The Treatment of Hypogonadism in Men of Reproductive Age: 
A Review of Non-Testosterone Therapies

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Director Male Reproductive Medicine and Surgery
The Mount Sinai School of Medicine New York NY
Testosterone Levels and Aging
Partial Androgen Deficiency of the Aging Male

![Diagram showing testosterone levels over age]

- Normal testosterone values
- Normal testosterone range (age 20)

Age:
20, 30, 40, 50, 60, 70, 80 years
Prevalence of Low Testosterone in Other Conditions

- Chronic opioid use for pain\(^1\) 74%
- Obesity\(^2\) 52%
- Diabetes\(^2\) 50%
- AIDS\(^3\) (HIV 30\(^4\)) 50%
- Hypertension\(^2\) 42%
- Hyperlipidemia\(^2\) 40%

ED = erectile dysfunction
Testosterone: Adult Physiological Effects

**BRAIN** Helps concentration and possibly memory

**LIBIDO** Increases sex drive

**VOICE** Deepens voice at puberty

**MUSCLE** Increases lean muscle mass

**FAT** Cuts down on body fat

**HAIR** Stimulates growth on the face, chest, genital area and underarms

**BONE** Increases bone density and growth

**Skeletal Muscle, Amino Acids and Protein Synthesis**
- **Insulin**
- **Testosterone**
- **IGF-1**
- **Catecholamines**

**The Effect of Testosterone on Bone Physiology**
- Testosterone stimulates the formation of osteoid and periosteal bone
- Testosterone inhibits osteoclast differentiation
- Osteo progenitor
- Pre-osteoblast
- Osteoblast
- Osteoclast
- Pre-osteoclast
Exogenous Testosterone Suppresses Spermatogenesis

ITT concentration is 50-100x higher than in serum

Exogenous T suppresses ITT production

Spermatogenesis is dramatically compromised at ITT concentrations <20 ng/ml

<table>
<thead>
<tr>
<th>Reference</th>
<th>Number of Subjects</th>
<th>Androgen Dose</th>
<th>Azoospernia n (%)</th>
<th>Severe Oligospermia (&lt;1ml/mL n (%)</th>
<th>Oligospermia (&lt;3ml/mL n (%)</th>
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<tbody>
<tr>
<td>WHO, 1996</td>
<td>225</td>
<td>TE 200mg IM/ wk</td>
<td>157 (70%)</td>
<td>29 (13%)</td>
<td>8 (4%)</td>
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</tbody>
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MEN ARE FATHERING CHILDREN AT AN OLDER AGE

In 1970, less than 15% of all men fathering children were over 35.

Today that percentage has risen to almost 25%.

20-30% of infertile men are found to be hypogonadal.

“Of concern is that 25% of respondents use exogenous testosterone, a medication known for its contraceptive potential, for male infertility treatment.”
Common Reasons that Patients Desire Alternatives to Testosterone Therapy

Fertility preservation

Testicular hypotrophy

A desire to try a pill first, improve overall health and avoid life long dependence

Intolerance of the variability associated with injection therapy, mood instability
The treatment of hypogonadism in men of reproductive age

Edward D. Kim, M.D.,a Lindsey Crosnoe, B.S.,a Natan Bar-Chama, M.D.,b Mohit Khera, M.D.,c and Larry I. Lipshultz, M.D.d

a University of Tennessee Graduate School of Medicine, Knoxville, Tennessee; b Mount Sinai Medical Center, New York, New York; and c Scott Department of Urology, Baylor College of Medicine, Houston, Texas

* Cessation of testosterone
* hCG ± testosterone
* Selective estrogen receptor modulators (SERM’s) - clomiphene citrate
* Aromatase inhibitors

