Aromatase Inhibitors in Male Infertility: The hype of hypogonadism?

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03 NOVEMBER 2017
PHARMACOTHERAPY ROUNDS

Objectives
• Describe adult male infertility and hypogonadism
• Review the role of androgens in spermatogenesis
• Outline current management strategies
• Assess use of aromatase inhibitors in male infertility treatment
• Recommend plan for patients with hypogonadism and infertility

Infertility
• Inability of a couple to achieve pregnancy despite unprotected intercourse after 12 months
• Affects 6.1 million couples in the United States
  • 10% reproductive aged adult
  • 15% of couples trying to conceive
• Male factor contributes to 50% of all cases
• 20% cases solely due to male factor

Common Terms in Male Infertility
• Anorchia – Absence of both testes at birth
• Azoospermia – complete or near lack of sperm production
• Cryptozoospermia – type of azoospermia in which there is small amount of sperm only detected by centrifugation and concentration of the sample
• Cryptorchidism – condition in which testicles have not descended
• Oligospermia – Low sperm count <15 million spermatozoa/mL
• Varicoceles – Enlargement of veins in the scrotum

Male Infertility
• 50-60% of these men have an identifiable cause
• 40-50% idiopathic
• 20% of men diagnosed with an endocrine problem
• One-third of men have oligospermia or azoospermia
  • 43% of oligospermic due to hypogonadism
  • 45% azoospermic men due to spermatogenic dysfunction
• Degree of infertility variable and dependent on individual patient

Disclosures
No conflicts of interest to disclose
Why is this important?1,3,8,9

• Male partner factors are often neglected
  • High pregnancy rates with assisted reproductive techniques (ART)
• Area for improvement in current practice
  • Can often be reversed/cured
  • Risk of overlooking serious condition
  • ART can extensive and expensive and dangerous to mother and child
  • Treatment with medication cheaper than ART
  • Intrafertilization: $19,324 for first cycle + $6955 per additional cycle
  • Many insurances do not cover fertility treatment

Knowledge Check

Multiple choice:

What percent of cases have some sort of male factor involvement?

A. 20%
B. 30%
C. 50%
D. 70%

Diagnosis of male infertility4,7,10

• Medical history and physical examination
  • Involve urologist or specialist
  • Scrotal ultrasound
  • At least 2 semen analyses
  • Limits based on WHO criteria (Appendix B)
  • Abnormal sperm motility, morphology, and concentration
• Comprehensive andrological examination
  • If at least 2 abnormal semen analyses
  • Include testosterone and follicle stimulating hormone

Causes of male infertility1

<table>
<thead>
<tr>
<th>Pre-testicular</th>
<th>Testicular</th>
<th>Post-testicular</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hypothalamic-pituitary disorder</td>
<td>Varicocele</td>
<td>Epididymal obstruction/scarring</td>
</tr>
<tr>
<td>Thyroid Disorder</td>
<td>Trauma</td>
<td>Retrograde ejaculation</td>
</tr>
<tr>
<td>Adrenal Disorder</td>
<td>Infection</td>
<td>Antibodies to sperm or seminal plasma</td>
</tr>
<tr>
<td>Drugs</td>
<td>Drugs/Toxins</td>
<td>Developmental abnormalities</td>
</tr>
<tr>
<td></td>
<td>Chromosomal abnormalities</td>
<td>Androgen insensitivity</td>
</tr>
<tr>
<td></td>
<td>Developmental abnormalities</td>
<td>Poor coital technique</td>
</tr>
<tr>
<td></td>
<td>Defective androgen production</td>
<td>Sexual dysfunction, impotence</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Idiopathic</td>
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</tbody>
</table>

Androgens and spermatogenesis

Spermatogenesis1,6

• Testosterone (T) production and spermatogenesis controlled by the hypothalamic axis
  • Pulsatile
  • Stimulates anterior pituitary to secrete gonadotropins
    • Luteinizing hormone (LH)
    • Follicle stimulating hormone (FSH)
Spermatogenesis\textsuperscript{1,6}

