The Jones Institute for Reproductive Medicine
“Founded on Science, Dedicated to Life”
FDA Advisory Committee Meeting: treatment of secondary hypogonadism

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Outline

1. Brief review of some aspects of the physiology of the hypothalamic-pituitary-testicular axis

2. Hypogonadal states: definitions

3. Impact of aging and other co-morbidities

4. Treatment of men with hypogonadism

5. Fertility concerns: basic semen analysis, sperm function and quality assays

6. The future

Declaration: NO conflicts of interest
1. Brief review of the physiology of the hypothalamic-pituitary-testicular axis
Hypothalamic-Pituitary-Testicular axis
FSH plays a pivotal role in initiation and maintenance of spermatogenesis.

For completely normal spermatogenesis, FSH and testosterone (T) are important, and also the intratesticular T (FSH+hCG >> FSH+T).

Proliferation of Sertoli cells and gonias.
Schematic overview of the hypothalamic–pituitary–testicular axis: kisspeptin (KISS1) and leptin resistance or insensitivity

(Teerds et al, 2011 HRU)
2. Hypogonadal states: definitions
Hypogonadal states

- **“Classical” hypogonadism** (well controlled lab= testosterone (T) <300 ng/dl)

- **Primary (hypergonatrophic hypogonadism)**: is the result of testicular failure to produce adequate levels of T, and is identified by low T and elevated FSH and LH.

  Impaired Leydig cell and seminiferous tubule functions results in reduced T synthesis and secretion and also hypospermatogenesis (Klinefelter, toxicities, orchitis).

- **Secondary (hypogonadotropic hypogonadism)**: is the result of GnRH or GT deficiency (hypothalamic or pituitary), also called “central”, leading to reduced GT and low T

  congenital (genes such as KAL-1, GnRH receptor, gonadotropins, pituitary transcription factors -HESX1, LHX3, and PROP-1, orphan nuclear receptors -DAX-1, and SF-1, and three genes also associated with obesity (leptin, leptin receptor, and prohormone convertase )

- or **acquired**, secondary to pathological processes such as tumors (secretory or non secretory), granulomatosis, infections , trauma, or radiation.
Adult onset hypogonadism (AOH):
Sexual Medicine Society of North America
(Mayo Clin Proc 2016)

• AOH is a measurable clinical and biochemical syndrome characterized by low T, associated symptoms, and low or normal gonadotropin (GT) levels.

• It is clinically distinct from “classical” primary and secondary hypogonadism because the T deficiency is associated with a failure to mount an adequate compensatory pituitary response to low T levels

• Unclear prevalence (estimated 5 Million men in USA) (Aydogdu and Swerdloff, Expert Opinion Emerging Drugs, 2016)
3. Impact of aging and other co-morbidities
Association of AOH with common co-morbidities

- **Aging** (Leydig cells become less responsive to exogenous gonadotropin stimulation and the number of Leydig cells declines. Production of GnRH decreases with age and GnRH/LH pulse amplitude diminishes. In addition, androgen negative feedback suppression of LH secretion may be increased)

- **Obesity** (affects fertility via hypogonadism and its impact on sperm production, and atherogenic effect causing erectile dysfunction -ED)

- **Diabetes mellitus** (type 2)

- **Medication effects** (T levels can be affected by many pharmacologic agents eg, opioids, glucocorticoids, cimetidine, tricyclic antidepressants, nicotine, and marijuana)

- **Sleep disruption, stress**
How does obesity affect fertility in men: postulated central mechanisms underpinning the aetiology of decreased T secretion in obese men (Stokes et al, 2014)

KISS neuron: Kisspeptin
The impact of obesity on male infertility

*(Chambers and Anderson, Hormones, 2015)*

**Figure.** Factors contributing to reduced fertility in obese men.
Hypothalamic-pituitary-testicular axis disruptions in older men are differentially linked to age and modifiable risk factors: the European male aging study (Wu et al, JCEM, 2016)

