MAYO CLINIC | School of Continuous Professional Development

17TH ANNUAL WOMEN'S HEALTH UPDATE – 2021

COURSE DIRECTORS:

Juliana M. Kling, MD, MPH
Suneela Vegunta, MD
Ekta Kapoor, MBBS



November 4-6, 2021

MAYO CLINIC | School of Continuous Professional Development

ANDROGEN DEFICIENCY

DOES IT EXIST?

Taryn Smith, MD
Assistant Professor of Medicine
Mayo Clinic Jacksonville

DISCLOSURE OF RELEVANT FINANCIAL RELATIONSHIP(S) WITH INDUSTRY

- Nothing to disclose

REFERENCES TO OFF-LABEL USAGE(S) OF PHARMACEUTICALS OR INSTRUMENTS

- Testosterone in postmenopausal women

TARYN SMITH, MD

Assistant Professor of Medicine
Mayo Clinic Jacksonville
NAMS Certified Menopause Practitioner

Please insert presenter's Mayo staff photo here

LEARNING OBJECTIVES

- Review the role for checking serum testosterone in women with sexual concerns
- Review guidelines as it related to androgen deficiency in women.

CASE 1

REBECCA

- 35 yo female, premenopausal, menses regular, had tubal ligation at 30, healthy, takes no meds.
- Concerns: 20 lb weight gain x 1 yr, decreased energy level, decreased muscle mass, concerns about body image, decease in libido and decrease in sexual responsiveness.
- Married 10 years, good relationship with husband
- She had normal comprehensive labs and exam
- She wants to know if her symptoms are related to hormone imbalance. Particularly, she wonders if low testosterone is contributing to her sexual concerns.

CASE 2

NICOLE

- 45 yo female, premenopausal, menses regular, had tubal ligation in her 30s, healthy, takes no meds.
- Recently divorced and back on the dating scene. She has made some connections but has a lack of interest in sex. Otherwise no major concerns. Her PHQ-9 score 15 and she is tearful when discussing the divorce.
- Her local hormone specialist checked labs which showed low testosterone level. Testosterone pellet therapy was recommended.
- She would like your opinion before getting the first pellet next week.

CASE 3
MICHELLE

- 45 yo female, hysterectomy and bilateral salpingo oophorectomy for benign reasons at age 40. healthy, takes no meds.
- She has taken oral Premarin 0.625 mg since THBSO. Vasomotor symptoms are well controlled. She notes decreased libido and response to sexual cues. She denies vaginal dryness or dyspareunia. Has a great relationship with her husband of one year. This is a clear change from prior.
- She wants to know if her testosterone level should be checked and if testosterone therapy would improve her sexual function.

