Treatment of Hypogonadism in Men who Wishes to Preserve Fertility

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Financial and Other Disclosures

- Off-label use of drugs, devices, or other agents: SERMs, Aromatase Inhibitors
- Data from IRB-approved human research is presented

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<thead>
<tr>
<th>I have the following financial interests or relationships to disclose:</th>
<th>Disclosure code</th>
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<td>No financial relationships</td>
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TRT inhibits spermatogenesis

- Administration of T results in negative feedback on the hypothalamic-pituitary axis, inhibiting GnRH, and the secretion of FSH and LH.

Exogenous testostosterone suppresses intratesticular testosterone production and thus dramatically compromises spermatogenesis.
• Phase III efficacy trial
• TU 500 mg monthly for 30 months
• 855 fertile Chinese men entered efficacy phase

IM-testosterone Results in Azoospermia for 93% of men

- 93% developed azoospermia
- Median time of 108 days
- Median time to recovery was 3.5 months

Data regarding return of spermatogenesis after discontinuation of commercial T products is virtually non-existent.
“Of concern is that 25% of respondents use exogenous testosterone, a medication known for its contraceptive potential, for male infertility treatment.”

Common Current Scenarios

1. Symptomatic hypogonadism in a man who wants to preserve his fertility
2. Infertile male who presents on TRT
3. Subfertile male who has been prescribed TRT to improve fertility
Treating Hypogonadism while Preserving Fertility

• Cessation of exogenous testosterone
• hCG ± testosterone
• Aromatase inhibitors
• SERMs--clomiphene citrate
Alternative Testosterone Enhancement Routes

CNS Stimulation

Hypothalamus

Hypothalamic-Pituitary Portal System

Anterior Pituitary

Posterior Pituitary

GnRH

Testis

FSH

Sertoli Cells

LH

Leydig Cells

Sperm Inhibin

Testosterone

Estradiol

hCG

SERMs

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

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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

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

<table>
<thead>
<tr>
<th></th>
<th>Mean Pre-TRT</th>
<th>0–60</th>
<th>60–120</th>
<th>120–180</th>
<th>180–360</th>
<th>Greater Than 360</th>
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<tbody>
<tr>
<td><strong>Semen vol (million)</strong></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></td>
<td>0.84</td>
<td>0.04</td>
<td>0.86</td>
<td>0.56</td>
<td>0.39</td>
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<tr>
<td><strong>Density (million/ml)</strong></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></td>
<td>0.13</td>
<td>0.15</td>
<td>0.77</td>
<td>0.98</td>
<td>0.61</td>
</tr>
<tr>
<td><strong>% Motility</strong></td>
<td></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></td>
<td>0.68</td>
<td>0.51</td>
<td>0.93</td>
<td>0.08</td>
<td>0.08</td>
</tr>
</tbody>
</table>

No change in semen parameters
No patient became azoospermic
• Indicated for the treatment of breast cancer.
• Non-steroidal, 3rd generation
  • Anastrazole (Arimidex), letrozole
  • Aromatase inhibitors block the conversion of T→E$_2$, ↓The negative feedback of E$_2$ 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

AROMATASE INHIBITORS

SELECTIVE ESTROGEN RECEPTOR MODULATORS: CLOMIPHENE CITRATE

- Competitively binds to ER on the hypothalamus and pituitary
- Blocks the normal negative feedback of circulating estradiol; hence, increases LH secretion which in turn increases testosterone production & spermatogenesis
- **Off-label**: 12.5-50 mg po daily
- Tamoxifen, toremifene, enclomifene

Clomiphene Citrate Effectively Raises Testosterone Levels

- Raise serum T levels comparable to gels
- May improve semen parameters, but the effect is inconsistent
- Side effects: gynecomastia, weight gain, hypertension, acne

SERMs: Increase T levels

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<th>Baseline, mean (SD)</th>
<th>After Treatment, Mean (SD)</th>
<th>p</th>
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<tr>
<td>Total testosterone, ng/dL</td>
<td>192 (87)</td>
<td>485 (165)</td>
<td>&lt; 0.01</td>
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<tr>
<td>Free testosterone pg/mL</td>
<td>22 (16)</td>
<td>95 (35)</td>
<td>&lt; 0.01</td>
</tr>
<tr>
<td>Oestradiol pg/mL</td>
<td>26 (22)</td>
<td>39 (18)</td>
<td>&lt; 0.05</td>
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<tr>
<td>LH, IU/mL</td>
<td>2.6 (2.2)</td>
<td>6.8 (2.8)</td>
<td>&lt; 0.01</td>
</tr>
<tr>
<td>FSH, IU/mL</td>
<td>1.9 (1.7)</td>
<td>7.6 (1.9)</td>
<td>&lt; 0.01</td>
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CLOMIPHENE CITRATE IMPROVES SYMPTOMS: ADAM QUESTIONNAIRE

<table>
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<tr>
<th>Symptoms</th>
<th>Baseline %</th>
<th>After Treatment %</th>
<th>p</th>
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<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>
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<tr>
<td>Lost height</td>
<td>4</td>
<td>5</td>
<td>0.45</td>
</tr>
<tr>
<td>Decreased life enjoyment</td>
<td>85</td>
<td>40</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Sad/grumpy</td>
<td>60</td>
<td>30</td>
<td>&lt; 0.01</td>
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<tr>
<td>Erections weaker</td>
<td>12</td>
<td>8</td>
<td>0.29</td>
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<tr>
<td>Decreased sports performance</td>
<td>55</td>
<td>25</td>
<td>&lt; 0.001</td>
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<tr>
<td>Sleep after dinner</td>
<td>34</td>
<td>28</td>
<td>0.17</td>
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<tr>
<td>Decreased work performance</td>
<td>45</td>
<td>38</td>
<td>0.28</td>
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Safety and tolerability

• Treatment with CC is generally well tolerated
• Reported adverse events:
  – Headache
  – Visual disturbance
  – Dizziness
  – Gynecomastia
  – Enlarged testis

Clomiphene vs Enclomiphene

• Clomiphene citrate is a mixture of two diastereoisomers,
  – a cis isomer, zuclomiphene citrate (38%)
  – a trans isomer, enclomiphene citrate (62%)

• Zuclomiphene has both estrogenic and anti-estrogenic effects, while enclomiphene is exclusively anti-estrogenic.

Clomiphene Isomers

- Enclomiphene (Androxal) enhances testosterone secretion
- Zuclomiphene suppresses testicular function due to estrogenic activity
- Long Zucl. half-life might exacerbate any Clomid related AE’s

Effects of Clomid and its Isomers on Testosterone in Baboons
Enclomiphene improves testosterone and spermatogenesis after TRT

- Phase IIIB, randomized, open-label study
- 12 men with secondary hypogonadism treated previously with topical T (at least 6 months) were randomly received 25 mg daily oral dose of enclomiphene or daily dose T gel for 6 months

Enclomiphene improves testosterone and spermatogenesis after TRT

After 3 months, no individual in the testosterone gel arm demonstrated a sperm count higher than 12 million/mL, whereas there was no individual in the enclomiphene citrate arm with a count below 75 million/mL, and the mean count was 176 million/mL ($P = 0.004$).

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, although off-label use, are safe and effective therapies for treating hypogonadism in men who desire to preserve their fertility.