Fig. 1. Relationship between age and hormones. This shows the mean hormone values at 5-yr age bands with 95% CI (shaded area) in 3220 men. Total T and free T were significantly lower and LH and SHBG significantly higher in the older age groups. There was an apparent inflection point around 70 yr for LH.
Fig. 2. Relationship between age, BMI, and hormones. The cohort was stratified according to BMI into three groups: nonobese (BMI < 25 kg/m²), overweight (BMI ≥ 25 to < 30 kg/m²), and obese (BMI ≥ 30 kg/m²). Mean total and free T and SHBG were significantly lower in the overweight and obese at all ages, compared with nonobese. The total T and SHBG age trends in the three BMI categories were similar; the free T age trend in the obese group was less steep than in the other two groups. Mean LH was not significantly different among the three groups at the median age of 60 yr. LH was higher in the older than 70 yr nonobese, compared with the overweight and obese groups.

(Wu et al, JCEM 2008)
Subgroups of men by gonadal status and by decade of age from the European Male Ageing Study (EMAS, Khera et al, Mayo Clinic Proceedings, 2016)
4. Treatment of men with hypogonadism
4. Treatment of men with hypogonadism

a-Testosterone replacement therapy; primary option (unless fertility is a concern or there are contraindications)

Adequate monitoring: risks and safety: lack of definitive evidence derived from properly designed and powered prospective studies. Therefore patients must be monitored regularly for T efficacy and adverse events (which may include or not CVD, prostate cancer, BPH, erythrocytosis, and infertility)
Infertility as side effect of T treatment

T treatment (TT) is a form of male birth control: T suppresses endogenous LH and FSH production, which results in testicular atrophy (suppression of both seminiferous tubule volume and Leydig cell volume), and severe oligospermia or absolute azoospermia typically within 3 to 4 months of use.

Recovery of spermatogenesis after discontinuation of T treatment is dependent on the duration and intensity of treatment along with baseline fertility status. In a study of 271 men, median time to regain sperm counts of more than 20 million was 3.7 months and only 46% returned to baseline at an average of 6.7 months.

It is critical to understand that men with impaired fertility before the initiation of TT may remain permanently azoospermic. All men of child-bearing age should be asked before the initiation of TT whether they are considering fathering children. A recent disturbing study revealed that 25% of urologists reported using T to treat infertility.
Fig. 2. The changes in sperm concentration with log scale during the study period. Values were expressed as the mean ± sem. C, S, E, and R indicate the control, suppression, efficacy, and recovery phases, respectively.

4. Treatment of men with hypogonadism

b. Non testosterone therapies

INFERTILITY: SEMEN ANALYSIS

Gonadotropins (only FDA-approved medication)

Clomiphene citrate (CC)

Aromatase inhibitors (AI)

Other SERMs (selective estrogen receptor modulators= raloxifene)

Others (selective androgen receptor modulators, SARMs)
Infertility: it takes two to tango!!!

• Fertility is a complex multifactorial process

• While robust endpoints such as pregnancy and live birth are the key outcomes, surrogate endpoints such as analysis of spermatogenesis and semen analysis are often required
5. Fertility concerns: basic semen analysis, sperm function and quality assays
Semen analysis is useful in both clinical and research settings, for investigating male fertility status as well as monitoring spermatogenesis during and following male fertility regulation and other interventions.
## New WHO guidelines, 2010

<table>
<thead>
<tr>
<th>Parameter</th>
<th>&quot;New reference values&quot; [lower 95% C.I.]</th>
<th>Previous reference values [range]</th>
</tr>
</thead>
<tbody>
<tr>
<td>Viability (% alive/total sperm)</td>
<td>58% (C.I.= 55-63)</td>
<td>&gt;75%</td>
</tr>
<tr>
<td>Concentration (millions/ml)</td>
<td>15 x 10⁶/mL (C.I.= 12-16)</td>
<td>20-200 x 10⁶/mL</td>
</tr>
<tr>
<td>Total motility (%)</td>
<td>40% (C.I.= 38-42)</td>
<td>-</td>
</tr>
<tr>
<td>Progressive motility (%)</td>
<td>32% (C.I.= 31-34)</td>
<td>&gt;50%</td>
</tr>
<tr>
<td>Morphology (% strict criteria)</td>
<td>4% (C.I.=3-4)</td>
<td>5-14%</td>
</tr>
</tbody>
</table>
Basic semen analysis