ANDROGEN SYNTHESIS IN WOMEN

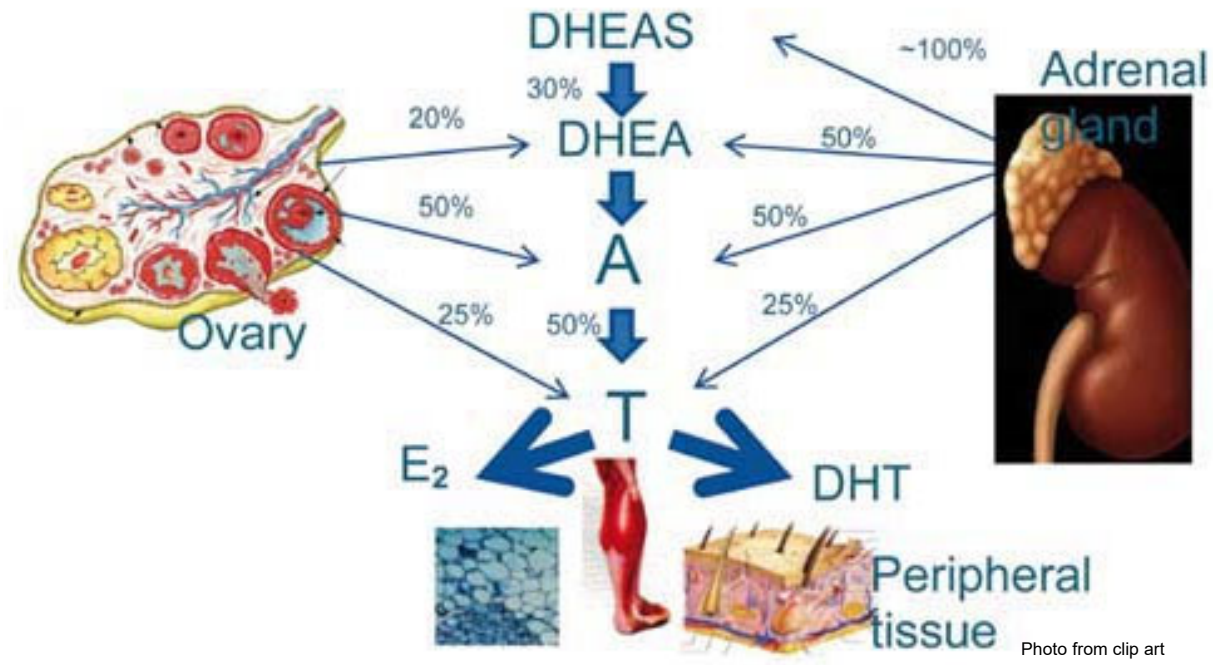
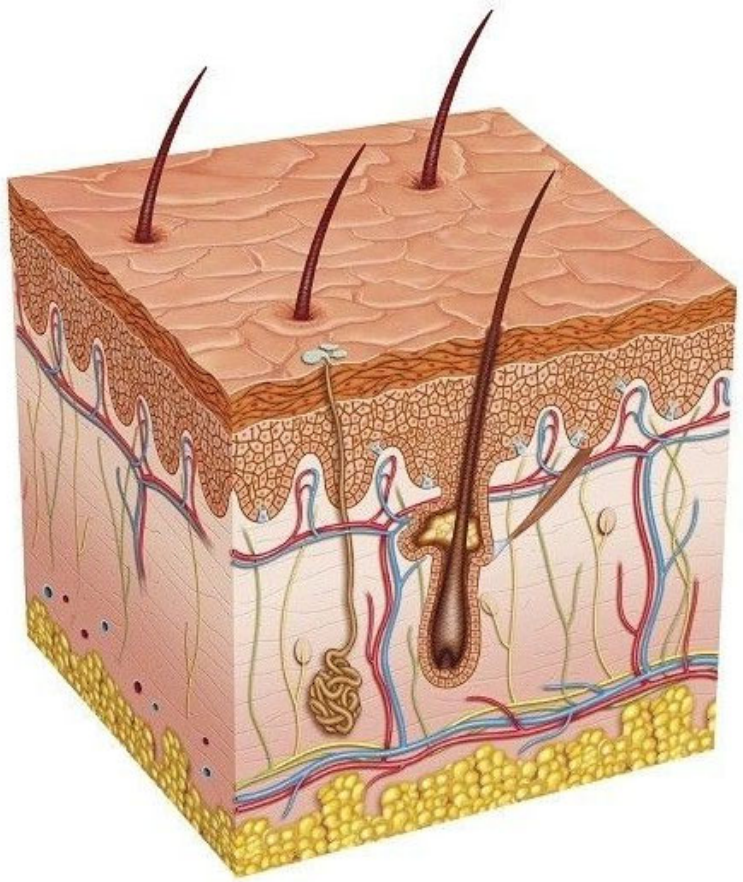


Photo from clip art

TESTOSTERONE IN WOMEN

- Serum Testosterone levels do not account for the testosterone synthesized in peripheral tissues or the sensitivity of androgen receptors
- The effects of androgens are
  - tissue specific
  - dependent on the level and activities of 5 alpha reductase and aromatase



