Hormone Pellet Therapy in Women

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Restore • Regenerate • Renew

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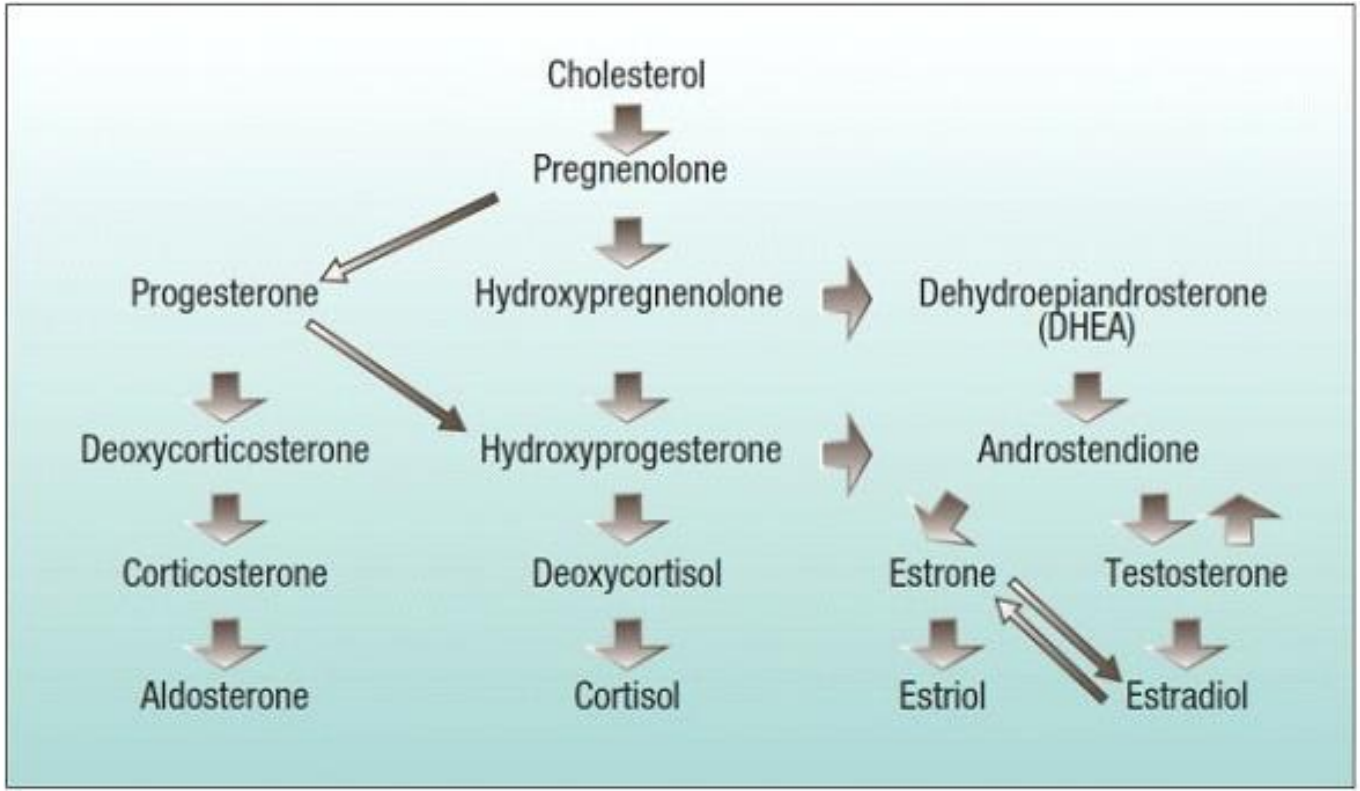
History

