Saturday General Session

Testosterone Replacement Therapy in Men and Women

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Educational Objectives
By the end of this educational activity, participants should be better able to:
1. Choose appropriate candidates for testosterone replacement therapy using lab findings and clinical data.
2. Distinguish the differences between the hormone delivery systems available and select the right one for patients.
4. Discuss the newest evidence in hormone replacement therapy principles for women and men.

Speaker Disclosure
Dr. Hart has disclosed that she has no actual or potential conflict of interest in relation to this topic.
Testosterone Therapy in Men and Women

REBECCA HART, MD, FAAFP
ASSOCIATE CLINICAL PROFESSOR
MCGOVERN MEDICAL SCHOOL

Speaker Disclosure

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Goals and Objectives

By the end of this educational activity, participants should be better able to:

- Choose appropriate candidates for testosterone replacement therapy using lab findings and clinical data.
- Distinguish the differences between the hormone delivery systems available and select the right one for patients.
- Safely administer testosterone therapy in women and men.
- Discuss the newest evidence in hormone replacement therapy principles for women and men.

What Can We Realistically Cover in 1 Hour?

- I recently returned from a 2-day HRT update conference
- Just 1 lecture on Testosterone therapy update took 2 hours
- It’s impossible to go over all you need to know about Testosterone in 1 hour
- How do you learn more about this?
  - I include an extensive reference list for reading at end of lecture
  - Many hormone replacement workshops available to attend. This is Testosterone 101

“Hormonophobia”

THE IRRATIONAL FEAR OF HORMONES

Testosterone, Cardiovascular Risk, and Hormonophobia

“Hormonophobia”

Testosterone Replacement in Men

Testosterone, Cardiovascular Risk, and Hormonophobia

Journal of Sexual Medicine 11(6) · May 2014
Why Replace Testosterone?

1. To improve quality of life
2. To relieve bothersome symptoms of testosterone deficiency
3. A Low testosterone level is associated with an increased risk of prostate cancer
4. A Low testosterone level is related to an increase in all cause mortality
   1. 2 Major Landmark studies:
      2. Khaw, 2007
      3. Shores, 2012

Khaw 2007 Study
Testosterone Decreased Overall Mortality in Men

- 10 year prospective study
- 11,606 men
- 40-79 years old
- Found men with High Endogenous T => low mortality from CV disease and cancer
- Low endogenous T predicted CV disease
- High T = No increase in Prostate Cancer
- Paradoxically, the fear of Prostate Cancer has kept men from T treatment


Testosterone Decreased Overall Mortality in Men

- This study was of men with endogenous T (not treated)
- 41% decrease in chance of dying in men with higher testosterone level
  - T>564 compared to T<250
  - For each increase of 173, chance of dying went down 14%
  - Comparing T=300 to T=1000
  - 57% decrease in chance of dying at T=1000

- Shores Study

- 1000 male veterans, >40 yrs. old, 4 yrs. on T therapy
  - Total Testosterone < 250
  - 400 men treated with Testosterone
  - Mortality of the treated group was 10% vs. 20% controls
  - p value <0.0001
  - Decreased risk of death
  - Hazard ratio of 0.61
  - Prostate Cancer lower in the treated group = 1.6%
  - Versus in the untreated group = 2.0%

Shores MM et al. Testosterone Treatment and Mortality in Men with Low Testosterone Levels. J Clin Endocrinol Metab. 2012 April
Patient Selection: Who Needs Testosterone Replacement?

- "Testosterone Deficiency"
- "Hypogonadism" = Low Total T levels with symptoms
- "Andropause" = Low Testosterone with Symptoms
  - Less sudden than menopause, but causes long term consequences
- Testosterone decline can begin as early as age 30
- From age 25-75 can see a 35-60% decline in Total T

Clinical Symptoms of Low Testosterone

- Fatigue
- Weight Gain
- Lack of Vigor
- Hair Loss
- Testicular Atrophy
- Depression, mood changes
- Irritability
- Sexual issues
- Reduced Libido
- Decreased Morning Erections
- Decreased Sleep
- Decreased Muscle Strength
- Stiffness in muscles and joints
- Decreased effectiveness of workouts

Testosterone Deficiency is a Clinical Syndrome

- New Consensus Statement
- October 1, 2015
- Prague, Czech Republic
- Convened to address large amount of misinformation in media and medical journals regarding T deficiency and its treatment
- Goal was to find common ground among experts
- 18 participants
- 11 countries, 4 continents
- Specialties: Internal medicine, urology, endocrinology, diabetology, basic science researchers
- All with extensive clinical or research expertise with Testosterone
TERMINOLOGY

- Experts agreed on the following terminology:
  - Testosterone deficiency (TD) is the preferred term for signs and symptoms related to low levels of serum testosterone
  - Preferred over "hypogonadism, late-onset hypogonadism", and others
  - Testosterone therapy (TTherapy) is the preferred term for the treatment with testosterone products
    - Over "testosterone replacement therapy"