DISCONTINUATION OF IM-TESTOSTERONE CAN RESTORE SPERM PRODUCTION

<table>
<thead>
<tr>
<th>Probability of Recovery (%)</th>
<th>Within 6 Months</th>
<th>Within 12 Months</th>
<th>Within 16 months</th>
<th>Within 24 months</th>
</tr>
</thead>
<tbody>
<tr>
<td>Individual baseline value</td>
<td>54% (46-60)</td>
<td>83% (75-89)</td>
<td>95% (89-98)</td>
<td>100%*</td>
</tr>
<tr>
<td>20 million per mL</td>
<td>67% (61-72)</td>
<td>90% (85-93)</td>
<td>96% (92-98)</td>
<td>100%*</td>
</tr>
<tr>
<td>10 million per mL</td>
<td>79% (73-83)</td>
<td>95% (92-97)</td>
<td>99% (97-100)</td>
<td>100%*</td>
</tr>
<tr>
<td>3 million per mL</td>
<td>89% (84-92)</td>
<td>98% (95-99)</td>
<td>100%*</td>
<td>100%*</td>
</tr>
</tbody>
</table>

*CI could not be obtained from this model.
HUMAN CHORIONIC GONADOTROPIN (hCG)

- Placental glycoprotein homologue of LH

- hCG can be used to induce testosterone production in the testis and is indicated for the treatment of hypogonadotropic hypogonadism

- Sources
  - Urine: Pregnyl®, Follutein, Profasi, Choragon and Novarel
  - Recombinant: Ovidrel®
Low-Dose Human Chorionic Gonadotropin Maintains Intratesticular Testosterone in Normal Men with Testosterone-Induced Gonadotropin Suppression


Concomitant Intramuscular Human Chorionic Gonadotropin Preserves Spermatogenesis in Men Undergoing Testosterone Replacement Therapy

Tung-Chin Hsieh, Alexander W. Pastuszak, Kathleen Hwang and Larry I. Lipshultz

From the Division of Urology, University of California-San Diego (TCH), San Diego, California, Scott Department of Urology, Baylor College of Medicine (AWP, LIL), Houston, Texas, and Department of Urology (KH), Brown University School of Medicine, Providence, Rhode Island

26 hypogonadal men wishing to preserve fertility (mean age 36 years)

Testosterone injections or gel AND hCG 500 IU qod

Followed serum T, semen parameters Mean of 6 months follow-up

Concomitant Intramuscular Human Chorionic Gonadotropin Preserves Spermatogenesis in Men Undergoing Testosterone Replacement Therapy

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Table 2. Mean pre-TRT and post-TRT semen analysis

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<th>Mean Post-TRT (days)</th>
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<tr>
<td></td>
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<tr>
<td>Semen vol (million)</td>
<td>2.9</td>
<td>2.7</td>
</tr>
<tr>
<td>p Value</td>
<td>0.84</td>
<td>0.04</td>
</tr>
<tr>
<td>Density (million/ml)</td>
<td>35.2</td>
<td>22.9</td>
</tr>
<tr>
<td>p Value</td>
<td>0.13</td>
<td>0.15</td>
</tr>
<tr>
<td>% Motility</td>
<td>49</td>
<td>46.7</td>
</tr>
<tr>
<td>p Value</td>
<td>0.68</td>
<td>0.51</td>
</tr>
<tr>
<td>FP</td>
<td>2.3</td>
<td>2.3</td>
</tr>
<tr>
<td>p Value</td>
<td>0.9</td>
<td>0.05</td>
</tr>
<tr>
<td>TMS (million)</td>
<td>84.6</td>
<td>63.4</td>
</tr>
<tr>
<td>p Value</td>
<td>0.44</td>
<td>0.11</td>
</tr>
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Predictors of Success to Restore Fertility Following Cessation of Testosterone Therapy and Utilizing hCG Therapy:

1. Duration of testosterone therapy
2. Male age
What Can We Conclude on HCG

- HCG can boost testosterone in aging males
- No evidence of superiority or inferiority in regards to effects of supplementation on low T symptoms
- More expensive than alternative methods of supplementation
- Preserves fertility
- Preserves testicular hormonal function
SELECTIVE ESTROGEN RECEPTOR MODULATORS: CLOMIPHENE CITRATE

- Competitively binds to estrogen receptors on the hypothalamus and pituitary
- The pituitary sees less estrogen, and makes more LH, increasing T production by the testis
- Off-label