Vegunta et al. Jour Wom Health 2019; DOI: 10.1089/jwh.2018.7494

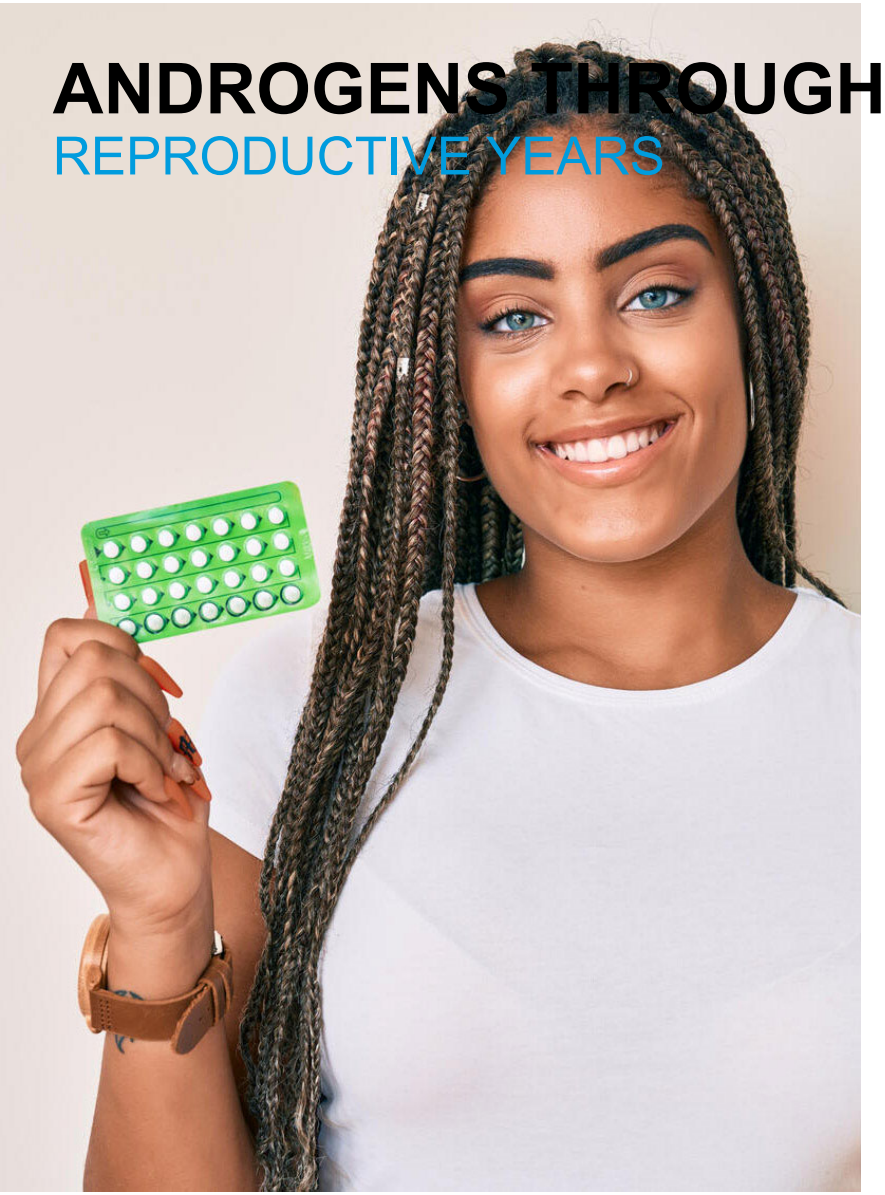
ANDROGENS THROUGHOUT THE LIFE CYCLE

ADRENARCHE

- Pubic/axillary hair
- Libido
- Bone density
- Stature
- Immune function
- Muscle mass

ANDROGENS THROUGHOUT THE LIFE CYCLE

REPRODUCTIVE YEARS



- Peak production occurs at 20-30 years
- Serum testosterone levels are about 1.5 times higher than estrogen levels
- Several studies have demonstrated a mid cycle increase in testosterone levels

Sarrel PM. Androgen deficiency: Menopause and estrogen-related factors. *Fertil Steril*. 2002; Rothman MS, Carlson NE, Xu M, et al. Reexamination of testosterone, dihydrotestosterone, estradiol and estrone levels across the menstrual cycle and in postmenopausal women measured by liquid chromatography-tandem mass spectrometry. *Steroids*. 2011.

ANDROGENS THROUGHOUT THE LIFE CYCLE

PERIMENOPAUSE

- Androgen levels decline with age with the greatest decline occurring during the late reproductive years.
- Perimenopause may be associated with a stable serum free testosterone levels due to declining estradiol and thus declining SHBG

ANDROGENS THROUGHOUT THE LIFE CYCLE

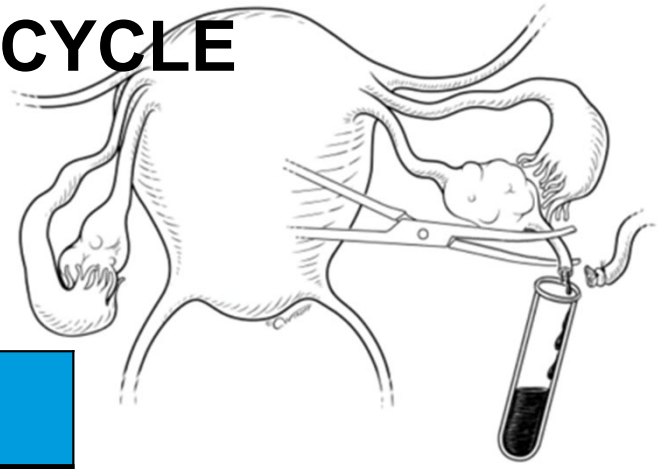
MENOPAUSE

- During menopause and a late menopause transition, androgen levels remain relatively stable or slightly increase.
- Postmenopausal ovary accounts for 40-50% of postmenopausal testosterone production
- Ten years following menopause onset postmenopausal circulating testosterone is half that of perimenopausal levels.

Fogle RH, Stanczyk FZ, Zhang X, Paulson RJ. Ovarian androgen production in postmenopausal women. *J Clin Endocrinol Metab*. 2007;92(8):3040-3043;
Laughlin GA, Barrett-Connor E, Kritz-Silverstein D, Von Mühlen D. Hysterectomy, oophorectomy, and endogenous sex hormone levels in older women: The Rancho Bernardo study. *J Clin Endocrinol Metab*. 2000;85(2):645-651

ANDROGENS THROUGHOUT THE LIFE CYCLE

SURGICAL MENOPAUSE



Sex Steroid levels in women pg/ml

	Pre-menopause	Natural menopause	Surgical menopause
Estradiol	150	10-15	10
Testosterone	400	290	110
Androstenedione	1900	1000	700
DHEA	5000	2000	1800
DHEA-s	3,000,000	1,000,000	1,000,000

Fogle RH, Stanczyk FZ, Zhang X, Paulson RJ. Ovarian androgen production in postmenopausal women. *J Clin Endocrinol Metab*. 2007;92(8):3040-3043;
Lobo RA. Treatment of the postmenopausal Woman. Philadelphia, Pa: Lippincott; 1999