Nine Resolutions Passed Unanimously

1. Testosterone deficiency (TD) is a well-established, significant medical condition that negatively affects male sexuality, reproduction, general health, and quality of life.
2. Symptoms and signs of TD occur as a result of low levels of testosterone, and may benefit from treatment regardless of whether there is an identified underlying etiology.
3. TD is a global public health concern.
4. Testosterone therapy for men with TD is effective, rational and evidence based.
   - Morgentaler et al, Mayo Clin Proc, in press

Nine Resolutions

1. There is no T concentration threshold that reliably distinguishes those who will respond to treatment from those who will not.
2. There is no scientific basis for any age-specific recommendations against the use of TTherapy in adult men.
3. The evidence does not support increased risks of cardiovascular events with TTherapy.
4. The evidence does not support increased risk of prostate cancer with TTherapy.
5. The evidence supports a major research initiative to explore possible benefits of TTherapy for cardiometabolic disease, including diabetes.

CLINICAL CONSIDERATIONS

Testosterone as a Pharmaceutical

- Began in 2000
- First commercially available Testosterone gel available to US physicians
- Only 16 years on the US market

Criticisms and Expert Responses

<table>
<thead>
<tr>
<th>Common Criticisms of TTherapy</th>
<th>Expert Responses from Consensus Conf</th>
</tr>
</thead>
<tbody>
<tr>
<td>Low T doesn’t exist</td>
<td>False. Well established condition. Low T is informal term, like heart attack for MI.</td>
</tr>
<tr>
<td>Symptoms of TD don’t merit treatment, especially low libido and fatigue</td>
<td>Symptoms are bothersome to many men. Relief of these symptoms is of considerable value.</td>
</tr>
<tr>
<td>Therapy is risky</td>
<td>All treatments entail risk. Primary risks of TTherapy are known, manageable, reversible. Evidence fails to support PCa and CV risk.</td>
</tr>
<tr>
<td>Therapy increases risk of VTE – pulm embolism, DVT</td>
<td>Evidence reveals no increased risk of VTE with TTherapy.</td>
</tr>
<tr>
<td>Therapy is investigational/experimental</td>
<td>False. Therapy has been standard medical treatment for &gt;70 yrs with well-documented results.</td>
</tr>
<tr>
<td>Decline in T represents normal aging and does not merit treatment</td>
<td>Age alone has little impact on T levels. No justification to single out TD deficiency as not deserving of treatment among many age-related med conditions (e.g., CVD, cancer).</td>
</tr>
</tbody>
</table>
Contraindications

- Elevated PSA (caution >2.5)*
- Allergy to cotton seed oil if injection planned
- Known hypersensitivity to the drug
- Males with carcinoma of the breast
- Males with known or suspected carcinoma of the prostate gland
- Patients with serious cardiac, hepatic, or renal disease

Adverse Reactions

- Acne
- Hair Loss or Growth
- Irritability
- Mood Swings (injections)
- Local Reactions such as injection pain, infection
- Fluid Retention
- Decreased Sperm Count – Can go to Zero
- Gynecomastia from aromatization

Adverse Effects from T Metabolism

- Aromatization causes Estrogen to increase
- Irritability
- Mood swings
- Weight gain
- Gynecomastia
- Excess 5 alpha reductase causes DHT to increase
- Acne
- Hair Loss

Labs, Baseline

- Baseline T level - 
  - Early morning Testosterone most accurate = highest of the day
- PSA
- CBC – H and H
- LH (rule out secondary hypogonadism – pituitary failure)
- Useful for younger patients presenting
- Consider prolactin in these patients
- Consider lipids and HgA1c - r/o vasculopathy
- Chem 20
  - Assess for existing serious Cardiac, Renal or Liver Disease

Method Selection

- Gels or Creams
- Patches
- Injections
- Pellets

Gels

- Alcohol-based gel that contains 1% non-esterified testosterone
- Alcohol considered the best carrier as it absorbs rapidly
- Fast-acting once absorbed by the skin
- Must be applied 1-2 times daily to maintain T levels
- Some are recommended to apply to the underarms, some to the shoulder
- Available in either unit-dose packets or multiple-dose pumps
- The unit-dose packets contain either 25 mg or 50 mg of testosterone
- Approximately 10% of the applied testosterone from the packets is absorbed into the system, resulting in an effective dose of 2.5 mg or 5.0 mg respectively
- Interesting Fact:
  - On average, men produce 6 to 8 mg of testosterone daily
  - Women make about 12 times less than men every day
Creams

- Available commercially or compounded
- Also both cream and gel formulations of testosterone can be made by compounding pharmacies
- Creams are typically safflower oil-based
- Applied once or twice daily to maintain T levels
- Can cause skin irritation or allergy
- Care must be taken to avoid skin-to-skin contact with a partner at the site of application
- Transfer of the testosterone from the site can be prevented by keeping the area covered
- Apply in the morning, shower before bed to avoid giving to others