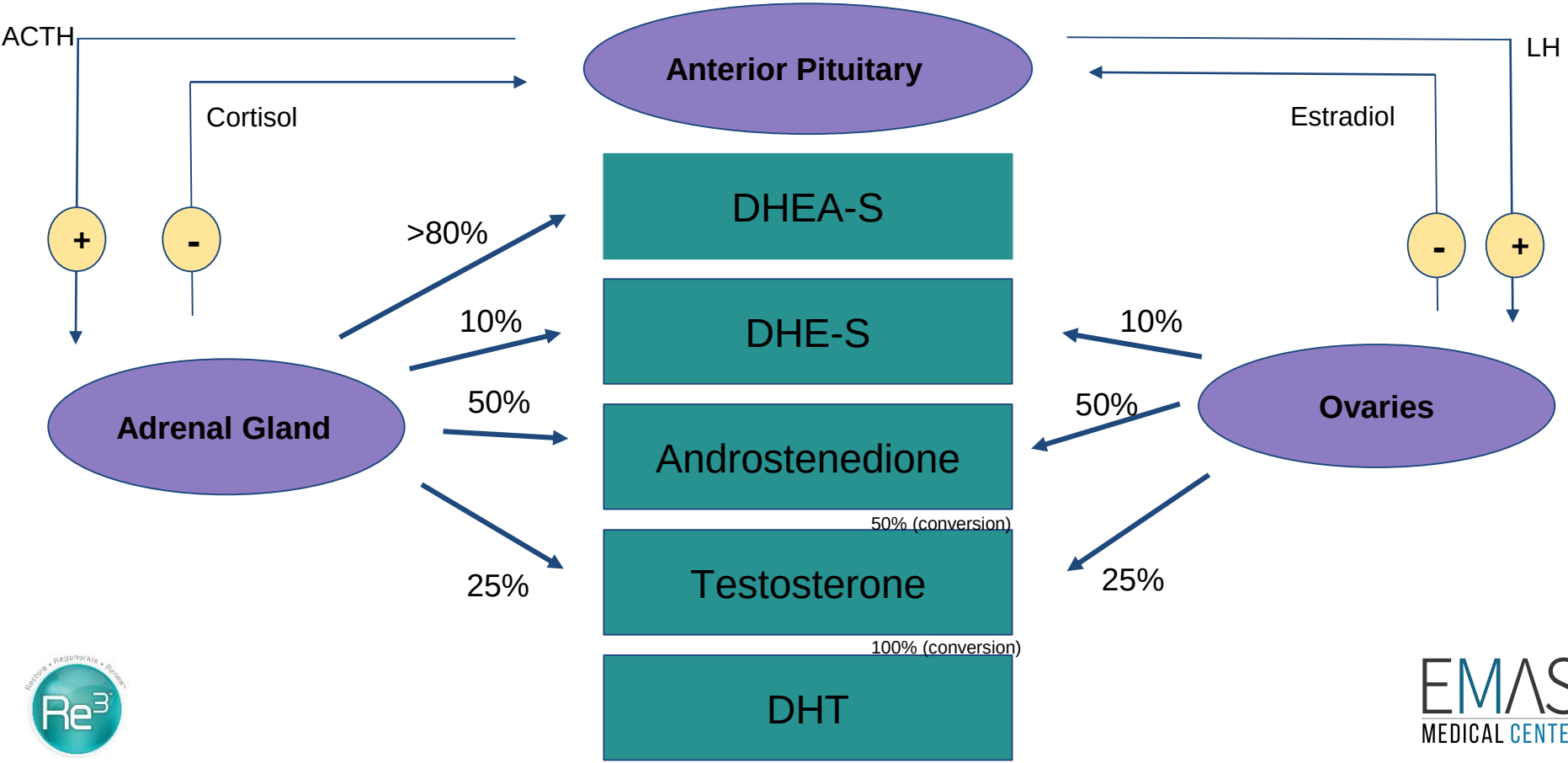
- Pellets have been successfully used for hormone replacement therapy for almost a century.
- 1938
  - Salmon concluded that “25 to 50 mg. (of crystalline estradiol benzoate) should maintain a patient symptom free for many months
  - suggested its prophylactic use on to patients following surgical BSO

