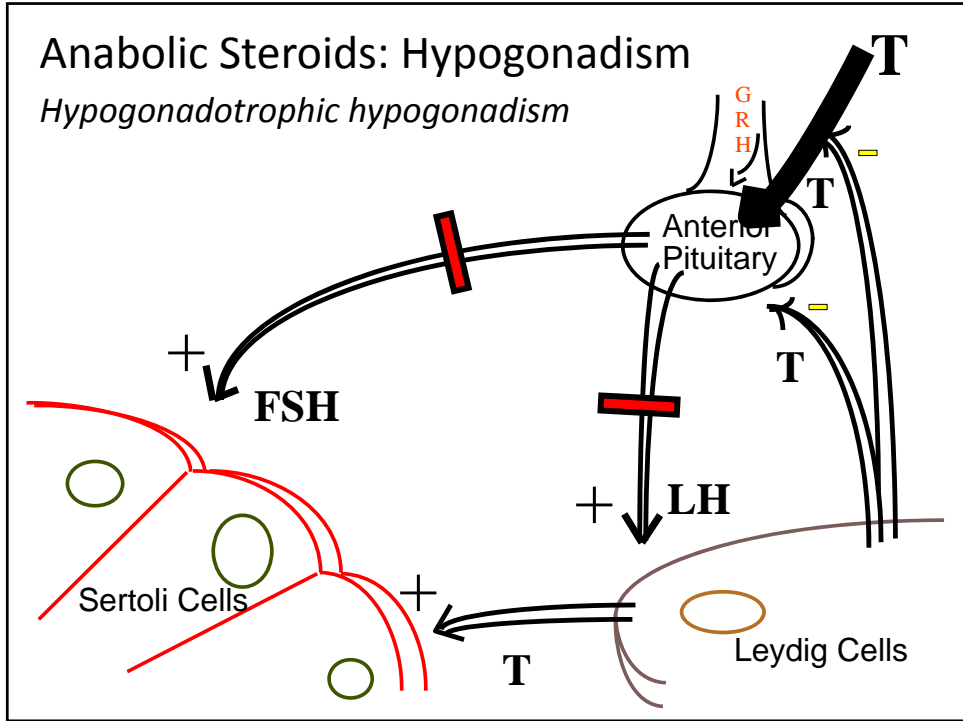
College Sports

NCAA drugs tests, 2002-4:
182/283 (**64%**) were positive
for steroids.

Pro Sports “rampant”

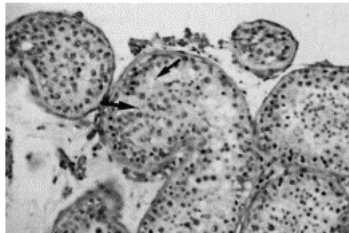
Testing in baseball began in 2003
with **>5%** of athletes testing positive.
Annually: 5 in majors and 50 in minors suspended



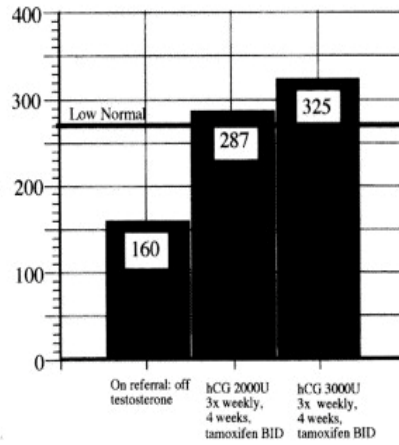


Anabolic Steroids: Reversibility in Testis

- Effects on native testosterone and sperm production thought to be reversible.
- But may not be...