Compounded Creams and Gels

- Compounded testosterone creams and gels can be mixed by compounding pharmacies, and are similar in dosing, application, and precautions as the commercially available products
- There are two advantages of using compounding pharmacies for testosterone gel or cream
  - Cost - low
  - Customized dosage

Transdermal Patches

- Apply to the back, abdomen, thighs, or upper arms
- Patches come in two doses: 4.0 mg/patch and 6.0 mg/patch
- Eliminates the problem with skin contact with a partner
- Dosages will vary between 4.0 mg - 10 mg daily, by applying a single patch or combination of patches

Dosages Transdermal

<table>
<thead>
<tr>
<th>Type</th>
<th>Strength of T</th>
<th>Frequency/Strength</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gel #1 (An)</td>
<td>25-50 mg/packet</td>
<td>Once or twice daily</td>
</tr>
<tr>
<td>Gel #2 (T)</td>
<td>50 mg tube</td>
<td>Once or twice daily</td>
</tr>
<tr>
<td>Gel #3 (Ax)</td>
<td>30mg/1.5ml</td>
<td>1-4 pumps/day</td>
</tr>
<tr>
<td>Patch 1 (An)</td>
<td>2.5 and 5 mg patch</td>
<td>One patch daily</td>
</tr>
<tr>
<td>Patch 2 (%)</td>
<td>4mg-10 mg daily</td>
<td>One patch daily</td>
</tr>
</tbody>
</table>

Injections

- Testosterone Cypionate, USP 200 mg/ml
- Administered in cotton seed oil (allergies?)
- Must be metabolized to testosterone, cypionate ester must be detached via hydrolysis
- Testosterone cypionate: Chemical formula = testosterone + cypionic acid
  - It is a slow-acting ester with a release time between 8-10 days
- Inject once weekly to once every 3 weeks depending on hormone levels
- Check levels about 5 days after dose for peak. Optimum 800-1100

Testosterone Cypionate

- 200 mg/ml
- For injection
- Usually start 1 ml q 2 weeks and monitor levels and response
- Average doses range 50-150 mg IM or SQ per week
- Many people start with 200mg every 2 weeks - can have nadir
- 10 ml vial may cost around $30-50 with insurance. Can last up to 5 months
- Prepared in Cottonseed oil
Testosterone Undecanoate
- FDA approved recently Testosterone Undecanoate (after 3 failed trials)
- A long-acting depot formulation of testosterone in castor oil and benzyl benzoate
- Available as a single-use vial. Dosage titration is not necessary. Following the first intramuscular injection of 3 mL (750 mg), a second 3 mL dose is injected 4 weeks later, and then 3 mL is injected every 10 weeks thereafter.
- Problems limiting use:
  - Severe complications related to post injection reactions
  - Primarily pulmonary microembolism and anaphylactic reactions
  - Some requiring hospitalization

"Anabolic Steroids..."
- Testosterone propionate:
  - Chemical formula small: testosterone + ester of propionic acid
  - Testosterone propionate is a fast-acting ester with a release time of 3-4 days
  - Injected 1-3 times a week
  - Not used by medical professionals - used in the body building arena
  - Can be easily abused and cause very high T levels
  - At high levels can cause “steroid Rage”
  - Generally a more painful injection, with swelling and noticeable pain around the injection site.

Testosterone Propionate
- SHORT ACTING
- Half Life is short
- Usually injected every 3 days or so
- Abused, some men injecting daily
- Not available in pharmacies

Pellet Therapy
- Available in the US, some are FDA approved
- Free testosterone, not an ester
- Microcrystalline pressed together with steric acid
- Pellets insert into fatty tissue, subcutaneously
- Produce stable blood levels over longer periods of time, usually 6-8 months
- Negatives: Can cause local inflammation, infection and expulsion
- Cost similar to gels, patches
- Dosage: Calculators available to individualize
- Usually dose range between 1200 and 2400 mg for 4-6 months depending on age and weight

Comparison of Methods
<table>
<thead>
<tr>
<th>Gels / Patches</th>
<th>Injections</th>
</tr>
</thead>
<tbody>
<tr>
<td>Expensive $$$</td>
<td>Budget friendly $</td>
</tr>
<tr>
<td>Messy (not patched)</td>
<td>Easy to do</td>
</tr>
<tr>
<td>Inconvenient</td>
<td>Moderate hormone levels achieved</td>
</tr>
<tr>
<td>Non-Invasive</td>
<td>Can affect others if skin contact</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Pellets</th>
</tr>
</thead>
<tbody>
<tr>
<td>Expensive $$$</td>
</tr>
<tr>
<td>Internal, no mess</td>
</tr>
<tr>
<td>Not available in pharmacies</td>
</tr>
</tbody>
</table>