- FSH stimulates Sertoli cells
  - Production of paracrine growth factor
    - Support sperm growth
  - Production of androgen binding globulin
- LH stimulates Leydig Cells
  - T produced
  - Binds to androgen binding globulin
  - Secreted into seminiferous tubules and circulation

T role in Spermatogenesis\textsuperscript{1}

- T in seminiferous tubules are 80-100x more concentrated than in the general circulation
  - High concentration necessary for sperm production
  - Binds to androgen receptors
  - Spematogenesis in Sertoli cells
  - Inhibition of germ cell apoptosis
- T in the circulation provides negative feedback at hypothalamus and pituitary
  - GnRH, LH, FSH secretion
- T converted to estradiol (E2)
  - Aromatase: found in testes, prostate, bone, brain, adipose
  - E2 also provides negative feedback

APPENDIX C

Importance of Estrogen and Aromatase\textsuperscript{11}

- Effects growth, development, and function of Leydig cells
- Promotes maturation of spermatogonia
- Paracrine function: inhibits aromatase activity in Sertoli cells
- Autocrine function: low levels inhibit germ cell apoptosis
- Lack of aromatase leads to impaired spermatogenesis

APPENDIX D

Detrimental effects of Estrogen\textsuperscript{11}

- Negative feedback on Hypothalamus-pituitary axis
  - ↓ FSH and ↓ LH → ↓ spermatogenesis
- Inhibits spermiogenesis related genes and promotes spermatocyte apoptosis
- Inhibitory effects on Sertoli and Leydig cell functions
- Careful regulation needed for spermatogenesis

Knowledge Check

Multiple choice:

Aromatase is found in which of the following tissues?

A. Testes  
B. Brain  
C. Adipose  
D. Two of the above  
E. All of the above

Hypogonadism
Hypogonadism Etiology\textsuperscript{1,4}

- Primary:
  - Testicular failure
  - Hypergonadotropic hypogonadism (HerH)

- Secondary
  - Hypothalamus-Pituitary Axis failure
  - Hypogonadotropic hypogonadism (HoH)

Hypergonadotropic Hypogonadism\textsuperscript{1,4,5,12}

- Characterized by:
  - ↑ FSH and/or LH
  - Leydig cell dysfunction

- Low T (< 300 ng/dL) and associated symptoms
  - ↓ libido, poor erections, hot flashes, low energy, weight gain, mood change, sleep disturbance, ↓ body hair, infertility

- Deficient spermatogenesis

HerH Etiology\textsuperscript{1,4}

- Genetic
- Testicular tumor
- Trauma
- Varicocele
- Systemic diseases (liver cirrhosis, renal failure)
- Iatrogenic: Surgery, radiotherapy, medications

Hypogonadotropic Hypogonadism\textsuperscript{1,4,5,12}

- Uncommon cause of male infertility
- Characterized by either
  - ↓ GnRH production → ↓ FSH and/or LH
  - Rare disorders of the pituitary (normal GnRH levels)
  - Result in primary deficiencies of FSH and LH

- Low T and associated symptoms
- Deficient spermatogenesis

HoH Etiology\textsuperscript{1,4}

- Genetic
  - Abnormal synthesis/release GnRH (idiopathic)
  - Kallmann syndrome - failed GnRH axonal migration in fetal development
  - GnRH receptor abnormalities

- Pituitary mass lesions
- Hyperprolactinemia
- Anabolic steroid use
- Radiotherapy
- Obesity

Current treatment strategies

- The optimal evaluation of the infertile male:
  - American Urology Association Best Practice Statement
European Association of Urology Guideline-Based Treatment for hypogonadism

- Provide T replacement for symptomatic patients with primary and secondary hypogonadism
- In men with hypogonadotropic hypogonadism, induce spermatogenesis by an effective drug therapy (Human chorionic gonadotropin)
- Do not use T replacement for the treatment of male infertility