Testosterone Concentration (ng/dl)



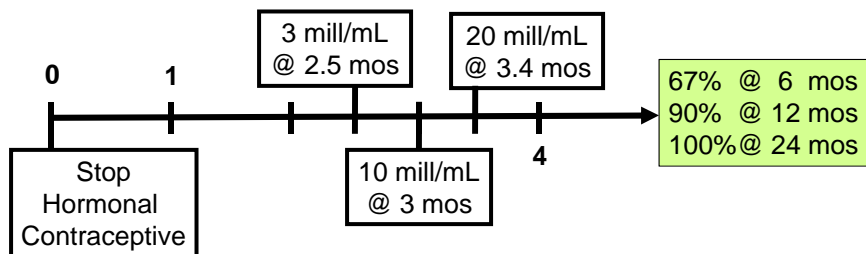
Turek et al. J. Urol. 1995, 153, 1628

Anabolics: Testis Recovery and Restoration

1. Spontaneous recovery
2. SERM treatment
3. Gonadotropin treatment (hCG, FSH)
4. Aromatase inhibitors



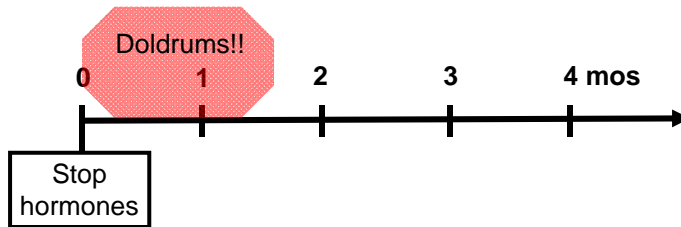
Anabolics: Spontaneous Recovery



- Analysis of **1549** eugonadal **men** age **18-51 years** (90% of published data)
- Followed after discontinuation of androgen or androgen-progestagen contraceptives
- Variables: older age, Asian, shorter treatment duration, higher baseline counts, less time to suppression, lower baseline LH

Liu et al. Lancet. 2006, 367: 1412

Anabolics: Recovery of Spermatogenesis with SERMS



- Initial hypogonadotropic hypogonadism may be intolerable
- Consider adding **clomiphene citrate** or **tamoxifen** to stimulate earlier return of anterior pituitary function
- May bring sperm production back faster than spontaneous recovery

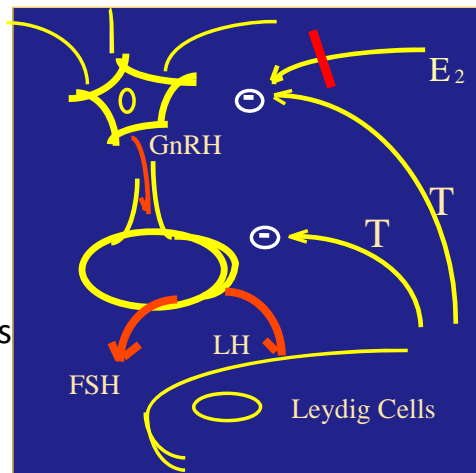
Moskovic et al. BJU Int. 2012. Epub March 28

Clomiphene Citrate

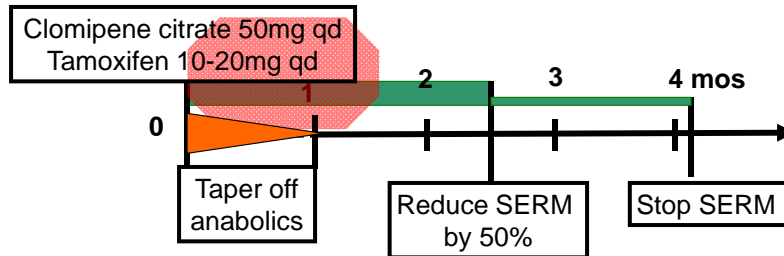
Nonsteroidal hormone
An anti-estrogen (SERM)
Increases GnRH output

R_x _____
12.5-50 mg/day or qod
Check FSH, T in 4 weeks
Monitor semen q 3 mos

Side Effects: gynecomastia,
weight gain, visuals, acne



Anabolics: Recovery of Spermatogenesis with SERMS



- Goal: drive native testosterone production while tapering off anabolics
- Goal: earlier return of endogenous T levels and sperm production (unproven)

Moskovic et al. BJU Int. 2012. Epub March 28

Gonadotropins

(hCG, hMG, Recombinant FSH)

Give LH and FSH formulations to drive testicle.