Monitoring
- Peak Level - 4-5 days after shot; 1 month after pellet; morning level after gel
- PSA - (don’t do gel/cream on day of test)
- Monitor PSA
- CBC – Hemoglobin > 18.5, phlebotomy
- Estradiol level – Aromatization if >5% of Total T
- If so, Add DIM – Diindolemethane, 300mg/day
Aromatization

Aromatase Inhibitors

- Diindolemethane, DIM
  - 300 mg daily
  - Over the counter
  - From broccoli and other cruciferous veggies
  - A natural product – easy to use, no side effects
- Commercially available aromatase inhibitors such as anastrozole
  - ***Not FDA approved for this use
  - Used for breast cancer
  - Literature recommends start at 1 mg per week, monitor response

Unintended Consequence of Aromatase Inhibition

- Pathway to estradiol is blocked
- More T can be converted to DHT.
- DHT causes:
  - Acne
  - Baldness

SAFETY

Is Testosterone Therapy Safe?

- In the extensive literature review by Dr. Morgentaler on CV risk:
  - VIDEO
  - https://www.youtube.com/watch?v=3j232kdcnSQ
- Multiple studies showed that low testosterone levels are correlated with more atherosclerotic lesions.
- Men treated with testosterone showed a decrease in the thickness of the carotid intima in some randomized trials.
- In men with known heart disease, those treated with testosterone had functional improvement over men treated with placebo.
- There was no evidence found that testosterone increases cardiovascular risk.
- Rather, testosterone deficiency is a risk factor for cardiovascular disease.

THE PROSTATE CANCER MYTH

- BASIS – ORIGINAL ARTICLE 1941
  - The study was done to see the effect of castration, estrogen, or testosterone on advanced metastatic cancer.
  - All men were castrated. 5 men were given estrogen, and 3 men were given testosterone.
  - Estrogen and castration caused reduction in levels of acid phosphatase.
  - Of the 3 T patients, results were reported for 2
    - 1 man had an erratic response of acid phosphatase – fluctuations of levels.
    - 1 man had a rise of acid phosphatase.
  - The final conclusion was based on 1 man treated with testosterone for 18 days.
  - The main finding of the study was that castration or estrogen admin. reduced acid phosphatase levels in advanced metastatic cancer.
  - The over-interpretation of this study was that testosterone causes prostate cancer. This was NOT the purpose of the study.
  - However, this MYTH propagated throughout the urologic world that Testosterone activates prostate cancer. All based on 1 patient….
Prostate Cancer - No Effect by T level

- Roddam 2008
- Global pooled longitudinal study of endogenous hormones and PCA risk
- THEY FOUND:
  - Highest 20% T level vs Lowest 20 % T level = no difference in risk of prostate cancer.

Roddam et al, Endogenous sex hormones and prostate cancer: a collaborative analysis of 18 prospective studies. JNCL 2008;100(3): 170-183

Is Testosterone Therapy Safe?

- Multiple recent studies - last 10 years
- Summary of all - Accepted in literature now that testosterone levels that are low predispose more to Prostate Cancer.

"There is not now - nor has there ever been a scientific basis for the belief that testosterone causes prostate cancer to grow"

Morgentaler 2006

- See full literature review in References: LASTPP slide.

Recent Controversy on Cardiovascular Risk

- JAMA published a paper in November 2013 stating that Testosterone therapy caused adverse cardiovascular events
- 2 months later, PLOS 1 paper – negative reports
- "Increased Risk of Non-Fatal Myocardial Infarction Following Testosterone Therapy Prescription in Men"
- A few days later, an FDA review of testosterone therapy was announced
- Preponderance of evidence showed before this time that testosterone therapy actually reduced cardiovascular risk factors.
- The press went wild, and many people became afraid of using testosterone.
- HORMONOPHOBIA!
- Let's look at the details of all of this:

JAMA Article

- Increased Risk of Non-Fatal Myocardial Infarction Following Testosterone Therapy Prescription, Vigen et al.
- Observational study, Retrospective study, VA, 2013 November
- Conclusion: Men with low levels of testosterone who got a prescription for Testosterone had a rate of CV death of 25% at 3 years, whereas the untreated men had a rate of death of 19%.
- The statistical methodology was new and not extensively validated:
  - Events that treated men had were counted as more than 1 event.
  - Events that untreated men had were counted as less than 1 event.
  - The numbers actually showed that the actual percentage of individuals with events in the treated group had half the event rate - 10.1% versus 21.2%.
  - The math was actually incorrect!!!
  - It also showed that in this all male study, 10% of the participants were women!