LOW ANDROGEN LEVELS IN WOMEN

- Bilateral oophorectomy
- Medications
  - OCPs
  - Glucocorticoids
  - Some antidepressants
- Hypopituitarism
- Primary adrenal insufficiency
- Eating disorders
  - Anorexia Nervosa
  - malnutrition

MEASURING TESTOSTERONE IN WOMEN

- Gold standard: Liquid/gas chromatography and tandem mass spectrometry assays.
- Not as reliable: Direct radioimmunoassay (RIA) measurement
- Salivary assays are neither sensitive or specific measures of testosterone and are not recommended for clinical use.
- Low serum testosterone levels in women should be interpreted with caution.
- Serum DHEAS is the most reliable measure of adrenal androgen production.

CASE 1

REBECCA

- 35 yo female, 20 lb weight gain x 1 yr, decreased energy level, sedentary lifestyle, decreased muscle mass, concerns about body image, decease in libido.
- She had normal comprehensive labs and exam
- She wants to know if her symptoms are related to hormone imbalance. Particularly, she wonders if low testosterone is contributing to her sexual concerns.

CASE 1
CONSIDERATIONS

- Low serum androgen levels do not reliably correlate with a clinically defined syndrome, including oophorectomized women.
- There is no serum testosterone reference range that has been shown to contribute to sexual dysfunction.
- Endocrine Society recommends against diagnosing female “androgen deficiency”.
- The Endocrine Society recommends against using androgens to treat women with low testosterone levels due to adrenal insufficiency, hypopituitarism or surgical menopause.

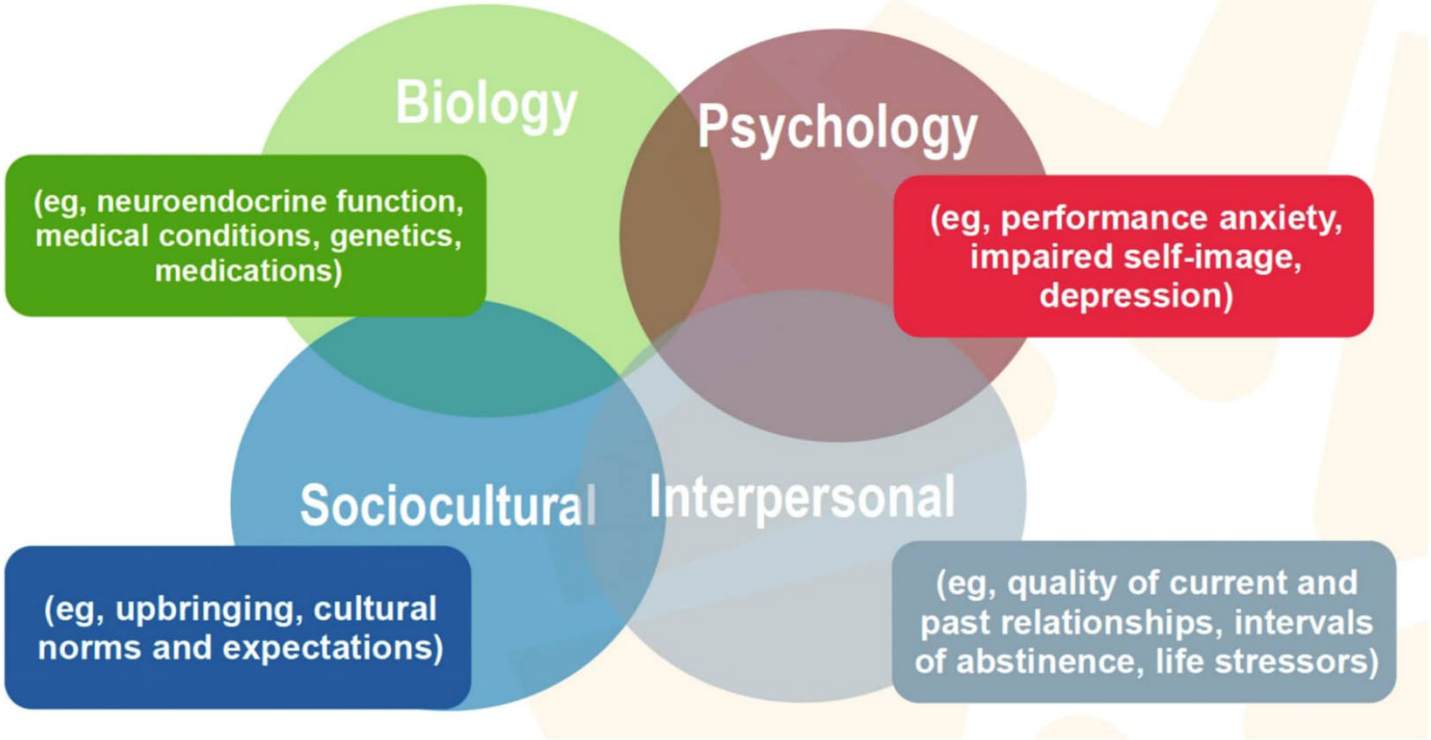
Aziz A, Brännström M, Bergquist C, Silfverstolpe G. Perimenopausal androgen decline after oophorectomy does not influence sexuality or psychological well-being. *Fertil Steril*. 2005.;
Wierman ME, Arlt W, Basson R, et al. Androgen therapy in women: A reappraisal: An Endocrine Society clinical practice guideline. *J Clin Endocrinol Metab*. 2014;99(10):3489-3510