R_x

hCG, 1,500-3,000 IU S.Q. 3x weekly

hMG 75-150 IU S.Q 2x weekly

rFSH 150 IU SQ 3x weekly

Check serum testosterone levels after 4 weeks

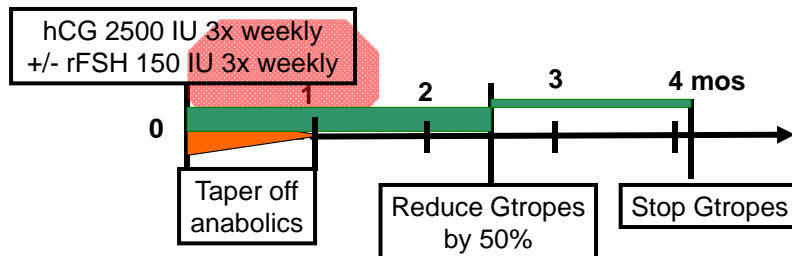
Follow semen analyses q 3 months.



Side Effects: expensive, compliance, cellulitis.

Efficacy: No controlled trials.

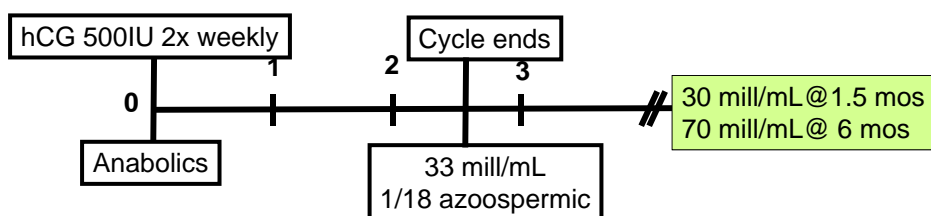
Anabolics: Recovery of Spermatogenesis with Gonadotrophins



- Goal: drive native testosterone production while tapering off anabolics
- Goal: earlier return of endogenous T levels and sperm production (unproven)

Menon DK. Fertil Steril. 2003, 79: suppl 3, 1659

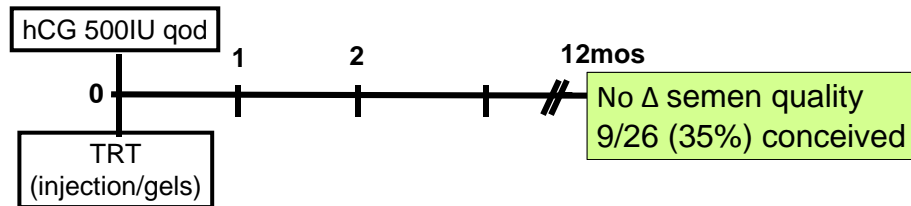
Anabolics and hCG Preserve Sperm Counts



- N=18 Finnish power athletes on “massive anabolic doses”
- Instructed to also take hCG 500 IU 2x weekly with anabolics
- Followed semen quality over time on combination therapy
- Spermatogenesis maintained despite prolonged, massive doses of anabolics

Karila et al. Int J Sports Med. 2004, 25: 257

Anabolics *and* hCG Preserve Sperm Counts



- N=26 hypogonadal men on TRT (19 injectables/7 gels)
- Baseline mean T 207; During Rx, mean T=1055
- Concurrent hCG 500 IU 2x weekly.
- Followed semen quality and hormones for mean 6.2 mos.