Vigen study, RESULTS REPORTED

- Conclusions OF STUDY:
  - Treatment group at 120, control group 120
  - Definition of "treatment" was at least 1 RX in system
  - 20% only had 1 rx
  - 60% had more than one
  - 69% had repeat testosterone level, mean 222 (60 U/L)
  - Treatment group may or may not have had more than one RX.
  - Patients started out Tdeficient, ended up Tdeficient
  - No assessment of LE, DHT or Hg/hct

Problems with the study
- Why were some patients started on T but others not? Sicker?
- Treatment group 175, control group 200.
- Definition of "treatment" was at least 1 RX in system
  - 20% only had 1 rx
  - 60% had more than one
  - 69% had repeat testosterone level, mean 222 (60 U/L)
- Treatment group may or may not have had more than one RX.
- Patients started out Tdeficient, ended up Tdeficient
- No assessment of LE, DHT or Hg/hct
Finkle Study, “Increased risk of non fatal MI following testosterone therapy Rx in men”,

- Results: ratio of non-fatal MI post Rx/Pre Rx
  - All ages: 1.36
  - >65: 2.19
  - >65 heart history: 2.16
  - <65 no heart Hx: 2.21
  - <65 not significant: NS
  - <65 no heart history: NS
  - <65 yes heart history: 2.9
  - Use of PDE5I: NS????

- Scary???

2014 Study = Finkle Problems with Methodology

- Study claims risk of non-fatal MI greater in 3 months after T therapy compared to year before T
- No info on fatal MI or CV mortality or all cause mortality
- No info on testosterone serum levels at all
- No info on dose, interval, or preparation used
- Was dose adequate to raise serum levels?
  - Was T used in long interval plan with low levels in second week?
- Did patients take the Testosterone?
- No information on clinic a effects of treatment
- Why were some given T versus PDE5I?
- Patients on nitrates not rx’ed with PDE5I

- Poor study, useless results.
- Yet, false conclusion was all over the press.

THIS CAUSED MASSIVE HORMONOPHOBIA

Remember:
Criteria for Good Scientific Studies

- Is the data reliable?
- Statistics done correctly?
- How was the study designed?
- Was data done via Convenience bias to get a paper published easily?
- What were the limitations of the study?
- How strong was the conclusion?

Randomized controlled double blind is the strongest level of evidence.

Testosterone Safety

- For more information on this safety issue, please see Dr. Morgentaler’s presentation:
  - European Association of Urology meeting:
    - “Testosterone Therapy and Hormonophobia” Cardiovascular Risk, the Media and the Authorities”
  - https://www.youtube.com/watch?v=NP2oRG1jRO
  - VIDEO
Testosterone Therapy in Women

Menopausal Symptoms - Typical

- Estrogenic symptoms
  - Vaginal dryness
  - Dry, lifeless skin
  - Hot flashes
  - Bloating
  - Weight gain

- Testosterone symptoms
  - Low libido
  - Low energy
  - Decreased muscle mass
  - Night sweats
  - Depressed mood
  - Poor sleep

Does Every Woman Need Testosterone?

- No, Only those with androgen deficiency syndromes
  - Low total testosterone level (generally <20 mcg/dl)
  - hFSD – hypoactive sexual desire disorder is only current indication
  - or
  - Low testosterone symptoms such as:
    - Low libido
    - Difficulty with climax
    - Lack of energy
    - Fatigue
    - Poor muscle tone
    - Poor sleep quality

Consensus Statement of Testosterone Replacement in Women

- No consensus statement exists from any group or organization worldwide. Next year leading physicians and researchers worldwide will convene to develop this statement.
- No consensus yet of “normal” testosterone levels in women.
- Stay tuned!

2017 CONSENSUS STATEMENT
### Safety of Testosterone in Women

- The predominant data shows that low dose testosterone use is safe in regards to the breast and endometrium with experimental data suggesting a decrease in estrogen-induced breast epithelial proliferation, and no adverse cardiovascular effects.

### Testosterone is Protective to the Breast!

- Predominant data from in vitro studies have shown that androgens have apoptotic and antiproliferative effects, not stimulatory effects.
- Animal models have shown similar results to in vitro studies, finding that androgens inhibit breast cancer growth.
- Hyperandrogenism in patients with polycystic ovarian syndrome with elevated levels of endogenous testosterone is not associated with an increased risk of breast cancer and may, in fact, be protective.
- Another human model with excess of testosterone is female-to-male transgenderism, in which genotypic women are treated with large doses of exogenous testosterone with no increased risk.
- High-dose androgen therapy also has been effective in treating patients with advanced breast cancer.
- Thus, the preponderance of data suggests that use in females is not associated with an increased risk of breast carcinoma.

### Testosterone and Breast Cancer

- From multiple studies, we now know that testosterone is protective to the breast.
- Testosterone down regulates the alpha estrogen receptor.
- This is the receptor that is upregulated in breast cancer.