Treatment of Idiopathic Hypogonadism

- Assisted reproductive treatment
- Empirical medical treatment
  - Gonadotropin
  - Human chorionic gonadotropin (HCG) ± follicle stimulating hormone (FSH)
  - Selective Estrogen Receptor Modulators (SERMs)
  - Clomiphene
  - Tamoxifen
  - Aromatase Inhibitors
  - Letrozole
- Lifestyle changes

Human Chorionic Gonadotropin

- Mechanism of action:
  - Has the bioactivity of LH
- Labeled use:
  - Hypogonadotropic hypogonadism
  - Ovulation induction
  - Prepubertal cryptorchidism
- Off label use:
  - Spermatogenesis induction in hypogonadism

**Dose:** IM injection

- HH
  - 500-1000 units 3 times weekly for 3 weeks, then 2 times weekly for 3 weeks
  - 4000 units 3 times weekly for 6-9 months, then 2000 units 3 times weekly for 3 months
  - Spermatogenesis in idiopathic HH (off-label)
  - 5000-2000 units 2-3 times weekly until T levels normal (2-3 months)
  - May then add FSH if needed to induce spermatogenesis
  - Continue HCG dose required to maintain T levels

Human Chorionic Gonadotropin

- Side Effects
  - Elevated liver enzymes
  - Gynecomastia
  - Injection site reaction
  - Mood changes
Human Chorionic Gonadotropin\textsuperscript{2,5,14,15}

**Pros:**
- Approved for treatment of hypogonadotropic hypogonadism

**Cons:**
- High cost
- Invasive

**Clinical use**
- Usually recommended if failed clomiphene or anastrozole

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Selective Estrogen Receptor Modulators\textsuperscript{13-15}

**MOA:** block negative feedback at hypothalamus and pituitary and indirectly enhance LH and FSH secretion

**Most studied oral drugs in male infertility**
- Drugs:
  - Clomiphene
  - Tamoxifen

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Clomiphene citrate\textsuperscript{3,13-15}

**Labeled use:**
- Infertility in women

**Off-label use:**
- Idiopathic oligospermia associated infertility

**Dose:**
- Optimal dosing not established: 12.5–400 mg/day
- Common:
  - 25 mg 3 times weekly or once daily
  - 50 mg every other day up to once daily

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Clomiphene citrate\textsuperscript{5,13-15}

**Side effects**
- Hot flashes
- Headache
- Nausea/Vomiting
- Weight gain
- Gynecomastia
- Visual disturbances

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Clomiphene citrate\textsuperscript{2,3,5,13-15}

**Pros:**
- Can ↑ FSH and LH
- Inexpensive
- Well tolerated
- Most evidence
- Longer duration in studies (15 months)

**Cons:**
- Can ↑ E2
- May not be best in patients with elevated FSH
- May worsen semen parameters

**Clinical use:**
- Low testosterone and symptoms of low testosterone in male infertility

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Aromatase inhibitors\textsuperscript{2,3}

**MOA:** inhibit aromatase and ↓E2
- May lead to stronger GnRH pulses and ↑FSH

**Drugs**
- Steroidal – irreversible
  - Testolactone
  - Formestane
  - Eimestane
- Nonsteroidal – reversible
  - Letrozole
  - Anastrozole
Aromatase inhibitors

- Labeled use:
  - Breast cancer
- Off label use:
  - Delayed puberty
  - Endometriosis
  - Infertility
- Dose:
  - Letrozole 2.5 mg daily
  - Anastrozole 1 mg daily
  - In practice: ½ – 1 tablet 2-3 times weekly

Half-life:
- Letrozole: 48 hours
- Anastrozole: 50 hours

Side effects:
- Headache
- Hot flash
- Hypercholesterolemia
- Weight gain
- Edema
  - ↓ bone density (long term in women)

Testosterone:Estradiol Ratio


Objective
- Assess serum T:E2 ratio in infertile and fertile men and the effect of testolactone on semen parameters