Hsieh et al. J Urol. 2013, 189: 647

TRT *and* hCG: Intratesticular Testosterone



- N=29 eugonadal men.
- Dose-response relationship between intratestis T and hCG

Combination Rx ITT	% Baseline
T and saline	-94%
T and 125 hCG	-25%
T and 250 hCG	-7%
T and 500 hCG	+26%



Coviello et al. JCEM. 2005, 90: 2595

The Role of Aromatase Inhibitors in Male Hypogonadism



- Blocks aromatase, a cytochrome P450 enzyme
- Aromatase converts T to estradiol
- FDA indicated to decrease estrogens in breast cancer
- **85%** hepatically metabolized
- Very popular for “gyno” with anabolic body builders
- **50-60%** reduction in estradiol levels in men
- Testosterone levels increase by **30-144%** in infertile men
- Bone demineralization seen in women but not men
- Generally not used in men as long term T supplements

McCullough. Asian J Androl. 2015, 17: 201

Case #2

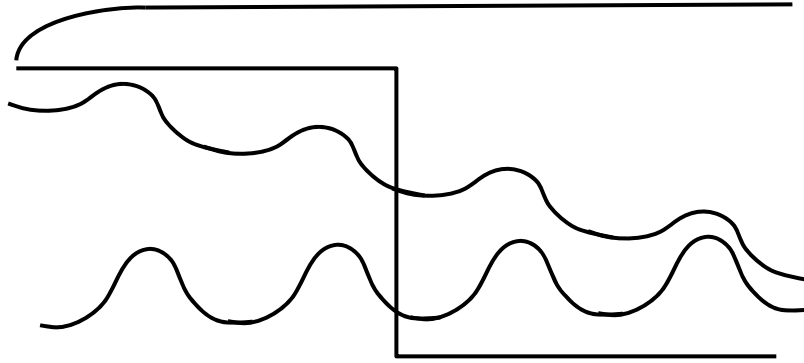
30 yo single man with recent low libido and erectile dysfunction. “I never see morning wood anymore.”

- Recently broke up with girlfriend after 6 years.
- Lost half of his personal wealth in Facebook IPO.

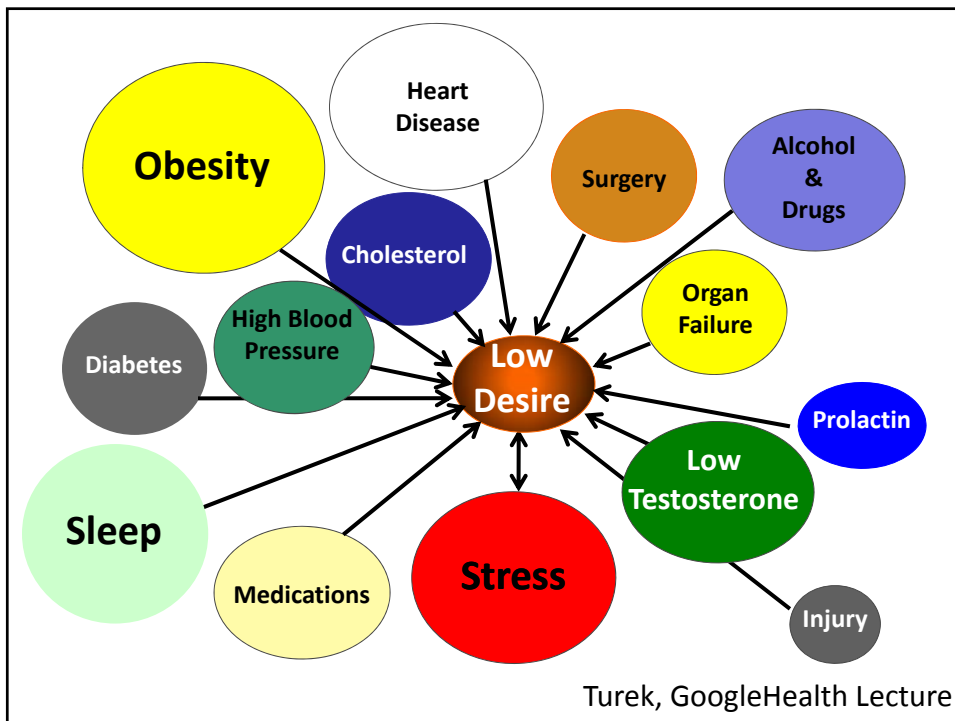
Labs: Testosterone 175 ng/mL
 LH 1.7 IU/mL
 FSH 1.9 mIU/mL
 Prolactin 10 ng/mL
 Iron studies, HgbA1c normal