### Adelaide, South Australia Study

- Cases of Breast Cancer/100,000 women years:
  - With estrogen, prog and testosterone: 283 cases
  - With estrogen-progesterone only: 380 cases
  - With estrogen and testosterone only: 235 cases

### Safety in Women – Summary of Studies

- **Lipids:**
  - Lipid profile women with oral, but not transdermal testosterone
  - Additionally, models of superphysiologic testosterone levels, such as PCOS, have not shown an increased risk of breast cancer
  - No increase in risk of hepatotoxicity, endometrial hyperplasia, or behavioral hostility
  - Short-term studies, up to 2 years
  - Levels at the upper portion or slightly above the reference range

- **Cardio:**
  - No adverse cardiovascular effects including changes in blood pressure, blood viscosity, arterial vascular reactivity, hypercoagulable states, and polycythemia
Forms of Testosterone for Women

- **Creams, Gels** - compounded
  - Dosage usually ranges from 1-10mg/ml rubbed into thin skin area daily
  - Available as mixed compounds with Estrogen and Progesterone
- **Pellets** - Available in individualized dosages
  - Dosage ranges from about 50mg to 185 mg for 4-6 months therapy

Other Routes of Administration

- **INJECTIONS**
  - Some clinics offer this in very low dose
  - No data available on this dose
  - Think about risk of unauthorized female use of testosterone injections if you allow home test shots for men.
  - (Male dose - 200mg/cc = way too high for females)
- **PATCH**
  - Unavailable for women

Dosage of Testosterone

- Very small doses are successful to achieve results without side effects
- \( \frac{1}{12} \) THE AMOUNT NEEDED FOR MEN
- Creams range from 1-10 mg per day
- \( \frac{1}{2} \) to GOOD EFFECTS WITH NO SIDE EFFECTS
- Pellets range from 50-200 mg lasting 3-6 months per insertion
- Dose Calculators available from vendors

Use a Precise Symptom Checklist to Follow Patients

- FOLLOW UP 6 WEEKS AFTER THERAPY WITH TESTOSTERONE LEVEL, ESTRADIOL LEVEL, AND CBC
- CHECK SYMPTOM RELIEF AT THIS TIME.
- Use a symptom checklist to follow before and after effects

Adverse Effects of Excessive Testosterone Therapy in Females

- Hair growth
- Acne
- Deepening of voice
- Hair loss (DHT effect) or
- Hair growth (Chin, Lip)
- Swelling (edema)
- Weight Gain
- Virilization
- Clitoromegaly (very high dose)
- *Remember that Testosterone is used for Female to Male transformation*
**Treatment of Testosterone Side Effects in Women**

<table>
<thead>
<tr>
<th>Side Effect</th>
<th>Treatment</th>
<th>Mechanism</th>
</tr>
</thead>
<tbody>
<tr>
<td>Acne</td>
<td>Evening Primrose oil</td>
<td>Androgen receptor</td>
</tr>
<tr>
<td>Hirsutism</td>
<td>Spironolactone</td>
<td>Androgen receptor</td>
</tr>
<tr>
<td>Hair Loss</td>
<td>Saw Palmetto or finasteride</td>
<td>5 alpha reductase inhibitor of T to DHT</td>
</tr>
<tr>
<td>Swelling</td>
<td>HCTZ temporarily</td>
<td>Diuretic</td>
</tr>
</tbody>
</table>

*Can decrease Testosterone dose in all cases*

**Summary**

- Testosterone replacement improves the lives of men and women.
- Carefully evaluate your patients' symptoms and laboratory evidence before prescribing.
- Give individualized therapy and follow levels and patient response to be sure dosage and delivery method are optimal.
- Sufficient studies exist now so that you can safely prescribe hormones to your patients and improve their quality of life.

**Questions?**

THANK YOU!

Contact Dr. Hart:
Office Phone: 281-334-2826
Office Address: 201 Enterprise, Suite 900, League City, Texas 77573

**References: Testosterone**

- Association of Testosterone Therapy with Mortality, Myocardial Infarction and Stroke in Men with Low Testosterone Levels, JAMA November 2013
- Finkle et al, “Increased Risk of Non-Fatal Myocardial Infarction Following Testosterone Therapy Prescription in Men” PLOS one, January 2014
References: Female Hormone Replacement Therapy


References: Menopause

- Dimitrakakis et al Breast cancer incidence in postmenopausal women using testosterone in addition to usual hormone therapy. 2004 Menopause Sep-Oct;11(5):531-5
- NIH State of the Science Conference Statement on Management of Menopause-Related Symptoms, March 21-23, 2005

References: HRT

- Lobo RA: Where are we 10 years after the Women’s Health Initiative J Clin Endocrinol Metab. 2013 May; 98(5): 1771-80.
- NAMS 2004 Position Statement
- ACOG Hormone Therapy October 2004 Supplement to Obstetrics and Gynecology
- NIH State of the Science Conference Statement on Management of Menopause-Related Symptoms, March 21-23, 2005

References Re: Prostate Cancer

- Huggins, C et al, Cancer res. 1941;1:293.

