Depression and Altered Mood States in Peri and Post Menopausal Women: Understanding the Role of Sex Hormones.

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Objectives

- Investigate the global issue of depression and anxiety in women.
- Overview of the production and role female sex hormones.
- Understand the neurological, psychological and physiologic impact of androgens in the female patient.
- Interpretation of sub-optimal serum androgen levels in the female patient.
- Explore treatment options for sub-optimal androgen levels as well as understand the risks and benefits of androgen replacement therapy for the female patient.
- Glean insights from evidence based treatment outcomes utilizing case studies of androgen therapy in women.

Thought of the Day

"Too often we hold fast to the clothes of our forebears. We subject all facts to a prefabricated set of interpretations. We enjoy the comfort of opinion without the discomfort of thought." - John F. Kennedy

Defining Depression

The definition of non-major clinical depression holds a great deal of ambiguity. Depressive symptoms can be present that do not meet the diagnostic criteria of major depressive disorder (MDD), yet still have profound life altering consequences when they persist...

Thought of the Day

"...in a world of ready access to drugs, we are more prone to suffer from the disease of the cure than from the disease itself." - Thomas Szasz

Depression in Women: A Global Issue

Women are multi-functional, multi-relational and multi-role oriented!

Why is this important?

Women are multi-functional, multi-relational and multi-role oriented!

Hormone decline in the 35th decades of life can have a profound negative impact of quality of life (QOL) and sense of well-being.

Health Related Quality of Life (HRQOL) is paramount to overall sense of well being and productivity.

- Presenteeism vs Absenteeism.
The relationship between psychological symptoms of depression, anxiety and altered mood states and hormone deficiency in females plays a key role in HRQOL. A woman’s response to symptoms can have deleterious effects ranging from physiological, psychological, biosocial and behavioral outcomes. Only about 10% of women will report these symptoms to their primary care provider.

Many practitioners misunderstand and underestimate the encumbering effects of these symptoms. There is little consensus across National Guidelines regarding hormone replacement therapies. Confusion around the results of the WHI have left many providers with more questions than answers. There is confusion in the general medical and lay communities around the role of androgens in women.

The Women's Health Initiative (WHI) Why talk about it?

- The largest research trial to date focused on women's health.
- What was the focus? Outcomes?
- Because your colleagues & your patients will ask you about it.
- There is a great deal of confusion regarding the trial in the general medical and lay communities. Why?
- Post WHI, the notion was promoted that all hormone therapy products have a single class effect.
- After WHI trial results were published, people were typically referring to conjugated equine estrogen and progestins to mean every kind of estrogen and progesterone.
- We continue to unravel from this misuse of the terminology, study intention and results to this day, nearly 2 decades later.

What's missing from the conversation? Androgen insufficiency in women and the impact on HRQOL.

Dazed and Confused: Many healthcare Providers Lack Understanding

Many practitioners misunderstand and underestimate the encumbering effects of these symptoms. There is little consensus across National Guidelines regarding hormone replacement therapies. Confusion around the results of the WHI have left many providers with more questions than answers. There is confusion in the general medical and lay communities around the role of androgens in women.

Stages of Menopause: Based on Stages of Reproductive Aging Workshop (STRAW)*

**Menopause**
- A single day in time, defined as 12 months S/P last menstrual cycle

- Peri-Menopause - lasts 2-8 years
  - Early menopause transition
    - Menstrual irregularity
    - Frequent mood disturbances
    - Women report they feel “crazy”
  - Androgen decline peaks during this time

- Late menopause transition
  - Amenorrhea greater than 60 days
  - Possible vasomotor symptoms
  - Hormone related depression and anxiety at worst during this time secondary to major hormone fluctuations
  - Relationship strife in all areas of life reported

**Post-Menopause**
- Early post menopause
  - Lasts on average 2 years
  - Vasomotor symptoms, urogenital symptoms and psychosomatic complaints exacerbated
  - Bone loss rate increases rapidly*
- Late post menopause
  - Left untreated, symptoms persist throughout the lifespan
  - Vasomotor symptoms decline or cease
  - Urogenital symptoms, vaginal atrophy
  - Depression and anxiety continues to have a profound impact

**What about before the Menopause Transition (MT)?**

Estrogen Dominance = Androgen & Progesterone deficiency = Hormone imbalance

- Sources exogenous estrogens:
  - Oral Contraceptive Pills (OCP’s)
  - Xynoestrogens
  - Phytoestrogens
- Consequences of exogenous estrogens/estrogen dominance:
  - The body shuts down production of other hormones
  - Low Testosterone
  - Low Progesterone (heavy, painful menstrual cycle)
  - Low Natural production of Estrogen
  - Early Female Puberty
  - Premature disorders
- Increase risk of estrogen related cancers secondary to inability to metabolize and excrete estrogens correctly.
The Sex Hormones

- Estradiol, Progesterone AND Testosterone
- Hormone receptors are present on EVERY cell in the human body.
- Specifically androgen (testosterone) receptors are present in every body system.