USA Manufactured since 1946
Testosterone and estradiol pellets

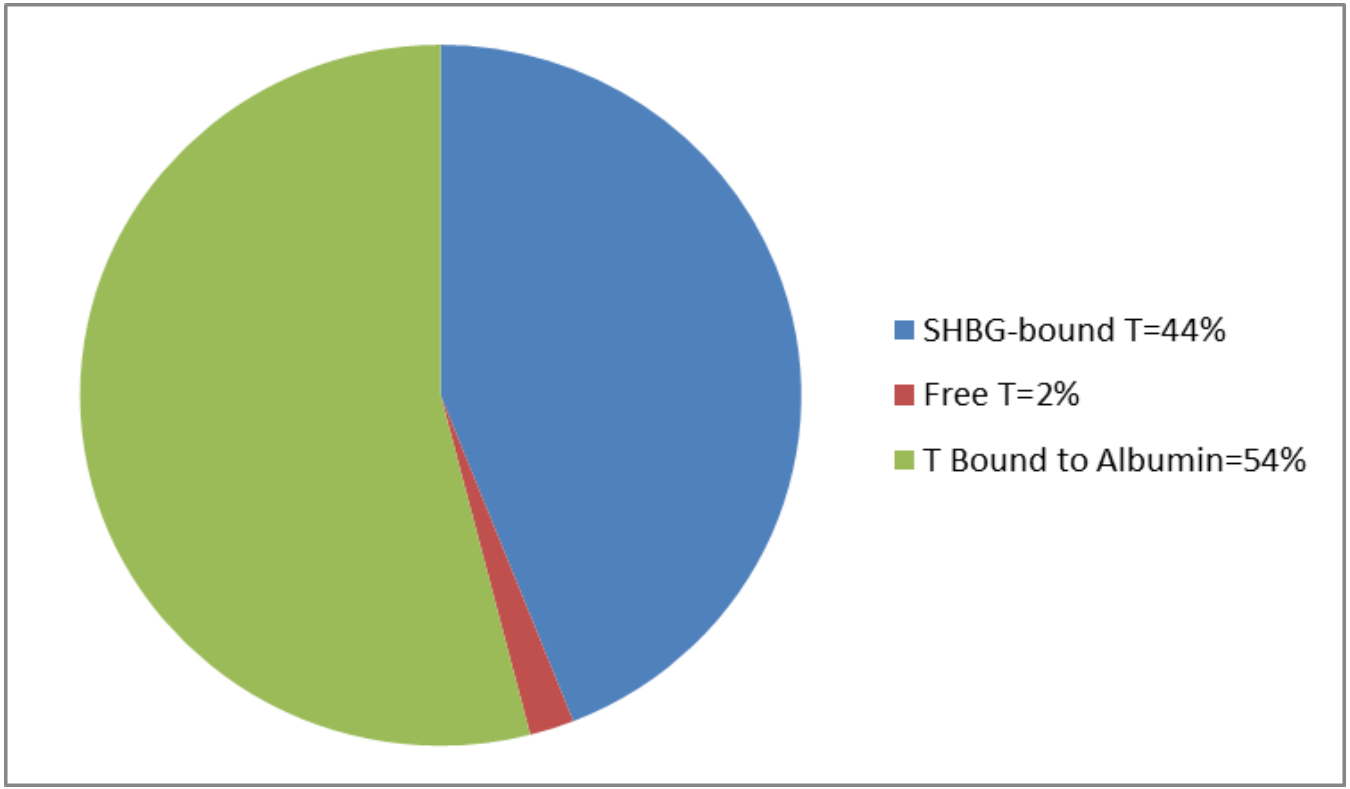
Hormone Synthesis Pathways



Androgen Dynamics in Premenopausal Women



Testosterone Fractions



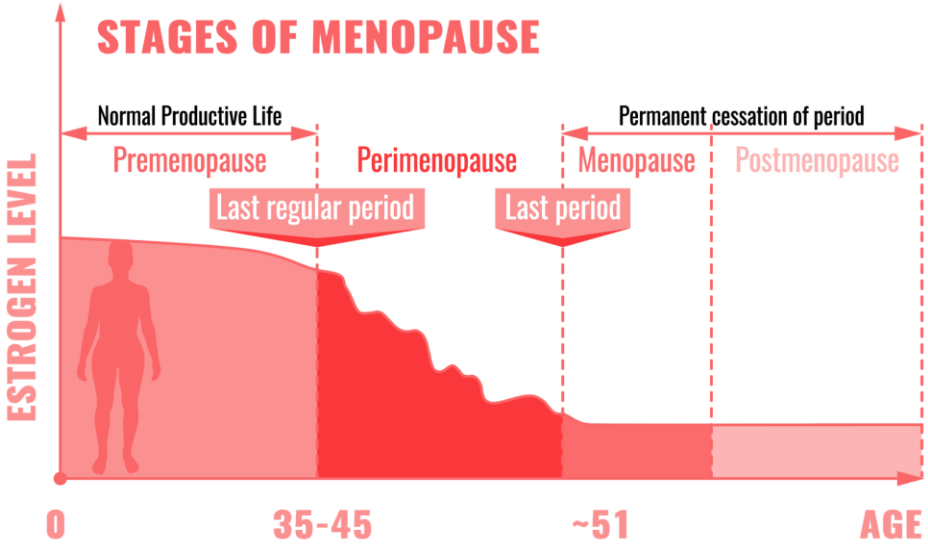
What are physiological levels of estradiol?

Vary widely throughout the menstrual cycle

Mid Follicular phase: 27-123 pg/ml

Mid luteal phase : 49-294 pg/ml

Menopause: 0-40 pg/ml



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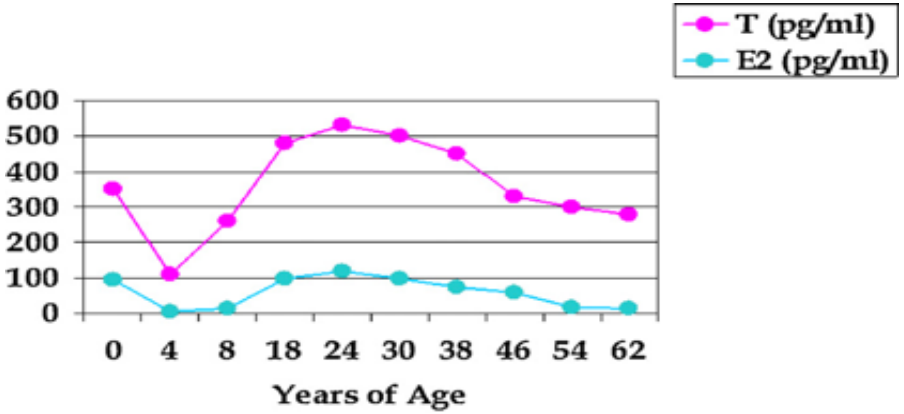
Myth Is Testosterone a Male Hormone?

- Testosterone declines in women between the age of 30 and 50. A 40y old has half the level of a 20y old (Zumoff)



- Daily production rate (of testosterone) ranges between 0.1-.4 mg" (Burger)
- Highest rates are between 0400 and 1200 hours (Vierhapper et al)
- Testosterone measured in serum is inaccurate at lower levels (Princeton consensus)

Vierhapper, H., Nowotny, P, Waldhausl. (1997). Determination of Testosterone Production Rates in Men and Women Using Stable Isotope/Dilution and Mass Spectrometry *The Journal of Clinical Endocrinology & Metabolism*, 98(5), 1492–1496

Bachman, G et al. Female androgen insufficiency: the Princeton consensus statement on definition, classification, and assessment. *Fertility Steril. 2002, 77, 660-665.*

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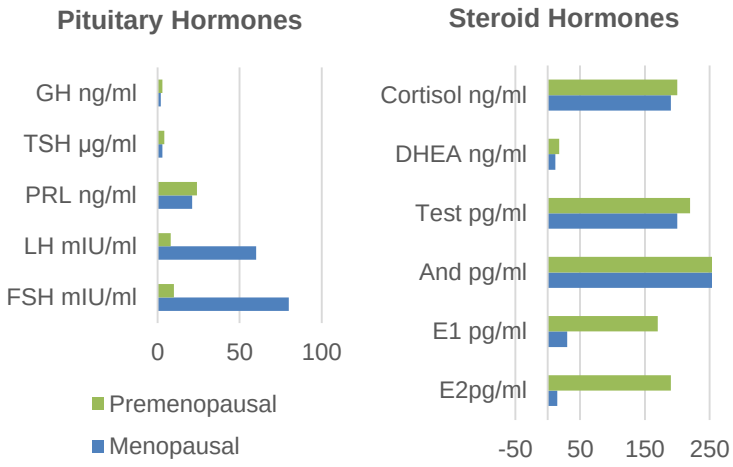
Serum hormone levels at menopause