BASIC HRT for next 27 slides are for your information - not presented in talk

Estrogen and Progesterone Replacement therapy in WOMEN

WHAT YOU NEED TO KNOW ABOUT HRT

First, A little Chemistry - Know your Estrogens

- In the human body, there are 3 estrogens made by the ovary
  - E1 - Estrone
  - E2 - 17-beta-estradiol
  - E3 - Estriol
Estrone (E1)

- Main estrogen made by women post-menopause
- Ovary not making estrogen, body wants estrogen, so fat cells take over production.
- Adipose cells make Estrone
- High levels can increase cancer risk

Estrone - 3 Subtypes

- 2-hydroxy estrone
  - The “good” estrogen
  - Protective against cancer when methylated - Methylation is protective
- 16-hydroxy estrone
  - May increase risk of breast cancer
  - High levels associated with inflammation, toxicity, hypothyroidism
- 4-hydroxy estrone
  - The “bad” estrogen
  - Mutagenic - Can directly damage DNA and cause mutations
  - See Yasui et al
  - Present in greater quantities in women with folic acid deficiency or women with fibroids

Estrone 2/16 Ratio

- Ratio of 2 OH-estrone to 16-OH-estrone
- Ratio too low - associated with an increased risk of breast cancer
- Ratio too high - associated with osteoporosis
- Has to be “just right”
- Can measure the 2/16 ratio in lab
- Estrogen Quotient (EQ) = E3/(E2+E1) = Estriol/Estrone + estradiol
  - EQ Less than 1 is poor. You want a level over 2 if possible!
  - Measured to evaluate the “good to bad” estrogen for risk assessment

E2 - Estradiol

- Human estradiol is the most potent of the estrogens
- Present in highest concentration in the premenopausal woman
- Estrone is 10X weaker than estradiol
- Estrol is 10X weaker than estradiol
- Controls 400 functions in the body
- Protects the brain
- Evidence supports benefits in neuronal survival against beta amyloid
- Functions to maintain bone structure, increase serotonin
- Decreases fatigue
- Is an Antioxidant
- Maintains memory
- Helps absorb calcium, magnesium, zinc

E3 - Estriol

- The Estrogen made in the largest quantity by the ovary (80%)
- Considered a “protective Estrogen”
  - Patients with More Estriol had lowered breast cancer rates in several studies. (Sillai et al.)
- It is the main estrogen for vaginal health
  - Restores vaginal pH
  - Benefits the Vaginal lining
  - Used in creams and gels to stimulate the growth of the vaginal wall and increase secretions of the vagina
  - Estrone is converted to Estriol
  - (Reaction is favored with iodine)

Know your Progesterones

- Progestins
  - Medroxyprogesterone Acetate
  - Norethindrone
  - Norethindrone Acetate
  - Progesterone
  - Molecularly equal to human progesterone
Recall the Issue with WHI

- Caused fear - most physicians to stop prescribing HRT
- CEE plus MPA arm of study had increased rate of Breast Cancer
  - Breast cancer: 8 more breast cancers in 10,000 women years
- Stroke and pulmonary embolism: 7 more in 10,000 women years
- CEE alone arm had reduced rate of risk
- MPA considered the offending agent (Medroxyprogesterone acetate)
- Risk of osteoporosis and colon cancer was decreased with HRT
- 2/3 of women were over 60 or over 10 yrs. post menopause
- Re-analysis continues...

WHI Re-analysis, Continued

- WHI reported aggregate results of all patients in the study - young and old
- Re-analysis looked at women within 10 years of Menopause (HERS study)
- Found risk reduction in breast cancer and cardiovascular risks of MI.
- Take Home: You can feel safe prescribing HRT to symptomatic patients within 10 years of menopause who have symptoms

Appropriate Patient Selection for HRT

- Younger than 60
- <10 years from menopause
- Symptomatic
- In women over 60
- Avoid in higher risk patient with diabetes, metabolic syndrome, hyperlipidemia
- If symptomatic and miserable, treat for the shortest time possible

Conjugated Equine Estrogen

What's really in it?

- These are the 10 sulfate esters in CEE
  1. Estriol
  2. 17β estradiol
  3. 17α estradiol
  4. Equilin
  5. 18b dihydroequilenin
  6. 17α dihydroequilenin
  7. Equilenin
  8. 17b dihydro equilenin
  9. 17α alpha dihydro equilenin
  10. Delta 8 estrone

- 4-hydroxy Equilin found to be mutagenic - 100% tumor rate
- Found increase risk of breast cancer in rodents injected with CEE
  Yasui M, Matsui S, et al. Mutagenic events induced by 4-hydroxyequilin in self shuttle vector/po1amid propagated in human cell
- So is it Safe?
**Is CEE Safe?**

- Maybe yes, maybe no. These were in hamsters, not humans.
- You don’t have to prescribe hormones that are not molecularly equal to human hormones.
- Jury is still out, but data is compelling.