Semen data: volume, physical characteristics, and sperm data: concentration, motility, total motile/ejaculate (raw and processed), and morphology (monomorphic and polymorphic defects)
Sperm Migration and Interaction with the Oocyte

- ZP binding and induction of acrosome reaction
- Hyperactivation
- Priming effect of progesterone and follicular fluid
Critical sperm functions: sequential analysis
(Oehninger, Franken, Kruger, F&S, 1997)

- Hyperactivation
- ZP binding
- ZP-induced acrosome reaction
- ZP penetration
- Egg activation
- Pronuclear formation
- Fusion
- Ca²⁺

ZP = zona pellucida
Ca²⁺ = calcium
Analysis of ejaculated spermatozoa

• Basic and extended semen analysis
• Sperm function tests
• Assays to monitor sperm quality:

Chromatin structure and DNA integrity/fragmentation
1. Sperm function tests: bioassays of gamete interactions

Research procedures as per WHO laboratory manual (2010)

• A. Sperm-zona pellucida binding assays

• B. Acrosome reaction testing

• C. Sperm-egg penetration assays
Age and semen quality

OVER THE HILL!
AGES study: age and genetic effects on sperm
(Eskenazi et al, 2003)
Relationship between male age and selected genomic defects in sperm

(Wyrobek et al, 2006)

SCSA = sperm structure chromatin assay
PCR = Polymerase chain reaction
FISH = Fluorescent in situ hybridization
DFI = DNA fragmentation index
ACH = achondroplasia gene
AS = Apert gene

Probabilities of producing an abnormal semen specimen with increasing age
Do sperm DNA integrity tests predict pregnancy with in vitro fertilization?  
*(Collins, Barnhart and Schlegel, F@S, 2008)*

Systematic review and meta-analysis= SCSA and TUNEL [Terminal deoxynucleotidyl transferase dUTP nick end labeling]  
(13 studies, 2,161 cycles)

**SCSA**

**TUNEL**  
*(Barroso et al, F@S, 2000,2009)*
American Society for Reproductive Medicine (ASRM), Committee Opinion, 2013

• Existing data do not support a consistent relationship between abnormal DNA integrity and reproductive outcomes.

• At present, the results of sperm DNA integrity testing alone do not predict pregnancy rates achieved through natural conception or with intrauterine insemination (IUI), IVF, or ICSI. However, further research may lead to validation of the clinical utility of these tests.
Concordance between SCSA DFI and TUNEL assay results
(Stahl et al, 2015)

The SCSA DFI is well-correlated with SA parameters, whereas TUNEL is not.

These data indicate that the SCSA and TUNEL assays measure different aspects of sperm DNA integrity and should not be used or discussed interchangeably.

At this time there are insufficient available data to guide selection of specific sperm DNA integrity assays for use in clinical practice.
4b. Treatment of hypogonadal states

Non testosterone therapies

INFERTILITY

Gonadotropins for secondary, central cases (only FDA-approved)

Clomiphene citrate (CC)

Aromatase inhibitors (AI)

Other SERMs, SARMs

Others? Combination of AI and hCG?
Pulsatile GnRH or hCG/hMG as effective treatment for men with hypogonadotropic hypogonadism: a review of 42 cases (Buchter et al, Eur. J. Endocrinol., 1998)

Figure 1 Pretreatment values of total testicular volume and increase of total testicular volume under GnRH or hCG/hMG therapy for 5–12 months. (□) Courses of GnRH treatment (n = 6) for IHH/KaLS patients. (●) Courses of hCG/hMG treatment (n = 16) for IHH/KaLS patients. (▲) Courses of hCG/hMG treatment (n = 14) for hypopituitarism patients.