- Decreased circulating estrogens
- Decreased ratio of estrogen to androgen
- Decreased sex hormone-binding
- globulin secretion
- Increased peripheral aromatization of DHEA to estrone
- Reversal of estradiol (E_2) to estrone (E_1) ratio (higher estrone)



Low Estrogen

Signs and Symptoms of Low Estrogen

Physical Symptoms:

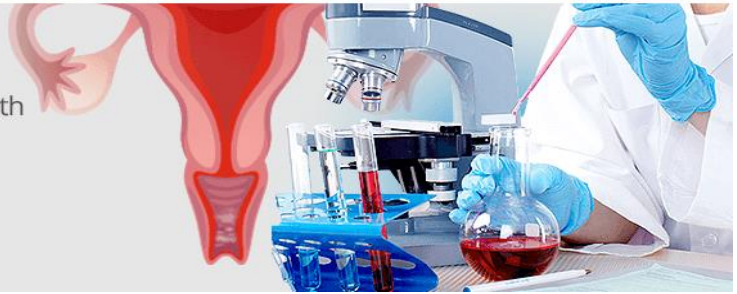
- Hot flashes
- Insomnia
- Vaginal dryness
- Irregular periods

Psychological Symptoms:

- Panic attacks
- Mood swings
- Memory lapses
- Low self-esteem

Signs of Low Estrogen:

- **Microscopy:** vaginal, bacterial fungal growth
- **ECG:** abnormal results
- **Blood tests:** low serotonin levels
- **Estrogen tests:** low levels



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Androgen Insufficiency in Women

Androgen deficiency (AD) is a syndrome in which either androgen production or activity is reduced and can occur at any age. The 2002 consensus defined it as a “syndrome consisting of reduced libido, reduced feeling of wellbeing or mood changes, persistent tiredness and inexplicable loss of bone mass, reduction in muscle strength, thinning of hair and altered cognitive function and memory”

- Muscle Loss
- Mood swings
- Tension
- Lack of sleep
- Memory loss
- Decreased sex drive
- Depression
- Hot flashes
- Night sweats
- Weight gain
- Joint pain
- Migraine
- Fatigue
- Loss of libido
- Bone loss
- Incontinence

Fonseca, H. (2010) Female Androgen Deficiency. *Rev Assoc Medical Bras 56*(5). doi.org/10.1590/S0104-42302010000500021

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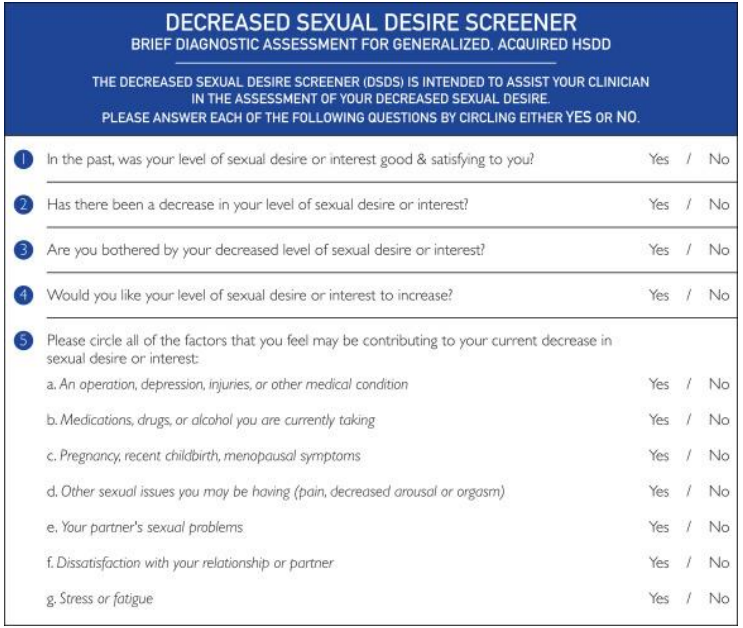
Hypoactive Sexual Desire Disorder

- The associations between endogenous androgen concentrations and sexual function in women remain uncertain because of issues relating to the sensitivity and specificity of androgen assays in some studies and insufficient data (Insufficient).

- No cutoff blood level can be used for any measured circulating androgen to differentiate women with and without sexual dysfunction

- Testosterone therapy, *in doses that approximate physiological testosterone concentrations for premenopausal women,* exerts a beneficial effect on sexual function

- The recommendations do not apply to injectables, pellets, or formulations that result in supraphysiological blood concentrations of testosterone, or compounded preparations



DECREASED SEXUAL DESIRE SCREENER
BRIEF DIAGNOSTIC ASSESSMENT FOR GENERALIZED, ACQUIRED HSDD

THE DECREASED SEXUAL DESIRE SCREENER (DSDS) IS INTENDED TO ASSIST YOUR CLINICIAN IN THE ASSESSMENT OF YOUR DECREASED SEXUAL DESIRE.
PLEASE ANSWER EACH OF THE FOLLOWING QUESTIONS BY CIRCLING EITHER YES OR NO.