Design
- Non-controlled trial

Inclusion
- Azoospermic or oligospermic men (n = 63) with clinical evidence of male factor infertility including:
  - Small testes
  - Increased serum FSH (mean: 21.2 ± 1.8 IU/L)
  - Abnormal semen analysis
- Fertile men (n= 40)
  - Age matched
  - Proved fertility
  - No evidence of testicular dysfunction

Intervention (n=45)
- 50 – 100 mg oral testolactone twice daily for 5 months

Outcome
- Population characteristics
  - Original population (n=63)
    - 43 azoospermic
    - 20 oligospermic
  - Hormone analysis
    - 12 azoospermic
    - 12 oligospermic

Primary Outcomes
- Hormonal evaluations: T, E2, T:E2, FSH, LH
- Seminal parameters

Secondary Outcomes
- Liver function tests

T:E2 ratio (p<0.01)
- Infertile men (n = 24)
  - FSH (ng/L) 6.9 ± 0.6
  - T:E2 ratio 5.0 ± 0.3
  - Sperm motility 27.1 ± 5.9%
  - Sperm concentration (million/mL) 16.1 ± 5.3
  - Semen volume (million/ejaculate) 20.1 ± 8.8
  - LFTs
    - Mild ↑ transaminase in 6 patients
    - Indirect bilirubinemia in 2 patients
    - None more than 2 fold above normal

Fertile men
  - FSH (ng/L) 66 ± 37
  - T:E2 ratio 5.0 ± 0.3
  - Sperm motility 27.1 ± 5.9%
  - Sperm concentration (million/mL) 28.9 ± 9.3
  - Semen volume (million/ejaculate) 20.1 ± 8.8

Author’s Conclusion:
- Aromatase inhibitors can improve semen parameters and increase the T:E2 ratios
T:E2 Ratio

Strengths
- T:E2 ratios not previously studied

Weaknesses
- Small group, only 12 oligospermic patients analyzed
- Varying etiologies, no exclusions
- Non-randomized or controlled
- Use testosterone
- Single semen analyses
- Possibility of sex hormone binding globulin decrease
- No side effect data reported

Overall conclusion
- An aromatase inhibitor can normalize the T:E2 ratio in men and may have an effect on semen parameters in oligospermic men

Questions remaining
- What is the normal T:E2 ratio in men?
- Do aromatase inhibitors affect SHBG levels?
- Can the nonsteroidal aromatase inhibitors affect male semen parameters and male infertility in men with decreased T:E2 ratios?


Letrozole and ↓T:E2


Objective
- To investigate the effect of letrozole in BMI, serum hormones, and sperm parameters in male infertility associated with ↓T:E2 ratios

Design
- Turkey
- Noncontrolled comparative trial

Inclusion
- Infertile men with low T:E2 ratio (<10) (n=27)
- T < 330 ng/dL

Exclusion
- Additional etiology (varicocele, ejaculatory duct obstruction)
- Female factor infertility

Intervention
- All treated with 2.5 mg letrozole daily for ≥ 6 months

Outcome all patients

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<th>Post-intervention</th>
<th>P value</th>
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<tr>
<td>BMI (kg/m²)</td>
<td>28.40 ± 3.86</td>
<td>28.90 ± 4.43</td>
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<td>Testicular volume (mL)</td>
<td>15.39 ± 4.49</td>
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<td>T (ng/dL)</td>
<td>255 ± 22</td>
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<td>E2 (pg/mL)</td>
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<td>T:E2 ratio</td>
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Letrozole and ↓T:E2


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- To investigate the effect of letrozole in BMI, serum hormones, and sperm parameters in male infertility associated with ↓T:E2 ratios

Design
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- Noncontrolled comparative trial

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<td>0.001</td>
</tr>
</tbody>
</table>
Letrozole and ↓T:E2