### Off-label Clomiphene Citrate

<table>
<thead>
<tr>
<th>Author (Year)</th>
<th>Design</th>
<th>N=</th>
<th>Age</th>
<th>Dose</th>
<th>Dur (mo)</th>
<th>Δ T</th>
<th>Δ E2</th>
</tr>
</thead>
<tbody>
<tr>
<td>Da Ros (2012)</td>
<td>Pro</td>
<td>125</td>
<td>62</td>
<td>25mg /day</td>
<td>≥3</td>
<td>333</td>
<td>NA</td>
</tr>
<tr>
<td>Katz (2012)</td>
<td>Pro</td>
<td>86</td>
<td>29</td>
<td>25-50mg qod</td>
<td>19</td>
<td>293</td>
<td>13</td>
</tr>
<tr>
<td>Moskovic (2012)</td>
<td>Retro</td>
<td>46</td>
<td>44</td>
<td>25-50mg qod</td>
<td>36</td>
<td>354</td>
<td>13</td>
</tr>
<tr>
<td>Shabsigh (2005)</td>
<td>Pro</td>
<td>36</td>
<td>39</td>
<td>25mg /day</td>
<td>1-1.5</td>
<td>362</td>
<td>T:E 5.5</td>
</tr>
<tr>
<td>Guay (2003)</td>
<td>Retro</td>
<td>178</td>
<td>54</td>
<td>50mg tiw</td>
<td>4</td>
<td>Free T:8.8-11.9</td>
<td>NA</td>
</tr>
<tr>
<td>Guay (1995)</td>
<td>DB, PC</td>
<td>17</td>
<td>61</td>
<td>50mg tiw</td>
<td>4</td>
<td>289</td>
<td>NA</td>
</tr>
<tr>
<td>Tenover (1991)</td>
<td>Pro</td>
<td>10</td>
<td>73; 29</td>
<td>50mg /day</td>
<td>2</td>
<td>Young: 870</td>
<td>Yng: 62</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Elderly: 489</td>
<td></td>
<td>Eld: 40</td>
<td></td>
</tr>
</tbody>
</table>

- Dosing: 25mg qod (200-300 ng/dl) to 50mg qday (400-900)
- Increases E2 - ? Clinical relevance
- Efficacious in elderly populations
- Improves BMD – Moskovic - 3 yr data
Clomiphene Citrate Effectively Raises Testosterone Levels

- Raise serum T levels comparable to gels
- Side effects: gynecomastia, weight gain, hypertension, acne

### Outcomes of clomiphene citrate treatment in young hypogonadal men

Darren J. Katz, Omar Nabulsi, Raanan Tal and John P. Mulhall

Male Sexual and Reproductive Medicine Programme, Urology Service, Department of Surgery, Memorial Sloan-Kettering Cancer Center, New York, NY, USA

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<thead>
<tr>
<th>Symptom</th>
<th>Baseline %</th>
<th>Treatment %</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Decreased libido</td>
<td>72</td>
<td>32</td>
<td>&lt; 0.01</td>
</tr>
<tr>
<td>Lack of energy</td>
<td>65</td>
<td>40</td>
<td>&lt; 0.01</td>
</tr>
<tr>
<td>Decreased strength / endurance</td>
<td>28</td>
<td>21</td>
<td>0.18</td>
</tr>
<tr>
<td>Lost height</td>
<td>4</td>
<td>5</td>
<td>0.45</td>
</tr>
<tr>
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<td>38</td>
<td>0.28</td>
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### Clomiphene improves serum T levels and symptoms

CLOMIPHENE CITRATE IS SAFE

“There were no major side effects recorded from CC during the course of follow-up and no patient ceased CC treatment because of adverse events.”

Clomiphene is safe with long-term use

Clomid Improves Erectile Function

• Importance of Time\(^1\)
  • Long-term assessment of erectile function with T
  • \(N=120\ T<350\), obese

\[\text{Mean IIEF-EF over years: Yr 1, Yr 2, Yr 3, Yr 4, Yr 5, Yr 6, Yr 7, Yr 8, Yr 9, Yr 10, Yr 11, Yr 12.}\]

\(\ast p<0.0001\) vs baseline \# \(p<0.0001\) vs previous year

SELECTIVE ESTROGEN RECEPTOR MODULATORS: CLOMIPHENE CITRATE

- For patients desiring alternatives to testosterone therapy, consider clomid as first-line therapy.