Sources of Sex Hormones

**Endogenous Production:**
- Estradiol & Testosterone
  - Ovaries produce estradiol and testosterone in RNA and protein synthesis.
  - Estradiol is produced by fat cells (reduced fat cells = reduced estradiol).
  - Estradiol aromatized from testosterone.
- Progesterone
  - Carried by ovaries
  - Post-menopause = no progesterone

**Endogenous Sources:**
- DHT or DCP
- Hormones in our food supply: meat/dairy (estrogens)
- Environmental or exogenous hormones
- Domestic Products
- Medicines
- Water Supply
- Food Supply

Estrogen: Its not just about hot flashes!

- Estradiol's pivotal role in all major organ systems:
  - Key hormone of reproduction
  - Heart health (anti-inflammatory)
  - Bone density
    - Osteoporosis prevention (bone builder, along with testosterone)
  - Colon cancer
    - Low estradiol levels linked to increased rates of colon cancer
  - Bone density
    - Osteoporosis prevention (bone builder, along with testosterone)
  - Heart health (anti-inflammatory)
    - Mood alterations & depression
    - Dietary alterations & depression
    - Mental clarity, memory, cognition

Testosterone Its not just for men!

- Emerging data supports the greater role androgens, primarily testosterone, play in neuropsychology.
- Testosterone is the most abundant active hormone in men AND women:
  - Acts at cellular level with direct effect at the androgen receptor (AR)
  - Precursor for DHT and Estradiol (ER)

Testosterone A Woman’s Most Important Hormone?

- Androgen receptors are found on virtually every cell in the female human body, indicating the role they play in normal tissue homeostasis.
- Androgen replacement has been shown in women to:
  - Improve mood, QoL anxiety and depression, and improve sleep patterns.
  - Prevent osteoporosis, increase muscle mass, increase muscle strength, increase bone density, reduce odoral fat, reduce total cholesterol levels, reduce plaque formation, increase metabolism, manage PMS, reduce severity and frequency of migraine headaches, improve cognition and memory, and prevent Alzheimer’s disease.
  - An protective and preventative for breast cancer, even in breast cancer survivors.

**All of the above impact HRQOL!**
Testosterone & Depression

- Hundreds of studies support the relationship between androgens and depression in both women and men.
- Testosterone levels are lower in women, primarily testosterone in the premenopausal phase.
- In men, falling testosterone levels contribute to a higher risk of depression.
- Estrogen fluctuations exacerbate these symptoms during peri/ Menopause.
- Androgen levels are at peak in the menopause transition.
- Therapy and supplementation have been shown to modulate serotonergic transmission.
- Sub-optimal testosterone levels in depressed women compared with women in a control group points to the role testosterone plays in depression.

Testosterone & Depression

- The hippocampus and amygdala, critical regions in the brain, show a high incidence of depression, are rich with androgen receptors, a key explanation of clinical response with androgen therapy.
- Testosterone plays a key role in the development of depression, and testosterone, as well as estrogen, has been shown to modulate serotonergic transmission.

Testosterone Therapy & Depression

- Prudent testosterone replacement is effective in relieving both physical and psychological symptoms of androgen insufficiency in clinically affected women.
- Testosterone supplementation has positive effects for depression, libido, and energy.
- Testosterone therapy shows an antidepressant effect in depressed patients; the route of delivery may play a role in treatment response.
- Testosterone therapy improves well-being, mood, and sexual function in pre-menopausal women.

Androgen Insufficiency in Women

- Androgens peak in women in their twenties.
- Symptoms of insufficiency occur across the lifespan.

Androgen Insufficiency: Clinical Signs and Symptoms

- Loss of energy/fatigue
- Loss of mental clarity/focus
- Loss of sexual interest
- Weight gain
- Decreased exercise tolerance
- Headache
- Depression
- Irritability
- Weakness
- Insomnia
- Decreased libido

How do we diagnose?