<table>
<thead>
<tr>
<th>Outcomes: Oligospermic</th>
<th>Baseline (n=10)</th>
<th>Post-intervention (n=10)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total motile sperm (million)</td>
<td>6.41 ± 2.72</td>
<td>15.77 ± 5.01</td>
<td>0.016</td>
</tr>
<tr>
<td>Motility (%)</td>
<td>19.60 ± 4.11</td>
<td>24.00 ± 3.31</td>
<td>0.017</td>
</tr>
<tr>
<td>Sperm count (million)</td>
<td>6.12 ± 2.46</td>
<td>17.00 ± 3.06</td>
<td>0.008</td>
</tr>
<tr>
<td>Ejaculate volume (mL)</td>
<td>2.62 ± 0.23</td>
<td>3.59 ± 0.31</td>
<td>0.031</td>
</tr>
<tr>
<td>Pregnancy</td>
<td>0</td>
<td>0</td>
<td>--</td>
</tr>
</tbody>
</table>

Letrozole and ↓T:E2

<table>
<thead>
<tr>
<th>Outcomes: Azoospermic</th>
<th>Baseline (n=17)</th>
<th>Post-intervention (n=4)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total motile sperm (million)</td>
<td>0</td>
<td>1.46 ± 1.23</td>
<td>0.253</td>
</tr>
<tr>
<td>Motility (%)</td>
<td>0</td>
<td>6.47 ± 3.34</td>
<td>0.071</td>
</tr>
<tr>
<td>Sperm count (million)</td>
<td>0</td>
<td>1.11 ± 0.69</td>
<td>0.125</td>
</tr>
<tr>
<td>Ejaculate volume (mL)</td>
<td>2.51 ± 0.24</td>
<td>2.94 ± 0.23</td>
<td>0.007</td>
</tr>
</tbody>
</table>


**Side Effects**

- No severe side effects observed
- Mild headache (n=2)

Author's Conclusion:

Letrozole may be used to effectively improve sperm parameters in infertile men with low serum T:E2 ratio and may lead to pregnancy, and may improve sperm count in azoospermia.

**Strengths**

- First study involving letrozole
- Excluded patients with other etiology
- Reported side effects
- Reported pregnancies
- Multiple samples

**Weaknesses**

- Small groups
- Non-randomized or controlled

**Overall conclusion**

- Letrozole may safely help improve sperm parameters in oligospermic men with ↓T:E2 in order to improve fertility and pregnancy rate
- Letrozole is well tolerated

**Questions remaining**

- Should T:E2 <10 be the standardized cut-off?
- Can anastrozole have similar effects?

Anastrozole and ↓T:E2

<table>
<thead>
<tr>
<th>Objective</th>
<th>To assess whether anastrozole can affect the sperm parameters in subfertile hypogonadotropic men with ↓T:E2</th>
</tr>
</thead>
<tbody>
<tr>
<td>Design</td>
<td>Retrospective study</td>
</tr>
<tr>
<td>Inclusion</td>
<td>Hypogonadotropic subfertile men (n=86)</td>
</tr>
<tr>
<td></td>
<td>Low T: &lt;135 mg/dl</td>
</tr>
<tr>
<td></td>
<td>Either: low T:E2 &lt;10 (n=78) or adverse reaction to clomiphene citrate (n=8)</td>
</tr>
<tr>
<td>Exclusion</td>
<td>History of sex chromosomal disorder</td>
</tr>
<tr>
<td></td>
<td>Past exogenous T use</td>
</tr>
<tr>
<td></td>
<td>Other concomitant hormonal treatment</td>
</tr>
<tr>
<td>Intervention</td>
<td>Anastrozole 1 mg daily for 4 months</td>
</tr>
</tbody>
</table>

Anastrozole and ↓T:E2

**Population characteristics**

- Median age: 37 (range: 32-41)
- Mean duration of unprotected intercourse: 24 months (18-48)
- 50 oligospermic
- 28 azoospermic
- 8 cryptozoospermic

**Outcomes**

- Hormone analysis: total T, bioavailable T, E2, SHBG, albumin, FSH, LH
- Semen analysis