IHH= idiopathic hypothalamic hypogonadism
KaLS= Kallman’s syndrome
**Figure 3** Duration of treatment (months as median) until appearance of first sperm and induction of pregnancy. Left column of each set: courses of GnRH treatment for IHH/KaI5 patients. Centre column: courses of hCG/hMG treatment for IHH/KaI5 patients. Right column: courses of hCG/hMG treatment for hypopituitarism patients.
Figure 4 Development of sperm concentrations until induction of pregnancy. (□) Courses of GnRH treatment ($n = 4$) for IHH/KaIS patients. (●) Courses of hCG/hMG treatment ($n = 5$) for IHH/KaIS patients. (▲) Courses of hCG/hMG treatment ($n = 17$) for hypopituitarism patients.
Hypogonadism and infertility: other therapeutic alternatives

- An alternative approach to TRT is based on T restoration with selective oestrogen antagonists (SERMs, selective ER modulators) acting in the pituitary via the hypothalamic–pituitary–gonadal axis. One such drug widely used ‘off-label’ in this indication is clomiphene citrate (Clomid), which is a mixture of two geometric isomers with different properties.

- Enclomiphene citrate (enclomid, the trans-isomer of clomiphene, Androxal) has effects consistent with oestrogen antagonism whereas zuclomid (the cis-isomer) often acts as an agonist.

- The clearance of each isomer from the blood differs with zuclomid persisting for much longer. Clomiphene citrate is used to raise sperm counts in men previously on exogenous testosterone treatments and in men with prior steroid abuse.

- Although widely used in women and having been used for many years to increase LH, FSH and total testosterone (TT) in men with idiopathic infertility and/or secondary hypogonadism, Clomid is not approved by the European or Food and Drug Administration (FDA) for use in men.
Clomiphene Citrate
Presumed Sites of Action
Aromatase Inhibitors: Selective Estrogen Suppression

Letrozole (Femara®)

**Table 56.1. Classification of Aromatase Inhibitors**

<table>
<thead>
<tr>
<th>Specificity/Potency</th>
<th>Type I Inhibitors</th>
<th>Type II Inhibitors</th>
</tr>
</thead>
<tbody>
<tr>
<td>1st Generation</td>
<td>4-hydroxy-androstene-dione Formestane</td>
<td>Aminogluthethimide (Cytadren®)</td>
</tr>
<tr>
<td>2nd Generation</td>
<td>Exemestane (Aromasin®)</td>
<td>Fadrozole</td>
</tr>
<tr>
<td>3rd Generation</td>
<td>Anastrozole (Arimidex®) Letrozole (Femara®) Vorozole</td>
<td></td>
</tr>
</tbody>
</table>

**Diagram:**

- Aromatic ring structure with nitrogen and halogen substitutions.
The role of estrogen modulators in male hypogonadism and infertility (Rambhatla et al, Rev Urol, 2016)
Important facts
(Rambhatla et al, Rev Urol 2016)

- High levels of **intratesticular T** are necessary for normal spermatogenesis

- In men **estrogen (E)** derives mainly from aromatization of T in adipocytes (aromatase is also present in bone, brain and hypothalamus)

- Animal studies suggest that high **intratesticular E levels** are associated with impaired steroidogenesis and spermatogenesis

- Despite success in some studies there are no long-term data evaluating the efficacy of AIs, and therefore their **use for hypogonadism cannot be routinely recommended at this time**
# Potential clinical uses of SERMs and AIs in Men’s Health

<table>
<thead>
<tr>
<th>Drug</th>
<th>Mechanism of Action</th>
<th>Effect on Testosterone</th>
<th>Effect on LH</th>
<th>Effect on Estradiol</th>
</tr>
</thead>
<tbody>
<tr>
<td>Clomiphene</td>
<td>$E2R_A$</td>
<td>↑</td>
<td>↑</td>
<td>↑</td>
</tr>
<tr>
<td>Tamoxifen</td>
<td>$E2R_A$</td>
<td>↑</td>
<td>↑</td>
<td>↑</td>
</tr>
<tr>
<td>Anastrozole</td>
<td>AI</td>
<td>↑</td>
<td>↑</td>
<td>↓</td>
</tr>
<tr>
<td>Letrozole</td>
<td>AI</td>
<td>↑</td>
<td>↑</td>
<td>↓</td>
</tr>
</tbody>
</table>
Multicenter, RCT of enclomiphene citrate (ECC) versus androgel