- Preferred for men with a testosterone:estradiol ratio greater than 10:1 and not having an estradiol >60 pg/mL

- Start clomiphene, 50 mg every other day and repeat an complete endocrine analysis. If the estradiol is >60 pg/mL and bioavailable testosterone is >200 ng/dL with good symptomatic relief, decrease the clomiphene dose to 25 mg every other day. If the estradiol is >60 pg/mL and bioavailable testosterone is <200 ng/dL, consider an aromatase inhibitor.

- Clomiphene is titrated up to 100 mg daily, repeating labs 2 weeks after each dosing change as necessary to achieve both symptomatic relief and bioavailable testosterone at least above 200 ng/dL.

- Once the patient is on a stable dose of clomiphene, we repeat a hematocrit, testosterone, and PSA every 3 months for a year and then annually for the duration of clomiphene therapy.
- Indicated for the treatment of breast cancer.
- In a patient with testosterone:estradiol ratio less than 10:1 or hyperestrogenemia (estradiol >60 pg/mL), we typically initiate therapy with an aromatase inhibitor.
- Non-steroidal, 3rd generation
  - Anastrozole (Arimidex), letrozole
  - Aromatase inhibitors block the conversion of T $\rightarrow$ E$_2$, $\downarrow$ The negative feedback of E$_2$ results in $\uparrow$ GNRH, LH, FSH $\rightarrow$ $\uparrow$ Testosterone
### Off-Label Anastrozole

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</tr>
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<tbody>
<tr>
<td>Burnett-Bowie (2008)</td>
<td>RCT, DB, PC</td>
<td>88</td>
<td>66</td>
<td>1mg /day</td>
<td>12</td>
<td>202</td>
<td>-3.7</td>
</tr>
<tr>
<td>Dougherty (2005)</td>
<td>RCT, DB, PC</td>
<td>37</td>
<td>67-68</td>
<td>1mg/day, 1mg biw</td>
<td>3</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td>Leder (2004, 2005)</td>
<td>RCT, DB, PC</td>
<td>37</td>
<td>68</td>
<td>1mg /day, 1mg biw</td>
<td>3</td>
<td>Daily: 229 BIW: 123</td>
<td>Daily:-9 BIW:-10</td>
</tr>
<tr>
<td>Holbrook (2003)</td>
<td>Pro</td>
<td>10</td>
<td>42</td>
<td>1mg /day</td>
<td>0.5</td>
<td>380</td>
<td>-20</td>
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- Estradiol reduced
- Burnett-Bowie – 12 mo resulted in significant reductions in spine BMD
WHO IS A CANDIDATE FOR AI THERAPY?

- Hypogonadal infertile men with T/E ratio < 10
- Hypogondal men treated with TRT and with elevated estrogen levels / (gynecomastia)
- Hypogonadal men seeking fertility preservation (especially if obese)
Conclusions

SERMs, Aromatase Inhibitors and hCG are safe and effective alternative therapies for men with hypogonadism who desire to:

- Start with an oral non-testosterone therapy
- Maintain future fertility
- Possibly overcome hypogonadal status and avoid life long testosterone dependence.
THANK YOU!
Treatment of Hypogonadism in Men who Desire to Preserve Their Fertility: Options for the Practitioner
INCREASED INCIDENCE OF HYPOGONADISM IN YOUNGER MEN IS DUE TO A RISE IN:

- Metabolic Syndrome / Obesity
- Diabetes Mellitus
- Cardiovascular Disease
- HIV/AIDS
- Steroid and Opioid abuse
- Stress / Lack of Exercise
MEN ARE FATHERING CHILDREN AT AN OLDER AGE

In 1970, less than 15% of all men fathering children were over 35.

Today that percentage has risen to almost 25%.