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Baseline</th>
<th>3 week</th>
<th>4 month</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total T (ng/dL)</td>
<td>258.4 ± 10.8</td>
<td>509.2 ± 20.4</td>
<td>449.4 ± 19.5</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Bioavailable T (ng/dL)</td>
<td>128.8 ± 6.7</td>
<td>297.5 ± 12.7</td>
<td>--</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>E2 (pg/mL)</td>
<td>40.8 ± 3.9</td>
<td>26.6 ± 2.1</td>
<td>23.2 ± 2.7</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>SHBG (nmol/L)</td>
<td>6.98 ± 0.33</td>
<td>36.5 ± 6.5</td>
<td>24.2 ± 3</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>FSH (IU/L)</td>
<td>5.64 ± 1.1</td>
<td>24.9 ± 1.2</td>
<td>--</td>
<td>Not significant</td>
</tr>
<tr>
<td>LH (IU/L)</td>
<td>6.45 ± 0.09</td>
<td>10.7 ± 1.1</td>
<td>--</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Volume (mL)</td>
<td>2.56 ± 0.25</td>
<td>--</td>
<td>2.32 ± 0.25</td>
<td>NS</td>
</tr>
<tr>
<td>Concentration (million/mL)</td>
<td>4.7 ± 1.2</td>
<td>--</td>
<td>13.1 ± 2.9</td>
<td>0.001</td>
</tr>
<tr>
<td>Motility (%)</td>
<td>39.9 ± 5</td>
<td>--</td>
<td>90.5 ± 4.8</td>
<td>NS</td>
</tr>
<tr>
<td>Total motile count (million)</td>
<td>4.6 ± 1.3</td>
<td>--</td>
<td>8 ± 2.4</td>
<td>&lt;0.01</td>
</tr>
</tbody>
</table>

- In oligospermic men only (n = 21)
- Total motile count correlated with ↑T:E2 (P<0.0001)
- Controlled for Age and FSH concentration
- Did not correlate to any other outcome

**Strengths**

- Excluded patients with other etiology
- Side effects reported
- 2 semen samples per patient
- Evaluated SHBG levels

**Weaknesses**

- Retrospective, noncontrolled
- Small group for seminal parameters
- Varicocele etiology
- Did not report pregnancy

**Anastrozole Side Effects**

- Bilateral ankle swelling, resolved with continued treatment (n = 1)
- Decreased libido, irritability, depression, bilateral breast tenderness, ocular pruritus/pain, and dry mouth (n = 1)
- Paradoxical increase in E2 (n = 1)

**Joint and tendon pain, and swelling in limbs (n=2)**

**Author’s Conclusion:** Anastrozole improved endocrine parameters in men with hypoandrogenism and sperm parameters in oligospermic men. Total motile count correlated to ↑T:E2, thus arguing for a physiologic effect of treatment.

**Overall Conclusion**

- Which is more effective, anastrozole or letrozole, improving seminal parameters and infertility?
- Which is better tolerated?
- Can aromatase inhibitors improve sperm retrieval in azoospermic men?

**Questions remaining**

- Anastrozole may help improve endocrinopathy and seminal parameters in oligospermic men.
- Anastrozole is well tolerated.
Anastrozole vs Letrozole