Evaluating Libido



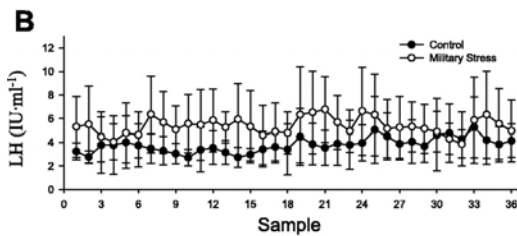
Turek, GoogleHealth Lecture



Turek, GoogleHealth Lecture

Effect of Extreme Physical Stress on LH and T

- N=10 male soldiers [mean 22 yr]
- Blood drawn every 20 min overnight:
 - After a “control” week
 - After 84 hrs of military “operational” stress



Mean LH level over 12 hrs

Physical: Continuous combat drills, marches
Sleep: 2 x 1 hrs/day
Caloric: 1 meal, 1 snack/day

Results:

- 46%** increase in LH levels with stress (but with increased burst interval)
- 24%** lower T and **30%** lower free T levels with stress
- Suggests decreased testis sensitivity to LH with stress

Libido and Stress



- What's a man to do?
- Encourage “**rest and restore**” nervous system with:
 - Regular exercise
 - Massage
 - Acupuncture
 - Yoga

Simple Rx
for Stress

Stress Reduction Kit

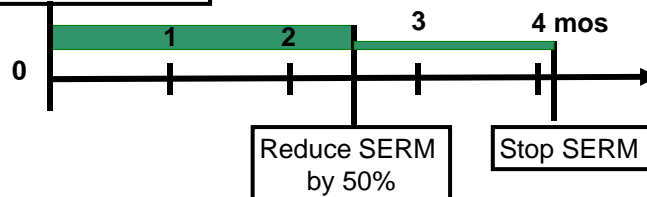
**Bang
Head
Here**

Directions:

1. Place kit on FIRM surface.
2. Follow directions in circle of kit.
3. Repeat step 2 as necessary, or until unconscious.
4. If unconscious, cease stress reduction activity.

Recovery of Testosterone with SERMS

Clomipene citrate 25mg qd
Tamoxifen 10mg qd



- Goal: support testosterone production during stress
- Goal: taper off SERM as stress falls
- Reasonable to consider for mild hypogonadotropic hypogonadism and sexual symptoms

Moskovic et al. BJU Int. 2012. Epub March 28

Clomiphene Citrate-Older Efficacy Studies

Author	Number Patients	Semen Improvement	Pregnancy Rate	Outcome
Foss, 1973	114	NR	17% both	Neg.
Paulson, 1979	40	70% vs 40%	35% vs 17%	Posit.
Ronnberg, 1980	56	78% vs 21%	10% vs 3%	Posit.
Abel 1980	187	0% vs 0%	17% vs 17	Neg.
Wang, 1980	37	NR	36% vs 0%	Posit.
Micic, 1985	101	32% vs 7%	13% vs 9	?
Sokol, 1988	46	NR	9% vs 32%	Neg.
Check, 1988	100	NR	58% vs 16%	Posit.
WHO, 1992	200	NR	8% vs 12%	Neg.