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

Susan Davis. Global Consensus Position Statement on the Use of Testosterone Therapy for Women
The Journal of Clinical Endocrinology & Metabolism, Volume 104, Issue 10, October 2019, Pages 4660–4666

Hypoactive Sexual Desire Disorder

- There is insufficient evidence to support the use of testosterone to enhance cognitive performance, or to delay cognitive decline, in postmenopausal women
- Testosterone may improve wellbeing in premenopausal women but data are inconclusive
- Available data do not show an effect of testosterone on depressed mood
- Few studies have evaluated the musculoskeletal effects of testosterone. The studies that have reported musculoskeletal outcomes, the number of included participants has been small
- No statistically significant effect of testosterone administered in physiologic doses has been demonstrated on lean body mass, total body fat, or muscle strength
- There is a need for clinical trials to evaluate the impact of testosterone treatment on musculoskeletal tissues

Susan Davis. Global Consensus Position Statement on the Use of Testosterone Therapy for Women. *The Journal of Clinical Endocrinology & Metabolism*, Volume 104, Issue 10, October 2019, Pages 4660–4666

Pre-Insertion Testing Females

- Free and total testosterone
- Estradiol, FSH,
- Progesterone
- DHEA
- TSH, free T4, free T3
- CBC (Hb & Hct) annually
- SHBG Optional
- Mammogram
- Pelvic Ultrasound
- Pap smear

Reliability of Testosterone Assays in Women

- Total testosterone can be measured with high accuracy and reproducibility using liquid/gas chromatography and tandem mass spectrometry assays
- Direct assays for the measurement of total and free testosterone are highly unreliable in the female range
- Measurement of testosterone using direct assays in clinical practice is appropriate, if liquid/gas chromatography and tandem mass spectrometry assay is not available, to exclude high baseline concentrations and also to exclude supraphysiological concentrations during treatment
- Current research into testosterone physiology and clinical effects should mainly focus on measuring total testosterone as the main biomarker rather than “free” testosterone because evidence that “free” testosterone is the biologically active testosterone fraction is lacking

JCEM THE JOURNAL OF CLINICAL ENDOCRINOLOGY & METABOLISM

Susan Davis. Global Consensus Position Statement on the Use of Testosterone Therapy for Women. *The Journal of Clinical Endocrinology & Metabolism*, Volume 104, Issue 10, October 2019, Pages 4660–4666

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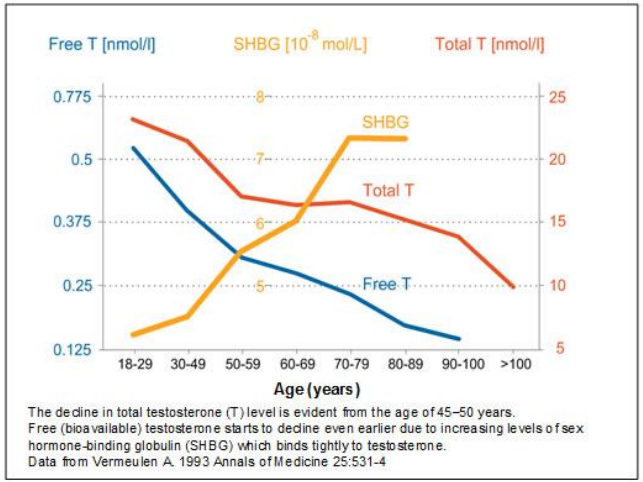
Sex Hormone-Binding Globulin

- SHGB is the carrier protein for estrogen and testosterone
  - SHBG-bound fraction is unavailable for biological activity
- Production regulated by estrogen-testosterone balance
  - Estrogen stimulates SHBG production
  - Testosterone decreases SHBG synthesis



The decline in total testosterone (T) level is evident from the age of 45–50 years. Free (bioavailable) testosterone starts to decline even earlier due to increasing levels of sex hormone-binding globulin (SHBG) which binds tightly to testosterone.
Data from Vermeulen A. 1993 Annals of Medicine 25:531-4

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Absolute Contraindications

- Breast cancer **active**
- Endometrial cancer **active**
- Acute thromboembolic disorder
- Acute myocardial infarction
- Undiagnosed vaginal bleeding
- Undiagnosed breast mass
- Severe liver disease
- Severe cardiac disease

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Relative Contraindications

- History of breast cancer, endometrial cancer, liver disease
- Enlarging uterine fibroids
- History of heart disease / valve replacement / pacemaker
- Atrial fibrillation on anticoagulant therapy
- CAD with 7-10% risk
- Autoimmune disease
- Smokers
- Estrogen-dependent migraine

- Severe Psychiatric disorders
- Abuse and poly-pharmacy use
- Anaphylaxis of unknown causes
- Self assessed “sensitivities to Hormones
- Acne
- Hair loss (Hirsutism)

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Female Testosterone Dosing

- Historical Dosing 50-225 mg Most common dosages used 100-160 mg
- Weight Based 2mg x Kg

  <100 lbs. (45kg) 75 mg

  100-120 lbs. (45-55 kg) 100-110 mg

  120-145 lbs. (55-65 kg) 110-125 mg

  145-165 lbs. (65-75 kg) 125-150 mg

  >165 lbs. (75 kg) 150-225 mg
- Based on daily production. Females produce .1 to 0.4 mg of testosterone per day. Testosterone Pellet 100 mg releases 0.65 mg per day. (50 mg T pellet releases0.32 mg per day and 25 mg T pellet releases 0.16 mg per day)
- Pelledoser on-line calculator: Uses Age, BMI, Hormone levels and adjusts for risks factors

Glaser, R. (2012). Testosterone implants in women: Pharmacological dosing for a physiological effect. *Maturitas, 74*(2)m 179-184.