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Pre-intervention</th>
<th>Post-intervention</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>BMI (kg/m²)</td>
<td>26.8 ± 2.5</td>
<td>26.8 ± 2.5</td>
<td>&gt;0.05</td>
</tr>
<tr>
<td>Testicular volume (ml)</td>
<td>13.7 ± 3.99</td>
<td>13.8 ± 3.94</td>
<td>0.86</td>
</tr>
<tr>
<td>FSH (mIU/ml)</td>
<td>8.25 ± 1.95</td>
<td>8.45 ± 1.95</td>
<td>0.89</td>
</tr>
<tr>
<td>LH (mIU/ml)</td>
<td>11.35 ± 3.58</td>
<td>11.35 ± 3.53</td>
<td>0.81</td>
</tr>
<tr>
<td>E2 (pg/ml)</td>
<td>24.3 ± 20.1</td>
<td>15.15 ± 3.19</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>TEZ ratio</td>
<td>8 ± 0.5</td>
<td>9 ± 0.5</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Ejaculate Volume (ml)</td>
<td>2.4 ± 0.15</td>
<td>3 ± 0.5</td>
<td>&lt;0.005</td>
</tr>
<tr>
<td>Spem count (million)</td>
<td>4.15 ± 3.88</td>
<td>8.9 ± 3.21</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Motility (%)</td>
<td>12.35 ± 3.89</td>
<td>22.85 ± 3.38</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Total functional sperm fraction (million)</td>
<td>1.94 ± 2.25</td>
<td>7.45 ± 2.96</td>
<td>&lt;0.005</td>
</tr>
</tbody>
</table>

Letrozole and Anastrozole Side Effects

<table>
<thead>
<tr>
<th>Letrozole</th>
<th>Anastrozole</th>
</tr>
</thead>
<tbody>
<tr>
<td>↑ liver enzymes (n=1)</td>
<td>↑ liver enzymes (n=1)</td>
</tr>
<tr>
<td>Transient weakness (n=2)</td>
<td>Mild diarrhea x 3 days (n=1)</td>
</tr>
<tr>
<td>Nausea x 10 days (n=1)</td>
<td>Transient nausea (n=2)</td>
</tr>
<tr>
<td>Mild headache (n=2)</td>
<td>Mild headache (n=2)</td>
</tr>
</tbody>
</table>

Author's Conclusion: Anastrozole and letrozole are equally effective in improving T levels and seminal parameters in men with severe oligospermia, low T levels, and normal gonadotropins.
Strengths
• Compared letrozole and anastrozole
• 2 semen samples per patient
• Reported side effects
• All patients were oligospermic

Weaknesses
• Small groups
• No baseline characteristics reported
• Not randomized or controlled
• Not powered to detect statistical significance between the two differences
• Pregnancies not reported

Anastrozole vs Letrozole
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Pros: • ↑ T without ↑ E2 • ↑ T:E2 ratio • Inexpensive
Cons: • Less evidence • No consistent regimen
Clinical use: • Hypogonadism with low T:E2 ratio (<10)
Knowledge Check

Multiple Choice:
Which of the following medications has an FDA indication for male hypogonadism? [Select all that apply]

A. Clomiphene
B. Anastrozole
C. hCG
D. Testosterone

Knowledge check

Multiple choice
Aromatase inhibitors may increase the following parameters except:

A. Sperm count
B. Testicular volume
C. Testosterone:Estriadiol ratio
D. Testosterone

Conclusion

• T:E2 ratio seems to be correlated with infertility in some oligospermic infertile men
• T:E2 < 10 should be used as a guide
• Aromatase inhibitors may help oligospermic men
  • ↑ T
  • ↓ E2
  • ↑ T:E2
  • ↑ sperm count
  • ↑ sperm motility

Future research

• Prospective randomized trials
• Normal/optimal T:E2 ratio
• Different dosing schedules
  • 2-3 times weekly vs daily
• Aromatase inhibitors and sperm retrieval in azoospermic men
• Tolerability and long term effects
  • Bone density
  • Hypercholesterolemia
• Guideline implementation
Acknowledgments

• Evaluator
  • Sharon Rush, R.Ph.
• Residency Program Director
  • Nathan Pope, Pharm.D., BCACP, FACA

• Preceptors
  • James Weems, R.Ph.
  • Amanda Stallings, Pharm.D.
  • Gretta Leckbee, R.Ph.
  • Jennifer Wilbanks, R.Ph.
  • Lauren Clark, Pharm.D.
  • Mark Comfort, Pharm.D.

Questions?

Aromatase Inhibitors in Male Infertility:
The hype of hypogonadism?

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