CASE 2
NICOLE

- Healthy 45 yo female, recent divorcee with untreated depression.
- Wants to date again.
- Has decreased libido.
- Her local hormone specialist checked labs which showed low testosterone level. Testosterone pellet therapy was recommended.
- She would like your opinion before getting the first pellet next week.

CASE 1 AND 2
CONSIDERATIONS

Biopsychosocial Model of Sexual Response



Althof SE, et al. J Sex Med. 2005; 2(6):793-800
Rosen RC, et al. Obstet Gynecol Clin North Am. 2006; 33(4):515-526

COMMON USES OF ANDROGEN THERAPY IN WOMEN

- Treatment of hypoactive sexual desire disorder in postmenopausal women
- Treatment of genitourinary syndrome of menopause and vulvar symptoms
- Adjunct to estrogen therapy when menopausal symptoms are not well controlled

ANDROGEN THERAPY IN WOMEN

SEXUAL DYSFUNCTION

1	In the past, was your level of sexual desire or interest good & satisfying to you?	Yes / No
2	Has there been a decrease in your level of sexual desire or interest?	Yes / No
3	Are you bothered by your decreased level of sexual desire or interest?	Yes / No
4	Would you like your level of sexual desire or interest to increase?	Yes / No
5	Please circle all of the factors that you feel may be contributing to your current decrease in sexual desire or interest:	
	a. *An operation, depression, injuries, or other medical condition*	Yes / No
	b. *Medications, drugs, or alcohol you are currently taking*	Yes / No
	c. *Pregnancy, recent childbirth, menopausal symptoms*	Yes / No
	d. *Other sexual issues you may be having (pain, decreased arousal or orgasm)*	Yes / No
	e. *Your partner's sexual problems*	Yes / No
	f. *Dissatisfaction with your relationship or partner*	Yes / No
	g. *Stress or fatigue*	Yes / No

Clayton et al. Mayo Clin Proc 2018; 93(4): 467-487.

ANDROGEN THERAPY IN WOMEN

SEXUAL DYSFUNCTION

- Most professional societies endorse off label treatment of hypoactive sexual desire disorder in postmenopausal women
- Multiple large RCTs, show that testosterone therapy improves
  - Sexual desire
  - Sexual satisfaction
  - Arousal
  - Sexual pleasure
  - *In postmenopausal women when levels approximate premenopausal range*
- No studies have successfully defined target serum androgen levels that correlate with female sexual function.

ANDROGEN THERAPY IN WOMEN

SEXUAL DYSFUNCTION

Randomized controlled trials of estrogen-androgen drugs and sexual functioning.

Study	No. of subjects	Naturally or surgically menopausal	Drug	Changes in sexual functioning in the E-A groups
Burger et al. (13)	17	5 NM 12 SM	estradiol 40 mg + testosterone 100 mg pellet	↑ libido ↑ enjoyment of sex ↑ orgasms ↑ initiation of sex
Burger et al. (14)	20	14 NM 6 SM	estradiol 40 mg or orstradiol 40 mg + testosterone 50 mg pellets	↑ libido ↑ enjoyment of sex
Davis et al. (15)	32	30 NM	estradiol 50 mg or estradiol 50 mg + testosterone 50 mg pellets	↑ sexual activity ↑ satisfaction ↑ pleasure ↑ orgasms
Sherwin et al. (19)	53	10 premenopausal 43 SM	estradiol 8.5 mg + testosterone 150 mg or estradiol 8.5 mg or testosterone 150 mg or placebo 1M	↑ sexual desire ↑ sexual arousal ↑ sexual fantasies
Sherwin et al. (20)	44	44 SM	estrogen 10 mg or estrogen 8.5 mg + testosterone 150 mg 1M	↑ sexual desire ↑ sexual arousal ↑ sexual fantasies
Sarrel et al. (22)	20	12 NM 8 SM	1.25 EE or 1.25 EE + 2.5 mg MT	↑ sexual sensation ↑ sexual desire
Shifren et al. (23)	75	75 SM	CEE + 150 μg testosterone or + 300 μg testosterone or + placebo patch in random order transdermal	↑ BISF with 300 μg T patch

Note: NM = naturally menopausal; SM = surgically menopausal; EE = esterified estrogens; MT = methyltestosterone; E-A = estrogen-androgen; ↑ = increased; BISF = Brief Index of Sexual Functioning for Women.