"Hung jury"

Recovery of Testosterone with SERMS

Response to clomiphene citrate

- N=86 men with T < 300 ng/mL from 2002-2006
- Given CC 25mg qod. Titrated dose to T 500-600
- Followed labs q 6 mos (T/gonadotropins); ADAM tool
- Indications: Infertility (64%) with other symptoms
- Mean follow-up 19 mos; age 29 yrs
- All men responded hormonally
- No tolerance to CC developed
- No major side effects



Katz DJ et al. BJU Int. 110: 573, 2012

Recovery of Testosterone *with* SERMS

3 Yr response to clomiphene citrate

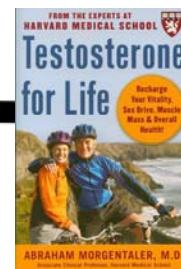
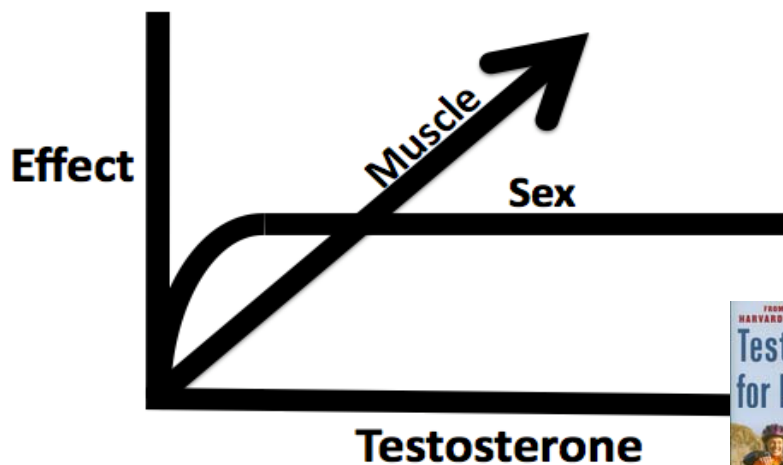
- N=46 men with T < 300 ng/mL from 2002-2006
- Given CC 25mg qod. Titrated dose to T 500-600
- Followed labs q 6 mos (T/gonadotropins)

- Mean age 44 yrs. Mean baseline T=**228** ng/mL
- Mean T @ 1 yr = **612** ng/dL
- Mean T @ 2 yrs = **562** ng/dL
- Mean T @ 3 yrs = **582** ng/dL
- Mean FN and LS BD higher
- ADAM scores 7 to 3 at 3 yrs



Moskovic et al. BJU Int. 2012. Epub March 28

The Morgentaler Theory



Case #3

30 yo married man with low libido and infertility.

PMhx: significant for _____ (Choose one:)

- Diabetes
- Chronic opiate use
- Obesity
- Prolactinoma
- Homozygous thalessemia major
- Sickle cell disease
- Hemochromatosis
- Other cause of secondary hypogonadism

Case #3 cont

Labs: Testosterone 180 ng/mL
 LH 0.9 IU/mL
 FSH 0.7 mIU/mL

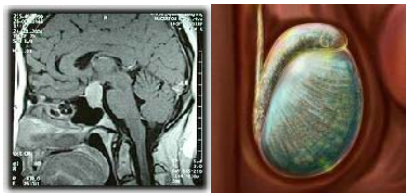
Exam: Left grade III varicocele

Semen analysis:

Volume 1.5 mL
Concentr 5 mill/mL
Motility 22%
Progression 2 (average)

How Semen Quality Changes *in* Hypogonadal Men *on* Clomiphene Citrate

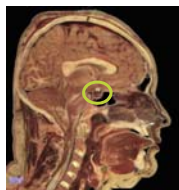
Carson Lawall MD
Uche Ezeh MD
Blake Tyrell MD
Paul Turek MD



ASRM 2004

Study Objective

Assess changes in hormones, symptoms and semen quality in men taking clomiphene citrate for secondary hypogonadotropic hypogonadism.