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Pellet Testosterone Therapy for women Facts

- Maintaining levels within the normal range has been shown to be inadequate for therapeutic effect
- Heavier women require higher doses of Pellets to relieve symptoms
- Higher levels do correlate with greater relief of symptoms
- Side effects is dose dependent
- There is no data to support that above normal serum levels from testosterone pellets correlated with any serious side effects.
- 98% of patients returned for testosterone implant therapy when symptoms returned

Glaser et,al Maturitas 68 (2011) 355-361

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Testosterone Therapy for Women

- Evidence based indication: treatment of postmenopausal women with formal diagnosis HSDD (level 1, Grade A).
- Need further studies for uses when testosterone in physiologic range for premenopausal women (Expert Opinion
- Off label prescribing of male formulations reasonable if kept in physiologic range.
- If compounded, pharmacy should be compliant with industry standard for quality and safety.
- Dosing limited to achieving testosterone concentrations in the physiologic premenopausal range
- Preparations resulting in supraphysiologic concentrations including but not recommended (Expert Opinion)
- A baseline total testosterone concentration should be measured prior to treatment and repeated 3-6 weeks after treatment. (Level IIA, Grade C).
- Clinical response to treatment for signs of androgen excess with a serum total testosterone level should be done every 6 months, to screen for overuse (Expert Opinion).

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Studies in patients treated with pellet implants

- Increased energy
- Improved sleep (Cintron)
- Relief of migraine or menstrual headache (Martin et al)
- Relief from depression, decreased anxiety (Glaser)
- Increased muscle mass and bone density (Smith)
- Decreased soft fatty tissue (Papadakis)
- Increased coordination and physical performance (Hellsten)
- Improved skin (increase collagen and elastin)
- Increased concentration and memory
- Improved overall physical health (BP, lipids, glucose) (Martin et al)
- Improved libido and sexual satisfaction
- ***No* increased** risk of strokes or blood clots

Cintron, D. et al (2017). Effects of oral versus transdermal menopause hormone therapy treatments on self reported sleep…. *Menopause,* 25(2), 145-153.
Glaser, R & Dimitrakakis, C (2013). Testosterone therapy. In women: Myths and misconceptions. *Maturitas 74, 230-234,* doi.org/10.1016/j.maturitas.2013.01.003
Hellsten Y & Gliemann, L. (2017). Limb vascular function in women: Effects of female sex hormones and physical therapy. *Transl Sports Medicine 1,* 14-24.
Martin, K., Barbieri,R.(2018)Treatment of menopausal symptoms with hormone therapy. *Uptodate.*
Papadakis, G. et al (2018). Menopausal hormone therapy is associated with reduced total visceral adiposity. The OsteoLaus Cohort. The Journal of Clinical Endocrinology & Metabolism 103(5), 1948-1957.
Smith, R, Studd, J(1993). Recent advances in hormone replacement therapy. *British Journal of Hospital Medicine 49*(11), 799-807.

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Pellets for Women

Optimal range is individualized

Total Testosterone; 50-200 ng/dl range.

- Glaser showed no standardized response in 100mg T implant.
- Free Testosterone my lab: 2 ng/dl LabCorp: 6 ng/dl

Estradiol pellet 25mg Serum level 50 pg/ml

- Concentrations were constant, Premenopausal e2:e1 ratio was maintained (Cravioto)
- Optimal Level: 50-150 pg/ml

Cravioto, M. et al, (2001) Pharmacokinetics and pharmacodynamics of 25 mg estradiol implants in postmenopausal Mexican women. *Menopause 8*(5), pp 353-360.
Glaser, R. (2013). Testosterone implants in women: pharmacological dosing for a physiologic effect. *Maturitas 74* , 179-184.