(Kim et al, BJU International, 2015)

Enclomiphene: not FDA approved

![Graph showing mean morning TT concentration with ECC, T, pooled enclomiphene citrate, testosterone gel, and placebo.]
Multicenter, RCT of enclomiphene citrate (ECC) versus androgel

(Kim et al, BJU International, 2015)

Enclomiphene: not FDA approved
Oral enclomiphene citrate (not FDA-approved) raises T and preserves sperm counts in obese hypogonadal men, unlike topical testosterone.
A Randomized Prospective Double-Blind Comparison Trial of Clomiphene Citrate (CC) and Anastrozole (AZ) in Raising Testosterone in Hypogonadal Infertile Men (Helo et al, J Sex Med, 2015)

**Figure 1** Total testosterone levels at baseline, 6, and 12 weeks with clomiphene citrate and anastrozole. $P < 0.05$ at 6 and 12 weeks. $x =$ clomiphene citrate; $\Diamond =$ anastrozole.
**Figure 2** Total testosterone to total estradiol ratio at baseline, 6, and 12 weeks with clomiphene citrate and anastrozole. $P < 0.05$ at 6 and 12 weeks. $\times =$ clomiphene citrate; $\diamond =$ anastrozole.
<table>
<thead>
<tr>
<th>Parameter</th>
<th>AZ Group</th>
<th>CC Group</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Semen volume baseline (mL)</td>
<td>2.48 ± 0.34</td>
<td>2.69 ± 0.34</td>
<td>0.6</td>
</tr>
<tr>
<td>Semen volume 12 weeks (mL)</td>
<td>3.15 ± 0.51</td>
<td>2.20 ± 0.54</td>
<td>0.2</td>
</tr>
<tr>
<td>P value for volume from baseline to 12 weeks</td>
<td>0.34</td>
<td>0.39</td>
<td></td>
</tr>
<tr>
<td>Concentration baseline (M/mL)</td>
<td>32.7 ± 12</td>
<td>32.0 ± 12</td>
<td>0.96</td>
</tr>
<tr>
<td>Concentration 12 weeks (M/mL)</td>
<td>26 ± 13</td>
<td>41 ± 13</td>
<td>0.44</td>
</tr>
<tr>
<td>P value for concentration from baseline to 12 weeks</td>
<td>0.70</td>
<td>0.62</td>
<td></td>
</tr>
<tr>
<td>Motility baseline (%)</td>
<td>37 ± 5</td>
<td>28 ± 5</td>
<td>0.26</td>
</tr>
<tr>
<td>Motility 12 weeks (%)</td>
<td>35 ± 5.4</td>
<td>41 ± 5.4</td>
<td>0.48</td>
</tr>
<tr>
<td>P value for motility from baseline to 12 weeks</td>
<td>0.87</td>
<td>0.08</td>
<td></td>
</tr>
</tbody>
</table>

AZ = anastrozole; CC = clomiphene citrate.
### Table 4  Comparison of semen analysis parameters at baseline, 6, and 12 weeks

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Emerging medications for the treatment of male hypogonadism
(Aydogdu and Swerldoff, Expert Opin Emerg Drugs, 2016)

Table 1. Competitive environment table: investigational drugs for the treatment of male hypogonadism.