Methods

- Prospective analysis of men treated with CC.
- Inclusion criteria:
 - Total testosterone <250ng/mL.
 - Normal or Low LH level.
 - Clinical symptoms (ED, infertility, libido)
- Given CC at 12.5-25mg daily. Hormone response assessed 3 weeks later. Titrated treatment to achieve testosterone levels in the 400-700ng/mL range

Results

- 22 men enrolled. Mean age 40 y.o. (range 21-56)
- Indications and pathology:

Infertility	14 patients
Infertility/libido	2 patients
ED and libido	2 patients
ED	1 patient
Infertility and ED	1 patient
Decreased libido	1 patient
ED and gynecomastia	1 patient

Prolactinoma Rxn	4 patients
Acromegaly	2 patients
Intracranial germinoma	1 patient
Idiopathic	15 patients

Results

- Chemical response to clomiphene citrate:

<i>Laboratory</i>	<i>Pre-clomiphene</i>	<i>Post-clomiphene</i>
Total Testosterone	143 ng/mL	479 ng/mL FSH
	3.4 mIU/mL	6.9 mIU/mL LH
	2.0 mIU/mL	5.7 mIU/mL

86% of patients had >50% increase in testosterone.

- A subset of 11 men with infertility had pre- and post-treatment semen analysis available for comparison

Results

- Semen quality response (mean values) to clomiphene citrate treatment (n=11 men):

<i>Parameter</i>	<i>Pre-clomiphene</i>	<i>Post-clomiphene</i>
Volume	2.5 mL	2.6 mL
Sperm concentration	15.7 mill/mL	30.8 mill/mL
Motility	15%	24%
Total Motile Sperm	11 million	33 million

- Responders*: 7/11 men (64%) had a >50% increase in total motile sperm count. Gains mainly in counts (5.8x). 2/7 men conceived naturally.
- Non-responders*: 2/4 had bilateral varicoceles and 2/4 had extensive pituitary resection.

Response to Clomiphene Citrate in HH men with Male Infertility

- n=10 men; 2 centers; 5 years. Testosterone <164 ng/dL
- Treated 3 classes of HH with CC 50mg 3x weekly

Category	# Pts	Semen Response
With anosmia (Kallmann)	4	0/4
No anosmia (idiopathic, acquired)	4	3/4
Panhypopituitary patients	2	1/2

- Stated that CC may work for idiopathic, adult onset, HH

Whitten et al. Fertil Steril. 2006, 86: 1664

Symptom Relief in Hypogonadal Men on Clomiphene Citrate

- Retrospective, cohort of 1150 men on T replacement
- Age-matched comparison of 3 T supplement groups
- Age matched controls; qADAM score 34

Treatment Group	# Subjects	T on Rx	qADAM Score
Clomiphene Citrate	31	504 ng/dL	35
Testosterone gels	31	412 ng/dL	36
Testosterone inject.	31	*1014 ng/dL	39

- Satisfaction scores similar across treatments.
- One difference: Libido higher in T injection group
- Enclomiphene citrate (Androxal®) in Phase III trials

Ramasamy et al. J Urol. 2014, 192: 875

Hypogonadism: What About the Varicocele?

- Compared baseline T levels in 2 cohorts before Rx:
N=200 infertile men clinical varicocele
N=510 men undergoing vasectomy reversal
- Mean T in Varicocele cohort= 416 ng/mL
- Mean T in Reversal cohort= 469 ng/mL ($p<0.001$)
- **70%** of men had “improvement” in T after repair
- Change in T level with varicocele repair
Pre-repair: **358** ng/mL
Post-repair: **454** ng/mL ($p<0.001$)



Tanrikut C et al. BJU Int. 2011, 108: 1480

Treatment *of the* Young Hypogonadal Male

- Consider fertility issues in managing hypogonadism in young men.
- Most cases of secondary hypogonadism respond to SERM therapy
- Tolerance to SERMs is uncommon
- hCG therapy is an excellent, albeit injectable, alternative
- hCG with testosterone replacement preserves fertility
- Don't forget that good ole' varicocele
- ***Take the opportunity to treat the whole man***

THE TUREK CLINIC