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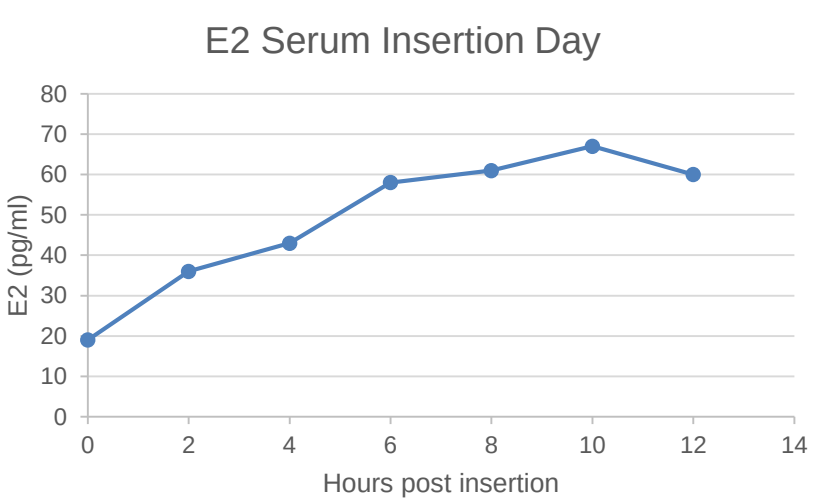
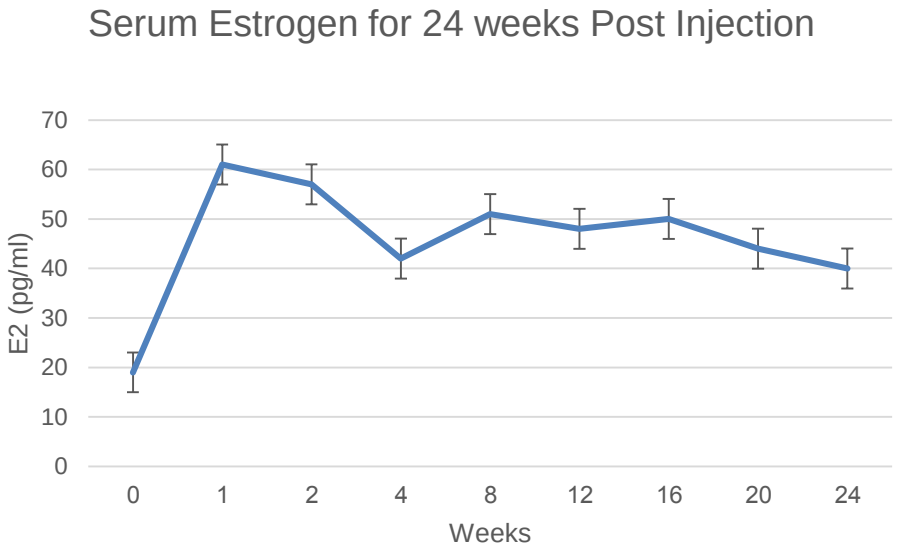
Estradiol Pellets for Women





Cravioto, M. et al, (2001) Pharmacokinetics and pharmacodynamics of 25 mg estradiol implants in postmenopausal Mexican women. *Menopause 8*(5), pp 353-360.

Glaser, R. (2013). Testosterone implants in women: pharmacological dosing for a physiologic effect. *Maturitas 74* , 179-184.

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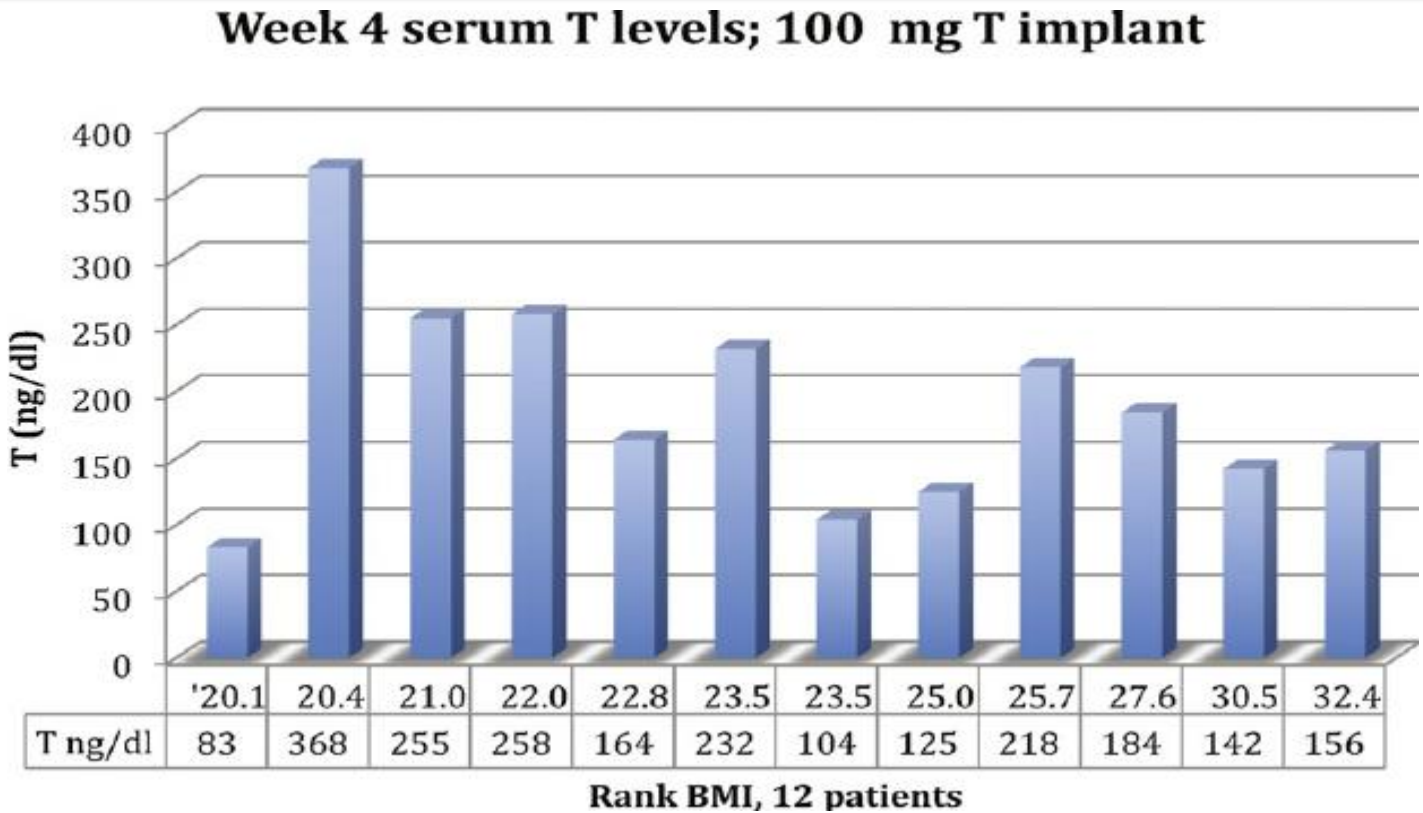
Serum T Levels in Women