Sherwin. Randomized trials of estrogen-androgen drugs. Fertil Steril 2002.

ANDROGEN THERAPY IN WOMEN

SEXUAL DYSFUNCTION

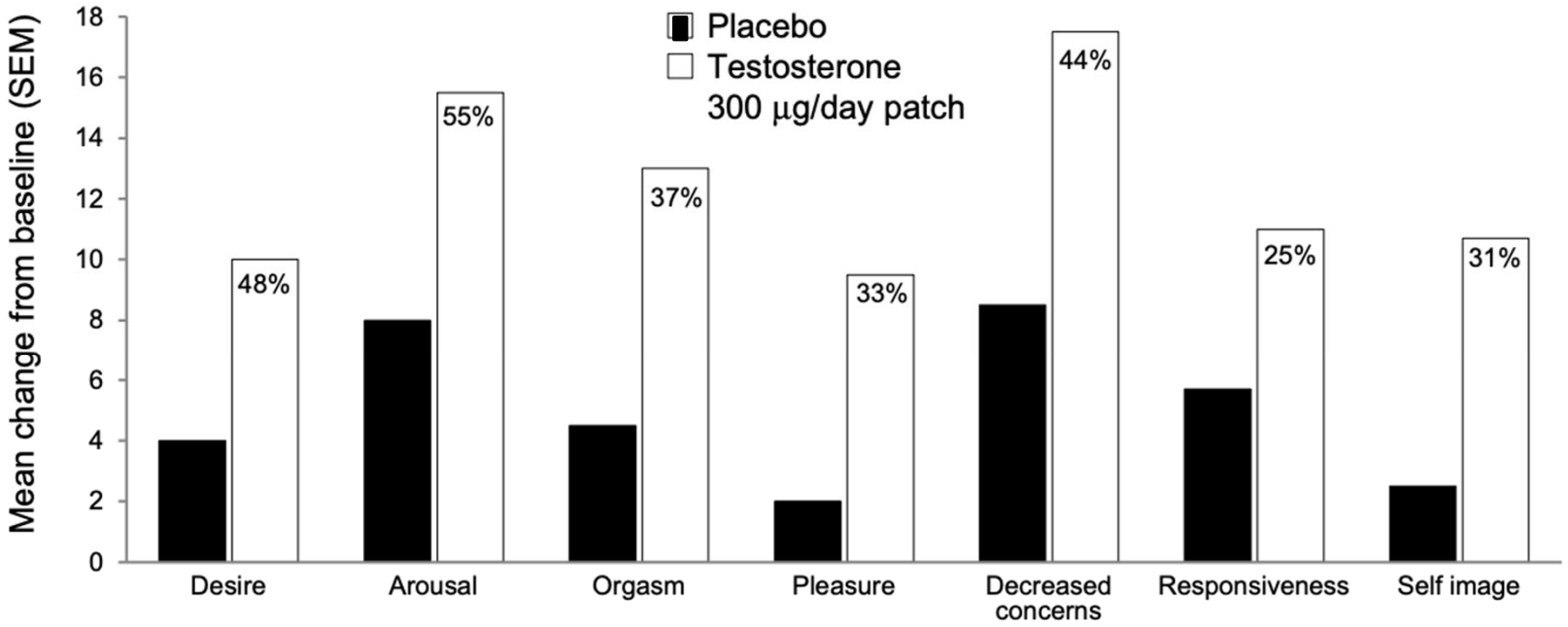
- Four 24-week phase 3 RCTs in NM and SM women with HSDD compared 300 mcg/d testosterone patch to placebo
  - Patch Inc sexual desire and satisfying events compared to placebo
  - Level of sexual related distress decreased significantly compared with placebo in ¾ studies
- Most common AEs in descending order
  - Application site reaction
  - Acne
  - Breast pain
  - Headache
  - Hirsutism
- No change in LFTs, lipid profile, CBC, CMB

Clayton et al. Mayo Clin Proc 2018; 93(4): 467-487.