Female Androgen Insufficiency (andropause in females)

- Key symptoms:
  - Reduced bladder, decreased well-being, anxiety and depressed, lowered mood.
  - Other symptoms also present (bone loss, memory impairment, joint pain, insomnia).
- Diagnosis is made on the basis of these symptoms in the setting of a low bone density or reference range serum free testosterone level or lower quintile of total testosterone level.*
- Currently no readily available inexpensive assay which reliably measures free testosterone levels in the female range.
- Further complicated by the lack of data demonstrating a minimum serum free testosterone level which, if below this, correlates with the symptoms.
- Despite the complications, evidence and shifting HTH, symptoms have been reported to respond well to testosterone replacement.

Diagnosing Androgen Insufficiency
Do the lab values matter?

- Poor correlation between symptoms of androgen deficiency and testosterone levels.
- Total and free, nor bioavailable testosterone are the definitive measures of androgen deficiency that endocrinologists would like them to be.
- There can be both insufficient production and variable degrees of resistance to the action of androgens operating at several levels in the body simultaneously.
- These factors becoming progressively worse with aging, adverse lifestyle, other disease processes, and a wide range of medications.

Androgen Deficiency etiology:
- Insufficient production
- Increased androgen binding
- Reduced tissue responsiveness
- Decreased Androgen Receptor activity
- Impaired transcription and translation

Why symptoms of androgen deficiency persist/exist with total testosterone levels “in range”?

1. Impaired androgen synthesis and regulation
   - Aging, infections, trauma, stress, diet, xenoestrogens, medications
2. Androgen binding
   - Only 1-3% available/free
3. Reduced tissue responsiveness
   - Aging, endothelial damage, DM, metabolic changes
4. Androgen receptor (AR) activity
   - Aging, number of AR decreases, genetics, xenoestrogens, zinc deficiency
5. Transcription and translation
   - Anti-androgens, new area of study as relates to disease

Diagnosis & Treatment of FAIS Take Home:

- There are no established “normal” ranges of testosterone in men or women.
- There are reference ranges, but they are “expected” and differ between labs.
- No validated assays or methodologies.
- Experiential levels and symptom presentation:
  - Men: <50 ng/dL, <300 nmol/L
  - Women: <200 pg/mL, <600 pmol/L
- Serum testosterone optimal ranges based on experiential data:
  - Men: >400 ng/dL, >2000 nmol/L
  - Women: >50 pg/mL, >150 pmol/L
Despite the plethora of data to support androgen replacement in women globally, and the fact that it has been used safely in women for almost a century, there are no testosterone only products licensed by the FDA for use in women in the U.S. As there are no FDA approved testosterone products for women on the market, many practitioners are not educated about the role of this vital hormone in women. Many practitioners have reported they were unaware women even made testosterone, much less needed it for optimal functioning.

Restoring Androgen Homeostasis

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Female Androgen Insufficiency Treatment Options

All testosterone replacement modalities prescribed for women in the U.S. are considered “off label” use. Testosterone is a controlled substance and is highly FDA regulated, no matter the modality.

Modalities prescribed in women include:
- Sub-cutaneous pellet implants
- IM injections
- Creams
- Oral / Sublingual

Androgen Insufficiency Treatment Options

Pellet implants

- Longest studied modality
  - Developed in 1939 for women who had radical hysterectomies.
  - 1940’s studies discussed the use of estradiol and testosterone pellets for the symptoms of menopause.
  - Are plant [soy or yam] based.
  - More widely used in states over past decade.
  - Dosing may be more individualized than other modalities.
  - Levels continuous over 3-5 months.
  - Cannot remove once placed.
  - Nuisance side effects may be longer lasting than oral or transdermal routes.

Injections

- Not widely used in women.
- Not widely researched in women.
- Higher side effect profile secondary to higher incidence of DHT conversion.
- Higher rates of aromatization than other modalities.
- Absorption is time released.
- Reported higher efficacy than oral or transdermal routes.
- Weekly or bi-monthly dosing.

Transdermal Creams

- Less side effect profile than other modalities.
  - Side effect of hair growth at area of application.
  - Little data to support sustained symptom relief.
  - Poor absorption transdermally.
  - Skin receptor desensitization over time.
  - Difficult to measure on laboratory assays.
  - Daily dosing.

Oral / Sublingual

- Combination Methyl testosterone/Conjugated equine estrogen.
  - First pass metabolism of methyl testosterone through liver may increase estrogen metabolites and side effects.
  - Little data to support sustained symptom relief of oral delivery.
  - Difficult to measure and monitor.
  - RDT [rapid dissolve tablets/sublingual] reported better clinical response and lower side effect profile than oral.
  - Direct to blood stream, no first pass metabolism.
Female Androgen Insufficiency  
Treatment Impact


Prospective, double blind, cross over study

Physical and Psychological Symptoms
- Estrogen androgen
- Estrogen alone
- Testosterone alone
- Placebo

- Testosterone was superior for relief of energy, well being, somatic complaints, and psychological symptoms.
- Worst was estrogen alone and placebo.