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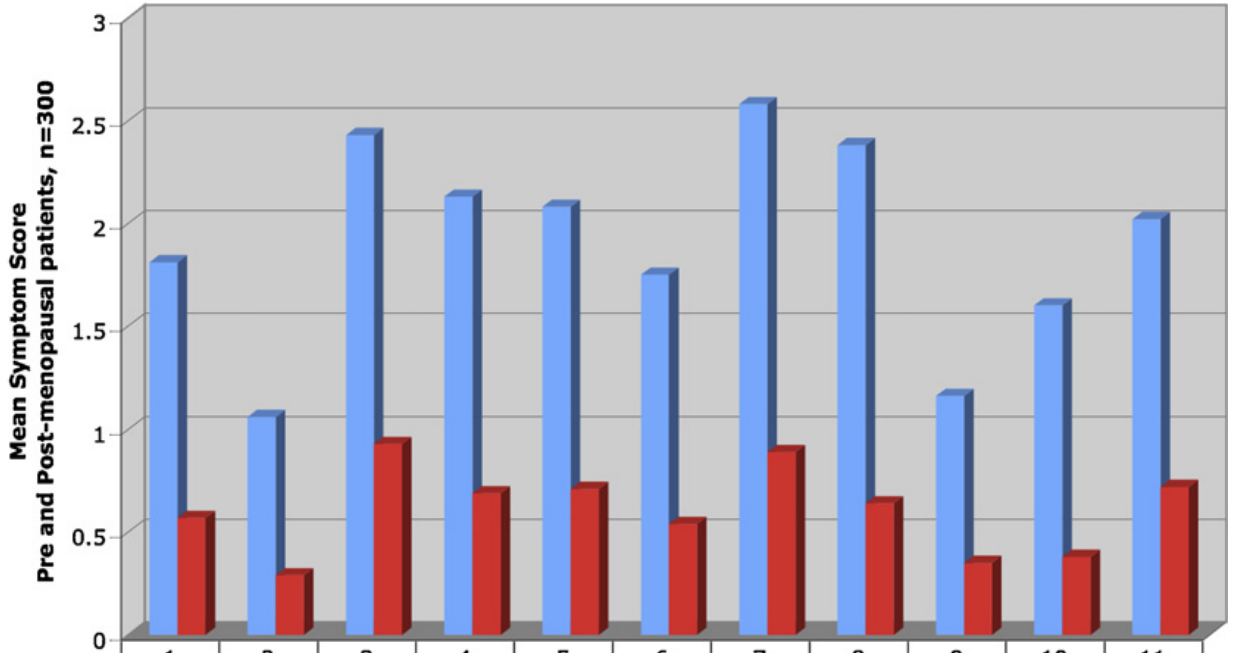
Symptom Control and Pellet Testosterone Therapy



	1	2	3	4	5	6	7	8	9	10	11
Baseline Score	1.81	1.06	2.43	2.13	2.08	1.75	2.58	2.38	1.16	1.6	2.02
Testosterone Therapy	0.57	0.29	0.93	0.69	0.71	0.54	0.89	0.64	0.35	0.38	0.72

MRS Symptom Category, 1-11

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Potential Side Effects with Testosterone Therapy

Therapy for postmenopausal women, *in doses that approximate physiological testosterone concentrations for premenopausal women*

- associated with mild increases in acne and body/facial hair growth in some women
- not associated with alopecia, clitoromegaly, or voice change

Oral testosterone therapy is associated with adverse lipid profiles

- Decreased high density lipoprotein-cholesterol
- Increased low-density lipoprotein-cholesterol levels

Non-oral testosterone therapies (percutaneous and injectable), *in doses that approximate physiological testosterone concentrations for premenopausal women,* have shown no statistically significant adverse effects on lipid profiles over the short term

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Potential Side Effects with Testosterone Therapy

- Not associated with increases in blood pressure, blood glucose, or HbA1c levels
- Nonsignificant trend for an increased risk of DVT
- Limited data on myocardial infarction or death (Insufficient data)
- Does not increase mammographic breast density (Level I, Grade A).
- Short-term transdermal testosterone therapy does not impact breast cancer risk (Level I, Grade A).
- Caution is recommended for testosterone use in women with hormone-sensitive breast cancer

Testosterone therapy for postmenopausal women, in doses that approximate physiological testosterone concentrations for premenopausal women, is not associated with serious adverse events

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Conclusion Pellets in Women

Myth:
The Safety of testosterone use has not been Established in women

Long-term data exists on the efficacy, safety and tolerability of doses of up to 225 mg in up to 40 years of therapy

Glaser, R., Kalantaridou, S., and Dimitrakakis, C.**Testosterone implants in women: pharmacological dosing for a physiologic effect.** *Maturitas*. 2013; 74: 179–184

GambrellJr, R.D. and Natrajan, P.K.. **Moderate dosage estrogen-androgen therapy improves continuation rates in postmenopausal women: impact of the WHI reports.** *Climacteric*. 2006; 9: 224–233

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Optimal Treatment Hormone levels

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