**What Can I Prescribe? Hormones Molecularly Equal to Human Forms**

- **Pharmaceutical preparations** as well as compounded preparations available for patients:
  - 17 beta estradiol cream - 4 brand names
  - 17 beta estradiol patches - 4 brand names
  - Estradiol transdermal spray - 1 brand
  - Progesterone in peanut oil capsule - 1 brand name
  - Progesterone vaginal gel - 1 brand

- **COMPOUNDED**
  - Micronized progesterone compounded forms (capsules, troches, transdermal creams, vaginal suppositories)
  - Combination of estradiol and progesterone compounds
  - Combination of estradiol, estriol and progesterone (E1, E2 and Progesterone)

**State of the Art - Principles of HRT for Women**

- Use HRT to treat menopausal symptoms only. Use lowest dose and shortest time period. Treat to symptom control. Individualize dosing to the patient.
- Use hormones for HRT that are molecularly equal to human hormones.
- Prefer not use oral estrogen or testosterone.
- (1st pass effect – liver damage, liver tumorigenic effect)
- Inflammatory effect of estrogen worse in oral forms.
- Use Progesterone and Estrogen plus Testosterone if deficient - All 3 made by ovary.
- Use Estrogen and Progesterone together for women. Multiple benefits of progesterone found.
- Multiple different vehicles for delivery:
  - Cream, gels, pellets, patches
  - Can combine vehicles

**Individualization**

- Take into account all aspects of the patient’s history:
  - Family history - breast cancer? - ovarian or uterine cancer?
  - Individual history - Thromboembolism? High risk metabolic syndrome? Diabetes?
  - What has she tried already?
  - Severity of symptoms.
  - Other options – other meds that could relieve symptoms?
  - Sexual dysfunction? Does she need testosterone?
  - Take hormone levels = FSH, LH, testosterone, even thyroid levels.
  - Lab – chemistry, etc. Is there something else causing problems?

**Symptom Checklist**

- Helpful to isolate issues she may be having by hormone class.
- Many screening tools available.

**Menopausal Symptoms – Typical**

- **Estrogenic symptoms**
  - Vaginal dryness
  - Dry, lifeless skin
  - Hot flashes
  - Bloating
  - Weight gain

- **Testosterone symptoms**
  - Low libido
  - Low energy
  - Decreased muscle mass
  - Night sweats
  - Depressed mood
  - Poor sleep
Other Causes – Differential Diagnosis

Thyroid Disease
- Fatigue
- Malaise
- Dry skin
- Cold intolerance
- Swelling
- Hair thinning, etc.

Other Endocrine Abnormalities, etc.
- Metabolic syndrome
- Diabetes or pre diabetes
- Poor diet
- Poor sleep habits
- Depression
- CVD
- Anemia
- Hypocortisolism

Lab Studies
- FSH in menopausal range usually >23 per most labs
- Goal to reduce FSH by half with adequate estrogen
- Estrogen levels fluctuate wildly during the day, so FSH more accurate
- Lab- Total T <20 usually considered deficient by most authors
- No actual recommended values for Max T in literature, some authors recommend max of 150-250 at peak level. Most women can do well with T=60-100.
- Progesterone usually not tested, but can be by 24 hour urine samples or salivary
- Recommended to get a baseline mammogram and pap before starting therapy

Once You’re Sure it’s Menopause

- Begin Hormone Therapy
- Multiple modalities to choose from
  - Estrogen, progesterone, testosterone
  - Individualize, individualize, individualize

Treatment Options: Estrogens
- Estradiol cream
- Estradiol pill – 1st pass effect – not recommended
- Estradiol pellet – Direct to blood stream
- Estradiol patches – Commercially available
- Rings – Through mucous membrane of the vagina
- Transdermal spray!
- Vaginal Cream – For vaginal atrophy, not well absorbed systemically. Sometimes, this is the only therapy necessary
  - Estriol cream helps vaginal atrophy and prevents UTIs

Oral Estradiol
- Leads to higher 2 OH estrone and 16O H estrone metabolites
- Oral HRT is associated with increased CRP
- Oral estradiol raises triglycerides and VLDL
- Oral Estradiol increases the mean value of Prothrombin activation peptide and decreases mean anti-thrombin activity
- Oral Estradiol Increases SHBG

Compound Estrogen Cream Doses
- BEST = Estriol and Estradiol
  - No Estrone
  - Very low dose
    - Best 0.25 mg/ml
    - 0.25 mg Estriol and 0.05 estradiol
  - Low Dose
    - 0.5 mg/ml Best
  - Medium dose
    - 1 mg/ml Best
  - Higher dose
    - 1.5 mg Best
Progesterone

- Titrate to keep uterus from bleeding - oral works best
- Oral progesterone safe
- Use in women without a uterus for sleeplessness and anxiety if present
- Continuous
  - Commercially available products
  - Progesterone Capsule 100-200 mg qhs, usual dose
  - Compounded:
    - Mix estrogen with progesterone and titrate dose
    - Max dose: 400 mg progesterone daily, can divide bid
- Cyclic
  - For peri-menopausal patients with symptoms
  - Monthly menses - cycle to follow regular menstrual cycle