<table>
<thead>
<tr>
<th>Compound</th>
<th>Company</th>
<th>Structure</th>
<th>Indication</th>
<th>Stage of development</th>
<th>Mechanism of action</th>
</tr>
</thead>
<tbody>
<tr>
<td>TSX-002 [36]</td>
<td>TesoRx Pharma, LLC</td>
<td>T (pro-liposomal oral formulation of unmodified T)</td>
<td>Hypogonadism</td>
<td>Phase 2</td>
<td>Oral T formulation</td>
</tr>
<tr>
<td>Trestolone [37]</td>
<td>Population Council Repros Therapeutics Inc.</td>
<td>7-α-Methyl-19-nortestosterone C₁₂H₁₆ClNO₈</td>
<td>Male contraceptive, osteoporosis</td>
<td>Clinical Phase 2</td>
<td>T formulation SERM</td>
</tr>
<tr>
<td>Enclomiphene citrate [38]</td>
<td>Repros Therapeutics Inc.</td>
<td></td>
<td>Hypogonadism</td>
<td>Phase 2</td>
<td>SARM</td>
</tr>
<tr>
<td>BMS-564,929 [39]</td>
<td>BMS</td>
<td>SARM</td>
<td>Muscle wasting osteoporosis</td>
<td>Phase 2</td>
<td>SARM</td>
</tr>
<tr>
<td>VKS211 [40]</td>
<td>Ligand Pharmaceuticals Inc.</td>
<td>SARM</td>
<td>Muscle wasting osteoporosis (hip fracture)</td>
<td>Phase 2</td>
<td>SARM</td>
</tr>
<tr>
<td>AC-262,356 [41]</td>
<td>Acadia Pharmaceuticals</td>
<td>C₁₉H₁₈N₂O</td>
<td>66% of the anabolic action of T, but only around 27% of its potency as an androgen</td>
<td>Preclinical</td>
<td>SARM</td>
</tr>
<tr>
<td>S-23 [42]</td>
<td>GTX</td>
<td>(2S)-N-[4-cyano-3-trifluoromethylphenyl]-3-[3-fluoro-4-chlorophenoxo]-2-hydroxy-2-methylpropanamide</td>
<td>Hormonal contraceptive</td>
<td>Preclinical</td>
<td>SARM</td>
</tr>
<tr>
<td>JNJ-28330835</td>
<td></td>
<td>SARM</td>
<td>Muscle wasting</td>
<td>Preclinical</td>
<td>SARM</td>
</tr>
<tr>
<td>S-40503 [39]</td>
<td>Kaken Pharmaceuticals</td>
<td>C₁₅H₁₂N₂O₃</td>
<td>Osteoporosis</td>
<td>Preclinical</td>
<td>SARM</td>
</tr>
<tr>
<td>LGD-3303 [39]</td>
<td>Ligand Pharmaceuticals</td>
<td>C₁₅H₁₀ClF₅N₂O</td>
<td>Osteoporosis</td>
<td>Preclinical</td>
<td>SARM</td>
</tr>
<tr>
<td>DMAU [44]</td>
<td>National Institute of Child Health and Human Development</td>
<td>C₃₁H₅₀O₃</td>
<td>Male contraceptive</td>
<td>Phase 1</td>
<td>Testosterone</td>
</tr>
<tr>
<td>11β-MNTDC [45]</td>
<td>National Institute of Child Health and Human Development</td>
<td>11β-Methyl-19-nortestosterone-17β-dodecylcarbonate</td>
<td>Male contraceptive</td>
<td>Phase 1</td>
<td>Testosterone</td>
</tr>
</tbody>
</table>

DMAU: Dimethandrolone undecanoate; SERM: selective estrogen receptor modulator; SARM: selective androgen receptor modulators.
6. Treatment of men with hypogonadism: the future

NO FERTILITY CONCERNS: T, OTHER ANDROGENS?

INFERTILITY
[Non testosterone therapies: not FDA-approved, except gonadotropins]

If the objective of a drug in men with secondary hypogonadism is to maintain fertility (or improve it) how should this goal be assessed?

- Knowledge of prior fertility status-
  - Presence of Co-morbidities-
  - Changes in semen parameters?
- Establishment of pregnancy? Time to pregnancy?
Goals of treatment

Drug

- Central effect (Hypothalamus-Pituitary)
- Testicular effect (sperm number and quality, somatic cells)
- Sperm functional effect: DNA fragmentation

Fertility potential: sperm thresholds?
Pregnancy: time to pregnancy and outcome?
Natural conceptions? ART?
Diagnosis of Male Infertility

Identification of Female Factors

Therapeutic Options

Urological

IUI

Medical

IVF/ICSI
The “ICSI era”