ANDROGEN THERAPY IN WOMEN

SEXUAL DYSFUNCTION

Naturally menopausal women with HSDD: Intimate Study

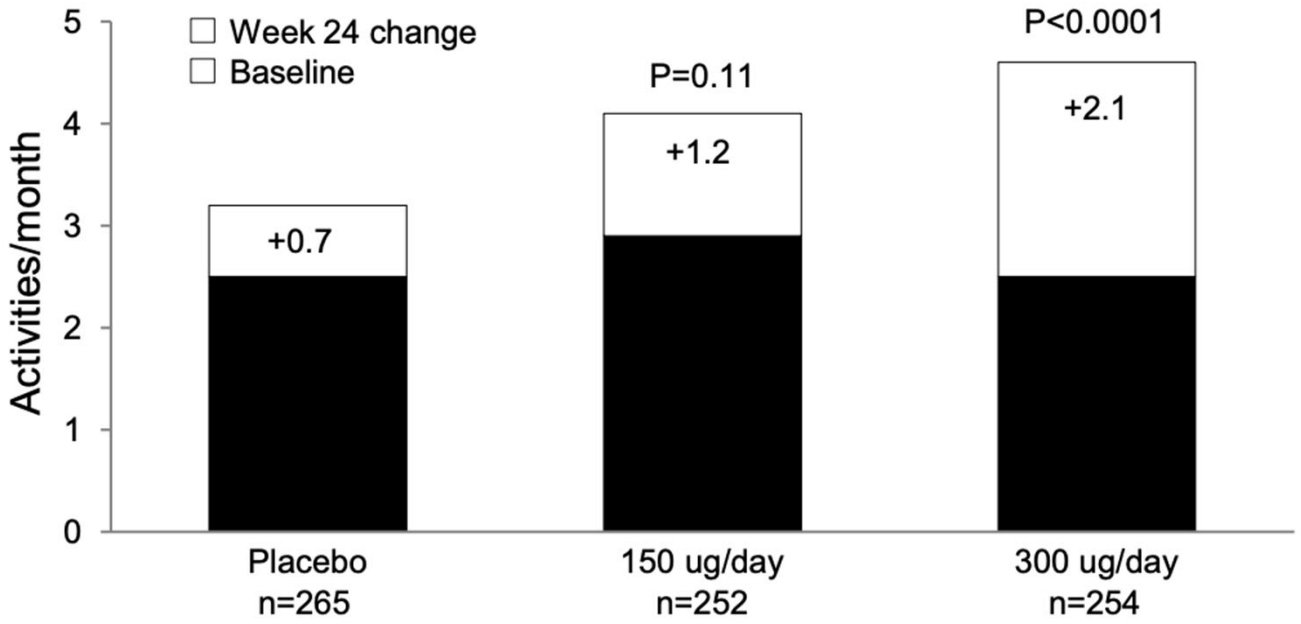


Redrawn from: Menopause 2006 Sep-Oct;13(5):770-9

ANDROGEN THERAPY IN WOMEN

SEXUAL DYSFUNCTION

Transdermal Testosterone Patch Therapy (300 mcg) Improves Sexual Function in Women NOT ON ESTROGEN



Redrawn from: Davis et al: NEJM, 2008

ANDROGEN THERAPY IN WOMEN

SEXUAL DYSFUNCTION

- Two large phase III RCTs showed no benefit of transdermal T gel, 0.22 g/d over placebo
- Endpoints
  - # of sexual satisfying events/month
  - Level of desire (via daily diary)
- There were no statistically significant differences between groups

Wierman et al. J Clin Endocrinol Metab 2014; 99(10): 3489-3510

ANDROGEN THERAPY IN WOMEN

SEXUAL DYSFUNCTION

- RCT of transdermal testosterone spray in women with low serum free-T[1]
  - Improved self reported sexual satisfaction in women with HSDD
  - No change in SSE compared to placebo
- RCT of testosterone cream 10mg/day, two double blind, 12 week treatment periods[2]
  - TC improved well being ($p= 0.003$), mood ($p< 0.6$), sexual function ($p< 0.001$) compared to placebo
  - Serum T stayed in the high normal range for PM women
  - No AEs noted

1. Davis et al. Ann Intern Med 2008;148 (8): 569-77. 2. Goldstat et al. Menopause 2003; 10(5): 390-398.

ANDROGEN THERAPY IN WOMEN

SEXUAL DYSFUNCTION

- No FDA approved testosterone formulations
- Lack of long term safety data
  - Cardiovascular
  - Cancer risk, esp breast
  - Bone
  - Cognitive/mood
  - *Safety data not available beyond 24 months*
- Adverse effects
  - Skin
  - Hair
- Inconsistent study designs, route of administration and concurrent use of estrogen therapy
- Elevated SHBG may impair response to therapy

ANDROGEN THERAPY IN WOMEN

SEXUAL DYSFUNCTION

TRANSDERMAL

- Transdermal is preferred with careful clinical and laboratory monitoring
  - Patched changed twice weekly-not available in the US
  - Typically well tolerated with fewer side effects
- Testim (male product)
  - 1/10 male dose
  - 3-4 drops to thigh or abdomen daily
  - Check serum T every 3-6 months
  - Single tube should last at least 10 days
- Compounded creams, gels, ointments are most commonly prescribed
  - 1% testosterone cream/ointment with 0.5g/day
    - Testosterone levels tend to stay within physiologic ranges
    - SE are rare
    - Applied to the lower body
    - Check levels 2-3 weeks after starting a new tube

ANDROGEN THERAPY IN WOMEN

SEXUAL DYSFUNCTION

IM/PELLET

- IM injections
  - tend to be painful
  - Tend to lead to supraphysiologic levels (transiently if not sustained)
- Pellet
  - Potential for prolonged exposure to high dose
  - Tends to lead to supraphysiologic levels