Testosterone and Estrogen implants (100mg/50mg)  
Studied over 4 years  
Peri and postmenopausal women

<table>
<thead>
<tr>
<th>Group</th>
<th>Peri-Menopause</th>
<th>Post-Menopause</th>
</tr>
</thead>
<tbody>
<tr>
<td>Energy</td>
<td>10%</td>
<td>20%</td>
</tr>
<tr>
<td>Mood</td>
<td>15%</td>
<td>25%</td>
</tr>
<tr>
<td>Sleep</td>
<td>30%</td>
<td>40%</td>
</tr>
<tr>
<td>Fatigue</td>
<td>20%</td>
<td>30%</td>
</tr>
<tr>
<td>Libido</td>
<td>10%</td>
<td>20%</td>
</tr>
</tbody>
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Group A: peri-Menopause  
Group B: post-Menopause

Androgen only therapy study

- 300 pre- and post-menopausal women with symptoms of relative androgen deficiency.
- Completed self-administered 11-item MRS (validated tool at baseline and 3 months after first insertion of the subcutaneous testosterone implant).
- Baseline hormone measurements, menopausal status and BMI were assessed to determine correlation with symptoms and clinical outcome.


- Continuous testosterone alone, delivered by subcutaneous implant, was effective for the relief of hormone deficiency symptoms in both pre- and post-menopausal patients.
- The validated, HRQOL questionnaire, Menopause Rating Scale (MRS), proved a valuable tool in the measurement of the beneficial effects of testosterone therapy in both cohorts.

Conclusions:
MRS- Study of Depression Relief - 2017

484 charts reviewed for women who received pellet HRT (androgen alone or androgen plus estradiol)

Design: Retrospective chart review of pre- and post- andropause hormone therapy (testosterone/androstenedione intervention) posttest using the validated, open access Health related Quality of Life Menopausal Rating Scale (HRQOL MRS) questionnaire.

Population: Pre- and postmenopausal females; 50-70 years with androgen deficiency who received androgen therapy and completed the pre- and post intervention MRS survey (in-clinical other exclusion criteria).

Setting: Primary care, hormone/endocrine specialty practice.

Measurement: HRQOL MRS Questionnaire at baseline and 6-12 weeks post therapy.

Conclusions

• 87% reported a decreased in depressive symptoms
• 11% reported an equivocal rating of depressive symptoms
• 2% reported an increased rating of depressive symptoms


Myths of Testosterone therapy in Women

A Lit review

The study proposed 10 common myths and misconceptions, and provide evidence to support what is physiologically plausible and scientifically evident:

◦ T is the most abundant biologically active female hormone
◦ T is essential for physical and mental health in women
◦ T is not masculinizing
◦ T decreases not increases
◦ T increases not decreases
◦ T reverses not uterine protection
◦ Premenopausal T levels not adversely affect the bone or ovarian function
◦ T is involved in hair loss and does not reverse aggression
◦ T is male protective
◦ The effects of T therapy in women is under research and being monitored.

The Patient Encounter

A Case Study

• 65 year old female, married to retired OB/Gyn
• G4P4, unremarkable gyn history
• Began to feel depressed in late 40's
• Symptoms exacerbated through 50's; patient became very moody, anxious and severely depressed.
• Began oral estrogen and progesterone combination with some improvement in symptoms in her mid 50's.
• Stopped oral therapy at age 60
• Pre-treatment MRS questionnaire ranked severe in all psychosomatic categories
• Labs reveal low serum testosterone, low estradiol and elevated FSH
  • Testosterone <12, FSH 69, Estradiol 13
• Labs and exam otherwise unremarkable
• Began MHT with estradiol and testosterone pellet implants and oral progesterone for uterine protection.
• Follow up in 6 weeks
• Post MRS questionnaire all psychosomatic symptoms reported as resolved, score of 0.
• No subjective negative side effects reported
• Follow-up hormone labs:
  • Testosterone in above upper range at 112
  • FSH 26, Estradiol 35

Husband states “you gave me my wife back”

Conclusion

Nurse practitioners have a unique opportunity to open the dialogue of altered mood states in their female patients.

It is imperative we expand our horizons in the areas of treating hormone related depression, anxiety and altered mood states and broaden the scope of our education and knowledge in the role of androgen-replacement in optimizing women's health.
Thank you for your attention!