Even among men in the 50 to 54 age group, there has been a notable increase in fatherhood.

Exogenous Testosterone Suppresses Spermatogenesis

Exogenous testosterone suppresses intratesticular testosterone production and thus dramatically compromises spermatogenesis

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Treating Hypogonadism while Preserving Fertility

- Cessation of exogenous testosterone
- hCG ± testosterone
- SERMs--clomiphene citrate
- Aromatase inhibitors
HUMAN CHORIONIC GONADOTROPIN (hCG)

- Placental glycoprotein homologue of LH
- hCG because of its similarity to LH, can be used to induce testosterone production in the testis and is indicated for the treatment of hypogonadotropic hypogonadism
- Sources
  - Urine: Pregnyl®, Follutein, Profasi, Choragon and Novarel
  - Recombinant: Ovidrel®
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Table 2. Mean pre-TRT and post-TRT semen analysis

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<tr>
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<th>Mean Pre-TRT</th>
<th>0–60</th>
<th>60–120</th>
<th>120–180</th>
<th>180–360</th>
<th>Greater Than</th>
</tr>
</thead>
<tbody>
<tr>
<td>Semen vol (million)</td>
<td>2.9</td>
<td>2.7</td>
<td>1.8</td>
<td>2.7</td>
<td>2.5</td>
<td>2.5</td>
</tr>
<tr>
<td>p Value</td>
<td>0.84</td>
<td>0.04</td>
<td>0.86</td>
<td>0.56</td>
<td>0.39</td>
<td></td>
</tr>
<tr>
<td>Density (million/ml)</td>
<td>35.2</td>
<td>22.9</td>
<td>20.7</td>
<td>32.9</td>
<td>35.6</td>
<td>30.2</td>
</tr>
<tr>
<td>p Value</td>
<td>0.13</td>
<td>0.15</td>
<td>0.77</td>
<td>0.98</td>
<td>0.61</td>
<td></td>
</tr>
<tr>
<td>% Motility</td>
<td>49</td>
<td>46.7</td>
<td>42.2</td>
<td>49.5</td>
<td>58</td>
<td>54.2</td>
</tr>
<tr>
<td>p Value</td>
<td>0.68</td>
<td>0.51</td>
<td>0.93</td>
<td>0.08</td>
<td>0.08</td>
<td></td>
</tr>
<tr>
<td>FP</td>
<td>2.3</td>
<td>2.3</td>
<td>2.7</td>
<td>2.4</td>
<td>2.5</td>
<td>2.3</td>
</tr>
<tr>
<td>TM</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

No change in semen parameters
No patient became azoospermic
SELECTIVE ESTROGEN RECEPTOR MODULATORS: CLOMIPHENE CITRATE

- Competitively binds to estrogen receptors on the hypothalamus and pituitary
- The pituitary sees less estrogen, and makes more LH, increasing T production by the testis
- Off-label, 12.5-50 mg po daily
- Tamoxifen, toremifene

### Outcomes of clomiphene citrate treatment in young hypogonadal men

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<td>21</td>
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<td>4</td>
<td>5</td>
<td>0.45</td>
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<tr>
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<td>34</td>
<td>28</td>
<td>0.17</td>
</tr>
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<td>45</td>
<td>38</td>
<td>0.28</td>
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**Clomiphene improves serum T levels and symptoms**

AROMATASE INHIBITORS

- Indicated for the treatment of breast cancer.
- Non-steroidal, 3rd generation
  - Anastrazole (Arimidex), letrozole
  - Aromatase inhibitors block the conversion of T → E₂, ↓ The negative feedback of E₂ results in ↑ GNRH, LH, FSH → ↑ Testosterone
- Minimal evidence for impact on hypogonadal symptoms
- Neither has been well studied in younger men.
- Potential negative effect on bone metabolism

- Exogenous T supplementation decreases sperm production.

- Studies of hormonal contraception indicate that most men have a return of normal sperm production within 1 year after discontinuation.

- SERMs, Aromatase Inhibitors and hCG are safe and effective therapies for treating hypogonadism in men who desire to preserve their fertility.
Thank You