ANDROGEN THERAPY IN WOMEN

SEXUAL DYSFUNCTION

IM/PELLET

- Recent retrospective study compared serum E2 and T in women receiving PHT vs FHT
  - Mean highest E2 pg/mL 237.70 PHT vs 93 FHT; p<0.00001
  - Mean highest T ng/dL192.84 PHT vs 15.59 FHT; p<0.00001
  - PHT group was more likely to experience SE including p<0.00001
    - Hair thinning
    - Mood changes
    - Hypertension
    - Anxiety
    - Breast tenderness
    - Weight gain
    - Dyslipidemia
    - Diabetes
    - Acne

ANDROGEN THERAPY IN WOMEN

SEXUAL DYSFUNCTION

ORAL

- Have shorter half life and may need twice daily administration
- Undergoes first pass metabolism which increases risk of
  - Increased LFTs
  - Decreased HDL, increased TG
  - Increased clotting factors

ANDROGEN THERAPY IN WOMEN

SEXUAL DYSFUNCTION

ORAL

COVARYX/ESTRATEST: ESTERIFIED ESTROGEN/METHYLTESTOSTERONE

- Doses: 1.25mg EE/2.5mg MT and 0.625mg EE/ 1.25mg MT
- Daily for 3 weeks/off 1 week or MWF
- Only generic available in the US
- Short term use (3-6 months) recommended
- Post marketing safety surveillance study 2003
  - Small number of serious adverse events reported compared to significant patient exposure

ANDROGEN THERAPY IN WOMEN

SEXUAL DYSFUNCTION

- Transdermal preferred
- 1% testosterone in Vanicream in meted dose dispenser (0.25g/click)
- In other countries
  - Androfeme 1% cream in Australia
  - Testosterone patch (Intrinsa) discontinued in Europe
- In development
  - On demand: intranasal spray, oral T + sildenafil, oral T + buspirone
  - Topical gel
  - Intrinsa patch withdrawn in the US
- No data to support use on premenopausal women or for indications other than HSDD in postmenopausal women.

CASE 3
MICHELLE

- 45 yo female, hysterectomy and bilateral salpingo oophorectomy for benign reasons at age 40. healthy, takes no meds.
- She has taken oral Premarin 0.625 mg since THBSO. Vasomotor symptoms are well controlled. She notes decreased libido and response to sexual cues. She denies vaginal dryness or dyspareunia. Has a great relationship with her husband of one year. This is a clear change from prior.
- She wants to know if her testosterone level should be checked and if testosterone therapy would improve her sexual function.

CASE 3
CONSIDERATIONS

- She is a surgically menopausal female with HSDD
- Discuss risk
- Check baseline testosterone
- Start 1% testosterone in Vanicream MDD to the inner thigh daily or few times per week
- Repeat testosterone in 3-6 weeks, again in 6 months then every 6-12 months
- Discontinue if no response in 6 months
- Monitor for signs of androgen excess (acne, hirsutism, virilization)
- Consider drug holiday after 6-12 months

SUMMARY OF RECOMMENDATIONS: "GLOBAL CONSENSUS POSITION STATEMENT ON THE USE OF TESTOSTERONE THERAPY FOR WOMEN"

- The only evidence-based indication for testosterone therapy in women is for the treatment of HSDD
- Meta-analysis show no severe adverse events during physiological testosterone use (women at high risk for CVD excluded)
- Diagnoses of HSDD should involve for clinical assessment
- Serum total testosterone level should NOT be used to diagnose HSDD
- Treat only with formulations that do not cause supraphysiologic testosterone levels
- The formulations can be judiciously used with regular monitoring
- Avoid the use of compounded testosterone

Davis et al. Climacteric 2019; 22(5): 429-434

SUMMARY OF RECOMMENDATIONS: ENDOCRINE SOCIETY

- Recommend against making a clinical diagnosis of androgen deficiency syndrome and healthy women
- Recommend against routine treatment of women with low androgen levels
- A 3 to 6 month trial of a dose of testosterone for postmenopausal women who request therapy for properly diagnosed HSDD
- Therapy is prescribed, suggest monitoring testosterone levels at baseline and after 3 to 6 weeks of initial treatment
- If ongoing therapy, suggest monitoring testosterone levels every six months
- Therapy should be stopped for women who have not responded to treatment by six months
- Non-oral therapies are preferred

Wierman et al. J Clin Endorinol Metab 2014; 99(10): 3489-3510

ISSWSH CLINICAL PRACTICE GUIDELINE FOR THE USE OF SYSTEMIC TESTOSTERONE FOR HSDD IN WOMEN

Parish SJ, Simon JA, Davis SR, et al. *J Sex Med (ISSWSH)* & *Climacteric* (IMS), &*J Women's Health (SWHR and AMWA)*

"To provide a clinical practice guideline for the use of testosterone including identification of patients, laboratory testing, dosing, post-treatment monitoring, and follow-up care in women with HSDD"

As a follow-up to the Global Consensus Position Statement

QUESTIONS & DISCUSSION

MAYO CLINIC | School of Continuous Professional Development

THANK YOU FOR JOINING US IN THIS COURSE

Rochester, Minnesota

Phoenix, Arizona

Jacksonville, Florida

